Basic Institutional Review Board (IRB) Regulations and Review Process

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Introduction

This module provides a basic understanding of the human subject protection regulations that govern the participation of human subjects in research in the United States.

Learning Objectives

By end of the module, you should be able to:

- Describe the role, authority, and composition of the IRB.
- List the IRB requirements for conducting research involving human subjects.
- Describe the types of IRB review.
- Describe the process of working with the IRB.
- Identify other regulations and regulatory groups that require compliance based on the type of research being conducted.

IRB Role, Authority, and Composition

IRB Role

An IRB is a review committee established to help protect the rights and welfare of human research subjects. Regulations require IRB review and approval for research involving human subjects if it is funded or regulated by the federal government. Most research organizations, professional organizations, and scholarly journals apply the same requirements to all human research. Although federal regulations refer to IRBs, an organization may have chosen a different name for this committee.

To clarify when IRB review is required, the table below reviews some definitions from federal regulations and guidance.

Definitions from Federal Regulations and Guidance	
Term	**Definition**
Research	"A systematic investigation designed to develop or contribute to generalizable knowledge" (Protection of Human Subjects 2009). If researchers are unclear about whether a planned activity is research, they should contact their IRB office.
Human Subject	"A living individual about whom a researcher (whether professional or student) conducting research obtains: 1. Data through intervention or interaction with the individual, or 2. Identifiable private information" (Protection of Human Subjects 2009). **Note:** Some state laws include deceased individuals and fetal materials as "human subjects." Check with the local IRB about the definition of a human subject that applies in the state where the research will be conducted.
Private Information	Information about behavior that occurs in a setting in which the individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes, other than research, where the individual can reasonably expect that it will not be made public (such as, a medical record) (Protection of Human Subjects 2009).
Coded Private Information or Biological Specimens	The U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP 2008) guidance considers private information or specimens to be individually identifiable when they can be linked to specific individuals directly or indirectly through coding systems. OHRP (2008) guidance recommends that only a knowledgeable person or entity be authorized to determine if coded specimen or data constitute research. OHRP recommends that researchers not be given authority to make an independent determination that research involving coded private information or specimens does not involve human subjects.

Clinical Investigation	"Any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to the Food and Drug Administration... or need not meet the requirements for prior submission to the Food and Drug Administration... but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit" (Institutional Review Boards 2015).

IRB Authority

Federal regulations stipulate that an IRB can:

- Approve research
- Disapprove research
- Modify research
- Conduct continuing reviews
- Observe/verify changes
- Suspend or terminate approval
- Observe the consent process and research procedures

IRB Composition

Federal regulations dictate that the IRB membership will include:

- At least five members
- Member of both sexes
- Members that come from varied professions
- At least one member whose primary concerns are in nonscientific areas
- At least one member whose primary concerns are in scientific areas
- At least one member who is not otherwise affiliated with the organization

The regulations also stipulate that the IRB membership will include:

- Reviewers with experience and expertise in all of the areas of research being reviewed. At its discretion, an IRB may invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB.
- Diversity of backgrounds, including racial and cultural diversity.
- Sensitivity to community attitudes.

- Knowledge of organizational commitments and regulations, applicable laws, and standards of professional conduct and practice.
- Knowledge and experience with vulnerable populations.

Note: If an IRB reviews research that involves vulnerable populations, the IRB must consider the inclusion of an individual who has knowledge of, and experience with, these vulnerable populations. The regulations may also require a voting IRB member who has relevant research expertise (for example, research involving prisoners). IRBs may call experts to help with problematic reviews, but those persons may not vote on the disposition of the application. If an IRB member has a conflict of interest, that member cannot be present for the review of that project (except to provide the IRB with information as requested) and may not vote on that project.

