Responsible Research Conduct

Instructions for Legal and Ethical Research Practices

General Policy for Research

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1. Regulations of Major Historical Significance

A. The Belmont Report

The Belmont Report is based on the deliberations of the National Commission, including an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center. The Belmont Report identified three basic principles relevant to the ethical conduct of research involving human subjects:

- **Respect for Persons (Composed of two parts)**
    - Individuals should be treated as autonomous agents
    - Individuals with diminished autonomy need additional protections based on age, health, cognitive ability, lack of education, poverty, social status, etc.
    - **Informed consent is an application of this rule**
        - Information provided for consent should be such that a "reasonable volunteer" of similar circumstance would be able to decide whether to participate
        - Information must be comprehensible to the potential participant to be valid
        - Consent must be given voluntarily, without significant social pressure or undue reward
    - **HIPAA Privacy Policy is an application of this rule**
        - All participants have a RIGHT to privacy and to control access to their self and their information; confidentiality of any identifiable information about a subject is protected by HIPAA laws and permission for the use of such information must be obtained from the participant with regard to the specific use of the information (**if I collect it for one study, I am not guaranteed to be allowed by the patient to use their data again unless this is agreed upon with the patient**)
- **Beneficence**
    - Researchers are ALL obligated to minimize risks of harm and maximize benefits to the participants

- **Justice**
    - The Selection of research subjects must not be done on the basis of convenience but rather on the scientific need for those participants
        - Researchers should be able to scientifically justify the inclusion or exclusion of subjects
        - Subjects should not be denied access to potential benefits of participating in the research because of considerations such as whether they speak English
    - Performing experiments on individuals with limited ability to refuse or under significant social pressures is highly regulated – refer to IRB

B. The Nuremberg Code

The Primary principles identified in this are as follows:

- A requirement for voluntary consent
- That the research have scientific merit
- That the benefits of the research outweigh risks
- That the subjects have the ability to terminate participation in the research at anytime

C. The National Research Act

This **established** the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research" (**The National Commission**) to identify the basic ethical principles underlying human subjects research and develop guidelines for ensuring that human subjects research is conducted according to those guidelines and it **required** the establishment of **Institutional Review Boards** (IRBs) at organizations receiving **PHS** support for **human subjects research.**

2. Institutional Review Board permissions and Researcher Responsibilities

A. Vocabulary

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).”

B. Understanding the Common Rule Delay and The 2018 Transition

The Final Rule to update the current regulations at 45 CFR 46, Subpart A - "Federal Policy for the Protection of Human Subjects" (the Common Rule) was published by HHS and other Common Rule agencies and departments on 19 January 2017 in the *Federal Register* (HHS 2017). This rule was not immediately effective.

On 19 June 2018, HHS and 16 other agencies published a Final Rule (“2018 Final Rule”) to delay the general compliance date until 21 January 2019, but allow for three provisions from the revised Common Rule (2018 requirements) to be available in the delay period from 19 July 2018 to 20 January 2019 (HHS 2018).

This delay gives additional time for regulated bodies to prepare for the revised rule. Regulated parties have the option but are not required to implement three burden-reducing provisions from the 2018 requirements during the delay period (19 July 2018 – 20 January 2019), including (HHS 2018):

- The definition of “research” at 46.102(l) of the 2018 requirements
- Elimination of continuing review requirement for no more than minimal risk research at 46.109(f)(1)(i) and (iii) of the 2018 requirements
- Elimination of IRB requirement to review grant applications at 46.103(d) of the 2018 requirements

Note: If an institution chooses to implement any or all of the three burden-reducing provisions for research during the delay period, then the affected research must comply with all of the 2018 requirements after the revised Common Rule’s general compliance date (21 January 2019). Institutions or IRBs must also document and date such determination to transition the ongoing research to the 2018 requirements during the delay period. During this delay period, some studies may be subject to the pre-2018 requirements and others

subject to the 2018 requirements. It is important to know which regulation is in effect for each research study.