IRB Requirements for Human Subjects Research

IRB Requirements

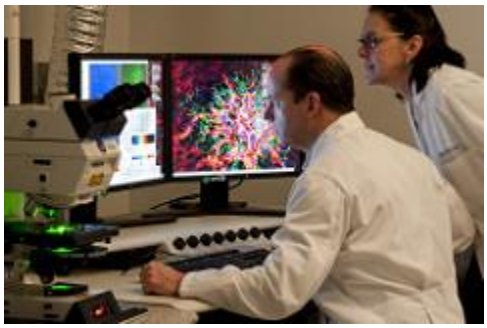
Organizations and IRBs vary in the practices that assure they meet the federal regulations and in the details of the standards they apply. What follows are the minimum federal requirements. Organizations and/or IRBs may add additional protections or procedures to these minimum requirements.

Minimum Information on an IRB Application for IRB Assessment	
Risk/anticipated benefit analysis	Identification and assessment of risks and anticipated benefits Determination that risks are minimized Determination that risks are reasonable in relation to potential benefits
Informed Consent	Informed consent process and documentation
Assent	The affirmative agreement of a minor or decisionally impaired individual to participate in research Assent process and documentation
Selection of Subjects	Equitable selection in terms of gender, race, and ethnicity Benefits are distributed fairly among the community's populations Additional safeguards are provided for vulnerable populations susceptible to pressure to participate

Safeguards	Ensure that subject recruitment does not invade individual privacy and that procedures are in place to assure that the confidentiality of the information collected during the research is monitored
Research Plan for Collection, Storage, and Analysis of Data	Clinical research studies often include data safety monitoring plans and/or Data Safety Monitoring Boards/Committees (DSMBs/DSMCs); IRBs will review the plans to ensure they are adequate to protect human subjects
Research Design/Methods	Are appropriate and scientifically valid, and therefore, justify exposing subjects to research risks
Additional Information	About identification, recruitment, and safeguards if the research involves special populations
Additional Items IRBs Must Review	Qualifications of the principal investigator (PI) and scientific collaborators Complete description of the proposed research Provisions for the adequate protection of rights and welfare of subjects Compliance with pertinent federal and state laws/regulations, and organizational policies HHS funding proposals (other funding agencies may also have similar requirements/expectations) Investigator's Brochure/Investigator Protocols (for U.S. Food and Drug Administration [FDA]-regulated research)

Responsibilities of the PIs and Research Staff

PIs and research staff have specific responsibilities. They are required to:



- Protect the rights and welfare of human subjects who participate in research.
- Understand the ethical standards and regulatory requirements governing research activities with human subjects.
- Personally conduct or supervise the research.

- Ensure that all staff, collaborators, and colleagues assisting in the conduct of the study are informed about the study, regulations governing research, and organizational policies.
- Ensure that all research activities have IRB approval and other approvals required by the organization before human subjects are involved.
- Implement the research activity as it was approved by the IRB.
- Obtain the informed consent of subjects before they are involved in the research and document consent as approved by the IRB.
- Maintain written records of IRB reviews and decisions, and obtain and keep documented evidence of informed consent of the subjects (or their legally authorized representatives [LARs]).
- Obtain IRB approval for any proposed change to the research plan prior to its implementation.
- Comply with the IRB requirements for timely reporting of unanticipated problems involving risks to subjects or others including adverse events, safety reports received from the sponsor, or data safety and monitoring summary reports.
- Obtain continuation approval from the IRB on the schedule prescribed by the IRB.
- Make provisions for the secured retention of complete research records and all research materials.
- Ensure the confidentiality and security of all information obtained from and about human subjects.
- Verify that IRB approval has been obtained from all participating organizations in collaborative activities with other organizations.
- Notify the IRB regarding the emergency use of an investigational drug or device within five working days (or sooner if required by the IRB's policies) of the test article's administration.

Potential Consequences When IRB Regulations Are Not Followed

- Suspension of research project
- Suspension of all of a PI's research projects
- Inability to use data or publish results
- Notification to sponsors, regulatory agencies, and funding agencies of noncompliance
- Debarment by FDA from using investigational products
- Inability to receive funding from federal grants
- Additional monitoring and oversight by the IRB and/or third party monitoring of research activities
- Termination of employment
- Loss of licenses
- Immediate shut-down of all research at an organization

These are not theoretical consequences. Some or all of these consequences have occurred at sites where human subjects research was conducted improperly or without IRB approval.

The Types of IRB Review

Contact the IRB office for the guidelines for submitting a study for IRB review. Under federal regulations, there are three possible IRB review procedures:

1. Full/Convened Committee Review
2. Expedited Review
3. Review for Exemption Status

Full/Convened Committee Review

Full committee review or review by the convened IRB is the standard type of review described in the federal regulations. It must be used for the initial review of all studies that are not eligible for expedited review or exemption status. The procedures and conditions for full committee review require that:

- The review must be conducted at a convened meeting of the IRB. A majority of IRB members (a quorum) must be present at the meeting.
- At least one member whose primary concerns are in nonscientific areas must be present at the meeting (in addition, FDA policy recommends that a physician be present).
- In order to approve research, the IRB must determine that all of the requirements specified in 45 CFR 46.111 (and if applicable, 21 CFR 56.111) are satisfied. See "**Frequently Asked Questions About Human Research**" and ***Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors*** for more information.
- A majority of the members present at the meeting must approve the research.
- IRB members who have a conflict of interest in a research project may provide information to the IRB, but cannot participate in the review of the plan or be present for voting. Members with a conflict do not count toward the quorum for the review of that study.
- The IRB must notify (in writing) researchers and the organization of its decision to approve, modify, or disapprove the research.
- IRBs must keep detailed documentation of meeting activities including attendance, voting on actions, the basis for the actions, and a written summary of the IRB discussion of controverted issues and its resolution.

Although not specifically addressed in the regulations, IRBs may employ a "primary reviewer system." In such a system, all IRB members receive basic information about the research application, but a "primary reviewer" with experience and/or expertise in the study area is assigned to conduct a thorough review of the IRB application and any accompanying documentation (for example, an Investigator's Brochure or grant application). The primary reviewer will then report his/her findings for discussion at a full/convened IRB meeting. At some organizations, reviewers may contact the researcher with questions or suggestions prior to the

meeting. Additionally, the IRB at some organizations may ask that researchers attend the IRB meeting or be available by phone to answer questions that may arise at the meeting.

Expedited Review

Federal regulations establish nine categories that IRBs may use to invoke the expedited review process. Organizations may adopt some or all of the categories when determining if a research activity can be appropriately reviewed by an expedited review process. Categories 1 through 7 pertain to both the initial and continuing IRB review. Categories 8 and 9 pertain only to continuing review. The categories are listed in the following section.

The federal regulations establish two main criteria for an expedited review.

- The research may not involve more than "minimal risk." Minimal risk means "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (Protection of Human Subjects 2009; Institutional Review Boards 2015).
- The entire research project must be consistent with one or more of the federally defined categories (OHRP 2003).

Some organizations/IRBs have additional requirements. Check with the IRB office to learn how the IRB at your organization handles expedited review.

Research Categories that Qualify for Expedited Review

Category 1

Clinical studies on drugs or medical devices for which an investigational new drug (IND) application or investigational device exemption (IDE) is not required. Similarly, a study with a cleared/approved medical device that is being used in accordance with its cleared/approved labeling. More details.

Category 2

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture. More details.

Category 3

Prospective collection of biological specimens for research purposes by noninvasive means. More details.

Category 4

Collection of data through noninvasive procedures routinely employed in clinical practice provided that:

- The noninvasive procedure must not involve general anesthesia or sedation routinely employed in clinical practice or 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 expedited review, including studies of cleared medical devices for new indications.)

Examples of Noninvasive Procedures

- Physical sensors that are applied either to the body's surface or at a distance, and do not involve input of significant amounts of energy into the subject or an invasion of the subject'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.

Category 5

Research involving data, documents, records, or specimens that:

- Have been collected; or
- Will be collected solely for non-research purposes (such as, for medical treatment or diagnosis).

Note: Some research in this category may be exempt from the HHS regulations at 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

Category 6

Collection of data from voice, video, digital, or image recordings made for research purposes.

Category 7

Research on individual or group characteristics or behavior. More details.