The Common Rule (2018 requirements) adds to the definition of research certain activities that are specifically excluded from the definition of research, including:

- Scholarly or journalistic activities, public health surveillance activities
- Criminal justice activities (collection and analysis of information, biospecimens, or records) conducted for criminal justice purposes, and
- Authorized operational activities in support of intelligence, homeland security, defense, or other national security missions.

Check with your HRPP/IRB office to see if this addition, which is permitted to be used during the transition period leading up to the compliance date in January 2019, is currently in effect at your institution, as it may help in the determination of whether or not your records activity constitutes research.

C. Understanding the IRB Submission Requirements

Table 2.C.1: IRB Submission 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)

D. Understanding the IRB Submission: Researcher Responsibilities

PIs and research staff share the following required responsibilities:

- 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.

E. Consequences for Failure to Comply

- 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.

F. Understanding the IRB Submission Process

The Types of IRB Review are as follows:

1. Full/Convened Committee Review
    a. It must be used for the initial review of all studies that are not eligible for expedited review or exemption status.
    b. 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.
    c. The IRB must notify (in writing) researchers and the organization of its decision to approve, modify, or disapprove the research.
    d. 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.
2. Expedited Review
    a. Federal regulations establish nine categories that IRBs may use to invoke the expedited review process. Note that for an expedited review, a study cannot be disapproved unless first the expedited review process is changed to full committee review. The categories are listed below:
        i. 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.
        ii. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.
        iii. Prospective collection of biological specimens for research purposes by noninvasive means.
        iv. 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.

v. Research involving data, documents, records, or specimens that:
    1. Have been collected
    OR
    2. Will be collected solely for non-research purposes (such as, for medical treatment or diagnosis).

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

vii. Research on individual or group characteristics or behavior.

viii. 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.

ix. 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.

3. Review for Exemption Status (check to see if this needs approval)
    a. 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:
        i. 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.
        ii. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:
            1. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
            2. 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
        iii. 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:
            1. The human subjects are elected or appointed public officials or candidates for public office; or
            2. Federal statutes require without exception that the

confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

iv. 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.

v. Research and demonstration projects conducted by heads of government departments or agencies, which are designed to study, evaluate, or otherwise examine:
    1. Public benefit or service programs
    2. Procedures for obtaining benefits or services under those programs
    3. Possible changes in or alternatives to those programs or procedures
    4. Possible changes in methods or levels of payment for benefits or services under those programs

vi. Taste and food quality evaluation and consumer acceptance studies.
    1. If wholesome foods without additives are consumed; or
    2. 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.

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.

G. Exceptions

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

H. Criteria for 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.
- The IRB must determine that these conditions exist at the time of

initial review and at each subsequent review conducted by the IRB.

I. Adverse Events and Problem Reports

The IRB may require reports for:

1. Adverse events or unanticipated problems involving risks to subjects or others
    a. 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).
    b. 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.
    c. Complaints concerning subject rights submitted by subjects or concerned parties, family members, or study personnel.
2. Incidents of noncompliance
3. Deviations from an approved study plan and violations of the terms of approval
    a. Research plan exception, which may be defined as enrollment of a research subject that fails to meet research plan inclusion/exclusion criteria.
    b. Research plan deviation, which may be defined as a departure from the research plan as approved by the IRB for a single subject.
4. Data safety and monitoring report summaries

3. Informed Consent Requirements

A. General Requirements

a. A statement that the study involves research, an explanation of the research's purposes and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
b. A **description** of any reasonably foreseeable **risks** or **discomforts** to the subject.
c. A **description** of any **benefits** to the **subject or to others**, which may reasonably be expected from the research.
d. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.
f. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
g. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
h. A **statement** that **participation is voluntary**, that **refusal to participate will involve no penalty or loss of benefits** to which the subject is otherwise entitled, and that the **subject may discontinue participation at any time** without penalty or loss of benefits to which the subject is otherwise entitled.
i. The Trial should be Registered on https://www.clinicaltrials.gov/
    - It should be updated regularly and instructions on why may be found here:

https://www.clinicaltrials.gov/ct2/manage-recs/background
- https://www.clinicaltrials.gov/ct2/manage-recs/how-register
- https://www.clinicaltrials.gov/ct2/manage-recs/how-apply
    - **Dr. Phillips is our responsible individual**