Category 8

Continuing review of research previously approved by the full/convened IRB where:

- The research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and, the research remains active only for long-term follow-up of subjects;
- No subjects have been enrolled and no additional risks have been identified; or
- The remaining research activities are limited to data analysis.

Category 9

Continuing review of research not conducted under an IND application or IDE, and where categories 2 through 8 do not apply, but the IRB has determined and documented at a full/convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Expedited Review Process

The IRB chair, or one or more experienced IRB members designated by the chair, can conduct an expedited review. IRB members with a conflict of interest cannot be designated to serve as an expedited reviewer. In conducting the review, a determination must be made that the research meets the conditions for expedited review procedures.

The reviewer conducting the expedited review may exercise all of the IRB's authorities with one important exception: the reviewer may not disapprove research. To approve a research activity, the reviewer must make the determination that all of the requirements specified in federal regulations (45 CFR 46.111 and 21 CFR 56.111) are satisfied. The reviewer(s) may either approve the research, require modifications (to secure approval), or refer the research to a full/convened IRB meeting for review in accordance with the "full committee review" procedures described previously, and set forth in **45 CFR 46.108(b)** and 21 CFR 56.108(c).

Expedited procedures can also be used to review minor modifications of previously approved research.

Review for Exemption Status

Federal regulations specifically define six categories of human subjects research that are **exempt** from the other provisions of the regulations. OHRP (2016) guidance indicates that determinations of exempt status should be made by individuals independent of the research who are well-acquainted with interpretation of the regulations governing the conduct of human subjects research. Many organizations grant the authority to make determinations of exempt status to the IRB. Check with the IRB office to find out who has been granted authority to make the exemption determination. **Note:** The determination must be made prior to initiation of research or of the activity; it cannot be made retroactively.

Research That is Exempt

The regulations at 45 CFR 46 (Protection of Human Subjects 2009) have determined that the following six categories of research are eligible for exemption status.

Category 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
- Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Category 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 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.

Note: The federal regulations specify that the exemption for survey or interview procedures do not apply to research with children. In addition, the federal regulations specify that the observation of public behavior procedure does not apply to research involving children, except when the researcher does not participate in any of the activities being observed.

Category 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 paragraph (b)(2) of 45 CFR 46.101, if:

- The human subjects are elected or appointed public officials or candidates for public office; or
- Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Category 4

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

Note: According to OHRP, exempt reviewer(s) should define "existing" to mean collected (that is, on the shelf) prior to the research for a purpose other than the proposed research. It includes data or specimens collected in research and non-research activities.

Category 5

Research and demonstration projects conducted by heads of government departments or agencies, which are designed to study, evaluate, or otherwise examine:

- Public benefit or service programs
- Procedures for obtaining benefits or services under those programs
- Possible changes in or alternatives to those programs or procedures
- Possible changes in methods or levels of payment for benefits or services under those programs

Note: Department or agency head means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

Category 6

Taste and food quality evaluation and consumer acceptance studies.

- If wholesome foods without additives are consumed; or
- 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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

When Review of Exemption Status is Not Appropriate

According to 45 CFR 46 (Protection of Human Subjects 2009), research involving the following is not appropriate for exemption:

- Prisoners
- Surveying or interviewing of children
- Observations of public behavior of children when the researcher(s) participates in the activities being observed

Special Considerations

Researchers and IRB reviewers should be aware that there may be special considerations for different types of research. For example, certain policies may limit the IRB's ability to waive the requirements for informed consent, or research that may normally be considered exempt will require IRB review.

At this point in time, National Institutes of Health (NIH)-funded research using newborn dried blood spots collected on or after 18 March 2015, is considered human subjects research according to the Newborn Screening Saves Lives Reauthorization Act of 2014. This research would require IRB review. The act also limits the IRB's ability to waive the requirement for informed consent. This means that researchers would need parental permission to use the dried blood spots. However, NIH-funded research with non-identifiable dried blood spots collected before 18 March 2015, is considered non-human subjects research and IRB review is not required. Furthermore, if the research is not NIH-funded (for example, privately funded through a foundation), then it is not subject to the act's restrictions.

Another example is the NIH Genomic Data Sharing Policy (GDSP) for Human and Non-Human Data. This policy has implications for researchers if they want to access data from this database or if they want to provide data to this database and they are NIH-funded. Under this policy, the IRB must review the research if the researcher will provide data to the Database of Genotypes and Phenotypes (dbGaP) and the research is NIH-funded. IRB review would not normally be required under the regulations because the research would typically be considered non-human subjects (NIH 2014).

If the PI receives funding from NIH and needs access to the database, the non-human subjects determination cannot be used. The research must be reviewed by the IRB to ensure that there were adequate consent provisions for the collection of the specimens.

Additional HIPAA Requirements That Indirectly Affect the Review Of Exemption Status

The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (45 CFR 160 and 164). If an IRB has been given the responsibility to consider HIPAA issues in research and if the research potentially falls under the purview of HIPAA, an IRB will be applying not only the 45 CFR 46 exemption categories but also determining if HIPAA applies. In some cases, HIPAA applicability requirements are more stringent than HHS exemption requirements and in other cases less stringent. A research project that is exempt from the human research subject IRB requirements may not be exempt from HIPAA provisions. In addition, a project that is not exempt from IRB review might be exempt from HIPAA. See the OHRP ***Guidance on Research Involving Coded Private Information or***

Biological Specimens, and the NIH guidance on ***Institutional Review Boards and HIPAA Privacy Rule***.

Process of Working with the IRB

Criteria for IRB Approval

Federal regulations at 45 CFR 46 (Protection of Human Subjects 2009) and 21 CFR 56 (Institutional Review Boards 2015) list basic criteria that the IRB must apply when reviewing research involving human subjects. To approve a research project, the IRB must determine that:

- The risks to subjects are minimized.
- The risks are reasonable in relation to any anticipated benefits to the subject, and to the advancement of knowledge.
- The selection of subjects is equitable.
- Informed consent will be sought.
- Informed consent will be documented.
- Where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure safety of subjects.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Where any of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect subjects.
- In addition, there are specific requirements regarding the informed consent process. These will be detailed in the CITI Program's *Informed Consent* module.

The IRB must determine that these conditions exist at the time of initial review and at each subsequent review conducted by the IRB.

Types of IRB Submissions

Types of IRB Submissions	
Application for Initial Review	The first request for approval of a specific project is the application for initial review.
Application for Continuing Review	The IRB must re-review studies at a minimum of once every 365 days. An IRB may require review more frequently depending on the IRB's assessment of the study's risk/benefit ratio. The review may be a full or expedited review.
Amendments or Modifications	Changes cannot be made to approved studies, including the informed consent document, without prior IRB review and approval. The review may be full or expedited, depending

	on the magnitude of the change and the affect of the change on the risks/benefits ratio.
Reports of Unanticipated Problems/Adverse Events/ Noncompliance to the IRB	The IRB may require reports for: a. Adverse events or unanticipated problems involving risks to subjects or others b. Incidents of noncompliance c. Deviations from an approved study plan and violations of the terms of approval d. Data safety and monitoring report summaries

Application for Initial Review

The initial review may be either a convened/full committee or an expedited review depending on the type of study, subjects, and level of risk.

Application for Continuing Review

The IRB must do substantive continuing review and consider the same issues as during initial review. Specifically:

- When conducting a continuation review, the IRB uses convened/full committee review procedures unless the research meets the expedited review criteria.
- To approve research, the IRB must determine that all the requirements for initial approval (specified in 45 CFR 46.111 and 21 CFR 56.111) continue to be satisfied.
- IRB should review, at a minimum, the research plan and any amendments, as well as a status report, including:
    - The number of subjects accrued
    - A description of adverse events, unanticipated problems, withdrawal of subjects, complaints, and summary of relevant new information
    - A copy of current informed consent document

Review the latest on applications for continuing review in OHRP's ***Guidance on IRB Continuing Review of Research***.