B. Additional Requirements: If Relevant to the Research

j. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.
k. Anticipated circumstances under which the subject's participation may be terminated by the researcher without regard to the subject's consent.
l. Any additional costs to the subject that may result from participation in the research.
m. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
n. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
o. The approximate number of subjects involved in the study.
p. Vulnerable populations (listed below) are subject to additional considerations. Please review these if necessary:
    - Children
    - Prisoners
    - Pregnant women
    - **Handicapped persons**
    - Mentally disabled persons
    - Economically or educationally disadvantaged persons
    - Patients in emergency situations
    - Subjects who are marginalized in society
    - Members of a group with a hierarchical structure (such as students)
    - Patients with fatal or incurable diseases
    - **Elderly persons**
    - Persons in nursing homes
    - Unemployed or impoverished persons
    - Ethnic minority groups

- Homeless persons, nomads, and refugees

C. Regulations on Vulnerable Populations

Refer 45 CFR 46.111 but:

- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

On the principle of Justice:

1. In some types of research, a vulnerable group may be the primary group on which the research is conducted because the investigation is focused on the source of vulnerability. This means that the research burden is heaviest on the group based solely on the presence of their vulnerability. This also could mean that those who experience this vulnerability may be the primary beneficiaries of the research results. What is important here is to be cognizant of the concept of justice in the *Belmont Report*. Therefore, it is important to remain mindful of the potential disparity in burden the group faces on account of this, noting that it may be acceptable.
2. Some individuals or groups who are vulnerable may become the study focus merely for ease or convenience of access, or because risks of harm or burdens to them are trivialized, as the group is undervalued. This is a significant issue and should be monitored carefully. There are historical cases of prisoners or wards of the state being studied because of convenience when there were more appropriate study groups to enroll. This was the case for both the Jewish Chronic Disease case and the Willowbrook case. In this instance, researchers enrolled populations that were both undervalued by

society and convenient for them to study.
3. Designing studies to exclude individuals or vulnerable groups from the research because of the complications and additional requirements for studying them is problematic (either real or perceived). In this case, the lack of inclusion hurts the ability to advance understanding and the underlying science, and denies the group the potential benefit of research.

There are four common abuses of vulnerable subjects that must be considered:

Physical control, coercion, undue influence, and manipulation

OF NOTE:

In deferential **vulnerability** the authority over the prospective subject is **due to informal power relationships rather than formal hierarchies**. The power relationship may be based on gender, race, or class inequalities, or they can be inequalities in knowledge (such as in the doctor-patient relationship). Like institutional vulnerability, deferential vulnerability increases the risk of harm that informed consent would be compromised because it is not fully voluntary. Another case:

The National Commission's 1977 report on research involving children provides a sliding scale classifying research according to the risk and the direct benefit to the child, and provides the requirements for assent and informed consent for participation in research involving children. Specific requirements include:

- Research involving no greater than minimal risk requires the permission of one parent and the child's assent.
- Research involving greater than minimal risk but presenting the prospect of direct benefit requires:
    - The benefit must balance or outweigh the risks of harm.
    - The risk-benefit relationship must be at least as favorable as that seen with standard care.
    - Permission of one parent and assent of the child.
    - Assent of the child, unless the research holds out a prospect of direct benefit to the child, which is not available outside the research.
- Research involving greater than minimal risk and no prospect for direct benefit requires:
    - The risk is only a minor increase over minimal risk.

- The risks of harm are commensurate.
- The research will likely yield knowledge of vital importance.
- Permission of both parents (unless the exceptions noted apply)
- Assent of the child.

D. Non-English Speakers

For all details other than those below, please consult your IRB.