Continuing review must occur, at a minimum, once per year (within 365 days) of previous approval. More frequent review is at the IRB's discretion, and may be the result of considering the risks associated with the study or the proposed population. It is a researcher's responsibility to know when IRB approval will expire. However, most organizations/IRBs, as a courtesy to their researchers, send out reminders that IRB approval is about to expire. Sometime prior to the

expiration of IRB approval, researchers will receive a request to complete a progress report for continuing review by the IRB. It is a researcher's responsibility to complete the continuing review request and submit it back to the IRB prior to the end of the current IRB approval period.

If a research plan's approval expires before the IRB completes its review, the researcher must stop all research procedures. When stopping the research could place subjects at risk, the researcher should contact the IRB immediately to obtain approval to continue treating subjects on that study.

Amendments and Modifications

All amendments and modifications to a study need IRB approval before they are implemented. If the researcher wants to change *anything* in the research that would affect the subjects (such as, recruitment procedures, key personnel, inclusion/exclusion criteria, research procedures, the informed consent document/process, or data elements collected), the researcher must obtain IRB review and approval prior to implementation of the changes. The only exceptions are changes necessary to immediately protect subjects' safety, as noted in 21 CFR 56.108(a)(4) and 56.115(a)(1). If researchers are unsure about reporting changes to the IRB, they should call the IRB office and ask for guidance. The IRB office can also provide researchers with instructions for submitting a request to modify IRB-approved research.

Reports of Unanticipated Problems/Adverse Events/Noncompliance to the IRB

Federal reporting requirements for IRBs, researchers, and funding sponsors can be confusing. Consequently, IRBs tend to develop their own idiosyncratic reporting requirements, based upon their interpretation of both FDA and OHRP guidance. This poses some difficulty for researchers because if the project is funded, the sponsor may have reporting requirements that differ from the IRB's policies and procedures.

At a minimum, to ensure compliance, the researcher is responsible for:

- Determining the IRB requirements for reporting with respect to what needs to be reported, when it should be reported, and the procedure for submitting the report.
- Setting up systems to ensure that reportable events are identified and submitted to the IRB in a timely manner.

Examples of Reportable Events

- An unanticipated problem, which may be defined as any unexpected event that affects rights, safety, or welfare of subjects. The event could be physical (such as, an adverse drug experience or adverse device effect) or involve some harm (such as, breach in confidentiality or harm to a subject's reputation).
- Serious adverse event, which may be defined as a death, life-threatening adverse drug or device experience, inpatient hospitalization or

prolongation of existing hospitalization, persistent disability/incapacity, or congenital anomaly/birth defect.
- Research plan exception, which may be defined as enrollment of a research subject that fails to meet research plan inclusion/exclusion criteria.
- Research plan deviation, which may be defined as a departure from the research plan as approved by the IRB for a single subject.
- Data and safety monitoring plan or board summary reports.
- Complaints concerning subject rights submitted by subjects or concerned parties, family members, or study personnel.

The IRB will use the reports to assess whether the risk/benefit ratio is still reasonable, whether changes in the informed consent document or study procedures are needed, or whether re-consent is necessary. IRB requirements for reporting vary regarding what should be reported, when the reports should be submitted, and how the reports are formatted. Check with the IRB to determine its specific requirements.

Basic IRB Regulations and Review Process

Best Medical Center (BMC) is a newly established academic medical center with state-of-the-art facilities. BMC wishes to conduct biomedical and social-behavioral research and is in the process of establishing an IRB and developing policies and procedures for human subjects research. BMC intends to seek federal funding, conduct industry-sponsored clinical trials, and engage in researcher-initiated research. Of course, being very concerned with its reputation and the relationship with patients, BMC wants to make sure that it complies with the regulations and adheres to the recommendations provided in federal guidance.