Best Practices When Human Research Subjects Do Not Speak English	
Consideration	Best Practice
The consent process must allow subjects to consider whether or not to participate.	Subjects must have an understanding of the information presented to them and be given time to decide. Although not specifically required by the regulations, additional resources, such as translators, interpreters, advocates, and family members may be needed to ensure that this is accomplished when enrolling a non-English speaking subject. Research subject advocates who are fluent in the subject's language can: ● Help subjects find information about a study ● Listen to subject's questions, concerns, and complaints and help find answers ● Communicate with the study team ● Accompany the subject when the study team explains the details and asks for participation, if requested Researchers should be cognizant that having a third party can lead to confusion if not handled in a professional manner.

The consent process must minimize the possibility of coercion or undue influence.	The best results usually occur when the person conducting the informed consent process speaks the preferred language of the subject. However, not speaking English in the U.S. may indicate a cultural difference (for example, deference to authority), which must be considered and addressed. Providing an oral explanation with examples of the questions that a subject might ask and answers to those questions, may increase the comfort level of the subject and his/her voluntary willingness to participate.
Information given in the consent process must be in language understandable to the subject or the subject's legally authorized representative (LAR).	Reading levels are important in all consent forms, whether in English or translated into another language. It is not safe to assume that a speaker of another language can read in their primary language. If an interpreter is utilized to sight read a document, the interpreter cannot change the writing style or tone of the document.
Additional safeguards may be needed.	Examples of additional safeguards are two-session consent (an information session followed by a later session that includes additional discussion and decision) and the involvement of interpreters, advocates, and family members. However, researchers should be aware that too many parties involved in the consent process could blur the process, as well as influence the subject's decision to participate.

The language of the consent form and corresponding documents should be the same; appropriate steps should be taken to ensure that the consent is completed in the proper language.	An accurate translated consent document should be prepared and given to subjects in their preferred language. It would be considered unethical to obtain consent from a subject in a language that he/she does not fully comprehend.
A short form written consent document should be used when a translated document is not available and consent procedures must facilitate communication.	See the "Short Form Consent" section below for more information.

When planning and developing the research plan and timeline for enrolling non-English speakers, IRBs and researchers should consider the unique issues and concerns that each research plan will present based on the research plan and available resources and conditions.

When the researcher and subject do not share a language, the researcher must depend on the accuracy of the translated consent documents and the working relationship with an interpreter. Trained interpreters help to assure effective communication between the researcher and subjects, improve understanding, and honor the ethical principle of respect for persons. ***Currently, certification is only available for medical, American Sign Language (ASL), and legal interpreters.***

The medical and technical information discussed during the initial consent discussion, as well as ongoing study-related information, should be communicated to non-English speaking subjects through an interpreter with training in and understanding of medical terminology. In addition, an individual with a professional commitment to maintain strict confidentiality should handle the private medical issues discussed with subjects. **Trained and certified interpreters should be experienced and able to handle the complex terminology required of the research study.**

When the study subject population includes persons who are non-English speaking, or the researcher or the IRB anticipates that the consent discussions will be conducted in a language other than English, the IRB should require a translated consent document to be prepared and assure that the translation is accurate (when there is a written version of the subjects' primary language).

In general, an IRB will require that the researcher translate the following before enrolling non-English speaking subjects on a study:

- The IRB-approved English informed consent (and an assent document when applicable for subjects who cannot consent themselves like minors or subjects with cognitive impairments)
- Information letter(s) (when applicable)
- Health Insurance Portability and Accountability Act (HIPAA) documents (when applicable)

A certified translation is one that has been formally verified by a licensed translator or translation company for use in official purposes. Certified translators can be located in the registry at the American Translators Association. Certified translators attest that the target-language text is an accurate and complete translation of the source-language text. Certified translation of consent documents ensures that the tone, meaning, and content of the translated documents remain consistent with the IRB-approved English version. It is recommended that a second translator back-translates (translate the translated document back to English) the translation to verify accuracy.