- **In setting up its IRB, what are the basic membership requirements that BMC must meet?**

Response: The BMC IRB must consist of at least five members, including at least:

- One member whose primary concerns are in scientific areas
- One member whose primary interests are in non-scientific areas
- One person not otherwise affiliated with BMC

A single member may fulfill more than one role. The membership should be diverse and have the expertise to review the research likely

to come before it. Organizations conducting FDA-regulated clinical research should include at least one physician as a scientific member. If the IRB will regularly review research involving a vulnerable category of subjects (such as, children, pregnant women, or individuals with diminished consent capacity) then the IRB should include one or more members who have knowledge and experience in working with these populations.

- **The researchers at BMC who will be conducting minimal risk social-behavioral research have expressed concern that their research may not be viewed as a priority and that this may be reviewed by the full/convened IRB at its periodic meeting, delaying the approval process for this type of research. How can BMC address the researchers' concern?**

Response: BMC could provide information to researchers about the expedited review mechanism. Under the federal regulations, the IRB may conduct its review of human research activities by one of two mechanisms: at a meeting of the full/convened IRB or by the expedited review procedure. Under the expedited review procedure, the IRB chair or one or more experienced IRB members designated by the chair may approve minimal risk research that falls within one or more designated categories. Using expedited review, the IRB can minimize the delay in the approval process for eligible research while still addressing all the approval criteria.

- **As conducting research can be an evolving process, researchers at BMC want to know when they may initiate changes to research after it had been approved by the IRB.**

Response: Only if a researcher believes that a subject(s) is in immediate risk, may changes be made to the research prior to IRB review and approval. If there is no immediate risk, all other changes, even if they are minor, must have prior IRB review and approval. Minor changes that do not affect the risk/benefit ratio may qualify to be reviewed and approved using expedited review procedures.

Additional Reporting Requirements

Besides the IRB, the PI is responsible for reporting to a variety of other entities. Minimum reporting requirements for each entity are summarized in the table below.

Entity	PI Reporting Requirements
Research Subject	While it might not be considered reporting in the strictest sense, the informed consent process is a report to the potential subject about the research, both before the research begins and on an ongoing basis throughout the study. Also, if new information becomes available during the research that might affect the subject's willingness to participate, a researcher is obligated to provide the subject with that information. This information will also need to be reported to the IRB. The IRB office can provide guidance on how additional information should be reported.
Organization	Most organizations have reporting lines set up so that the researcher makes reports to the IRB and it falls upon the IRB to keep the organization informed. However, check with the applicable IRB to make sure that the researcher does not have direct responsibility for reporting incidents to the organization.
Sponsor	Adverse events should be reported immediately to the sponsor. Researchers should also check the sponsor's proposed changes that might be made to the study, based on the adverse event that has occurred or preliminary findings. The sponsor also should be told about serious or ongoing noncompliance in a study.
FDA	Adverse events/unanticipated problems should be reported directly to FDA if the research is PI-initiated (without external sponsorship) and falls under the FDA's purview. Other reporting requirements related to FDA-regulated research may apply.
DSMB/DSMC	If the project has a DSMB/DSMC, check the DSMB/DSMC plan for reporting requirements.

Recordkeeping

The signed informed consent document is one of the most critical research records the researcher needs to obtain and keep. It provides verification that the research was explained to the subject and that the subject understood and voluntarily agreed to participate in the research study. Researchers are responsible for retaining signed consent documents, IRB correspondences, and research records for at least three years after the completion of the research activity (Protection of Human Subjects 2009). However, local organizational policy or sponsor requirements may dictate that records be kept longer. Check with the sponsor and IRB office to make sure that the minimum three-year retention requirement meets their needs.

The FDA regulations specify unique document retention requirements for FDA regulated studies (see 21 CFR 312.62 [c]). These requirements must be met for FDA-regulated studies.

Other Regulations and Regulatory Groups

Funding and Regulatory Agencies

Depending upon the nature of the research and the funding agency, there are a number of other regulations, policies, and procedures that may need to be considered. Below is a brief description of select regulations, regulatory bodies, and funding agencies that may oversee research. Funding agencies and/or local IRB offices can also provide guidance on whether any additional requirements apply to a research activity.

Funding/Regulatory Agencies	General Regulations
HHS	HHS is responsible for one group of human subjects federal regulations. 45 CFR 46 (Protection of Human Subjects 2009) applies to all human research submitted to or funded by HHS and is applied to all human research by most organizations. Subparts include: • **Subpart A:** Basic HHS Policy for the Protection of Human Subjects • **Subpart B:** Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research • **Subpart C:** Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects • **Subpart D:** Additional Protections for Children Involved as Subjects in Research • **Subpart E:** Registration of Institutional Review Boards
NIH	NIH includes funding agencies that provide federal funding for biomedical research. NIH requires grantees conducting certain types of clinical research studies to have either data safety monitoring plans and/or DSMBs/DSMCs. In general, NIH policy requires that a DSMB/DSMC be established for all Phase III randomized clinical trials. • NIH Policy for **Data and Safety Monitoring**

	• Policy for the **National Cancer Institute for Data and Safety Monitoring** of Clinical Trials • **Essential Elements of a Data and Safety Monitoring Plan** for Clinical Trials Funded by the National Cancer Institute • Further **Guidance on Data and Safety Monitoring** for Phase I and Phase II Trials • **Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research** (This policy will take effect 25 January 2018 [NIH2 2017]) • ClinRegs is an online database of country-specific clinical research regulatory information.
OHRP	OHRP is the HHS oversight body that provides guidance to IRBs and researchers conducting human subjects research. OHRP policy and assurance guidelines, regulations, ethical principles, the *IRB Guide Book*, OHRP/OPRR Reports, FAQs, and other materials relevant to the protection of human research subjects are available at www.hhs.gov/ohrp. OHRP's most current compilation of international standards may be found **here**.
FDA	FDA oversees the use of all drugs, devices, biologics, etc. including their use in research with human subjects. FDA has numerous regulations directly affecting informed consent.
ICH	The International Conference for Harmonisation (ICH) offers Good Clinical Practice (GCP) guidelines. Human subject research that is conducted in international settings may have additional requirements that must be met such as, the *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1).*
Department of Education	Research that is funded by the U.S. Department of Education may have additional requirements that must be met.
Department of Veterans Affairs (VA)	Research involving human subjects recruited from or conducted in a VA facility must also meet the requirements as set forth by the VA. The VA Office of

	Research Oversight provides a number of publications related to research on its website.
Other Federal Agencies	Other federal agencies may have additional policies, procedures, and/or requirements that must be applied to research involving human subjects. Examples are the Department of Defense, Department of Energy, and National Science Foundation.

Assurance Requirements

HHS human subject protection regulations and policies require that any organization **engaged** in non-exempt human subjects research conducted or supported by HHS must submit a written assurance of compliance to OHRP. The Federalwide Assurance (FWA) is the only type of new assurance accepted and approved by OHRP. FWAs also are approved by the OHRP for federal wide use, which means that other federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) may rely on the FWA for the research that they conduct or support. Organizations engaging in research conducted or supported by non-HHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question.

A compliance assurance is a written document submitted by an organization (not an IRB) that is engaged in non-exempt human subjects research conducted or supported by HHS. Through the assurance, an organization commits to HHS that it will comply with the requirements set forth in the regulations for the protection of human subjects (45 CFR 46).

IRB Registration

Both the FDA and HHS require IRB registration. Each IRB that is designated by an organization under an assurance of compliance approved for federal wide use by OHRP under 45 CFR 46.103(a) and that reviews research involving human subjects conducted or supported by the HHS must be registered with HHS. Additionally, any IRB in the U.S. that reviews research that is regulated by the FDA must be registered. All IRB registrations are completed through OHRP's website.

More Reasons to Contact the IRB Office

- Ensure the organization is registered with OHRP (if federal dollars are funding the research) and/or the FDA (if the research involves FDA-regulated products).
- Obtain the FWA number. Alternatively, this information may be found on OHRP’s website.
- Determine FWA requirements for multi-site research activities if federal dollars will pass to sub awardees.

Summary

The IRB has many roles and responsibilities in its mission to protect human subjects in research. Understanding the IRB is important for researchers in order to work together with the IRB.

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