A certified translation of the consent/assent form(s) has become a standard practice for studies that pose more than minimal risk of harm to subjects (that is, studies that require full committee IRB review). In most instances, a letter of certification from the translator or translation service must accompany the translated forms. Some organizations require a review and certification by a second translator, with both translators submitting a certification/attestation.

In general, when preparing for research with non-English-speaking subjects as a potentiality, it is best practice to prepare documents at an 8th grade reading level and budget as needed for a potential translation.

Researcher and IRB Considerations for Consent with Non-English Speaking Subject Populations

- Does a language barrier exist? If so, are there ethical/legal ramifications of enrolling subjects when a language barrier exists? How will these be addressed?
- Does the consent process allow sufficient time for discussion, given potential differences in language?
- Is the setting appropriate, recognizing differences in culture and language?
- Will the prospective subject feel pressured or overly reassured to decide immediately? The researcher represents a person of authority for most cultures. Therefore, the non-English speaking subjects may feel obligated to accept the researcher's request to take part in the study because they do not want to disrespect or disappoint the researcher. In addition, in some cultures it may be considered rude to ask a researcher questions, or rude to decline what is perceived of as a request for a favor. In these circumstances, the questions of who conducts the consent process and how it is explained become even more important; using a community leader or having staff members who represent the community can also be useful.
- Can the prospective subject seek advice from others before deciding?
- Does the consent form avoid using terms and idioms that subjects may misinterpret in their own language?
- Does the person obtaining consent have the ability to explain the information in the form and answer any questions?
- Is the form written at an appropriate reading level, writing style, and in a language that will be understood by the subject?
- Does the person obtaining consent have the ability to facilitate the discussion?
- Will a properly trained and qualified interpreter be helpful in facilitating the consent conversation?
- Is the information (written and oral) presented in a way that enables each person to voluntarily decide whether or not to participate?
- Does the study plan or organization's policy address what will happen if a non-English speaking subject is unexpectedly encountered?

4. Social and Behavioral Research (SBR) (surveys, etc.)

A. Examples of SBR

a. Questionnaires
b. Interviews
c. Focus groups
d. Direct or subject observation
e. Non-invasive physical measurements
    i. Non-invasive physiological measurement (such as, skin impedance and pupil dilation as reflection of emotional arousal or attention). Although these are considered physiological measures, they are often used by SBR researchers to document the physiological components of behavior
f. Data already collected for other purposes (such as, records from education, healthcare, social service programs, employment, and insurance coverage). These kinds of data are often used by health researchers in outcomes studies and epidemiological studies, or as adjuncts in clinical or basic science research.
g. Opinion data and other oral data from key informant interviews, focus groups, or group discussions. Biomedical researchers may use these data collection methods to provide qualitative data to enrich or support their physiologic data in testing hypotheses.

B. Particulars of SBR Research

The risks of harm associated with SBR are different from those associated with traditional biomedical research.

- They may include psychosocial stress and discomfort, disruption of personal and family relationships, economic harms, and even political harms that may result from identifiable data falling into the wrong hands. Stress and discomfort may result from being asked personal questions, from being deceived, or from being subjected to research procedures designed to manipulate emotions, feelings, and thoughts.
- They may be less predictable, more subjective and variable, and less remediable than physiological harms. For example, it is more difficult to predict how an individual will respond to answering a question about

childhood sexual abuse than to predict an individual's reaction to having blood drawn. Questions about certain behavior, attitudes, and beliefs may result in "inflicted insight." This can cause distress from learning something about oneself that one would not have learned without having taken part in the study.
- They may be more dependent on socio-cultural factors than physiological harms. For example, collecting demographic information from undocumented immigrants may be more risky than collecting the same information from citizens.

C. On Deception in SBR

If distress or deception must be experimentally induced, as in some psychological and physiological measurement research, the research design usually requires withholding certain information from the consent process in order to obtain unbiased results. After subjects have completed participation, it is important to provide this information to subjects from whom it was withheld, and to provide an opportunity for subjects to express their concerns and ask questions about the research. Strategies to accomplish this might include:

- Debriefing subjects with a description of what really happened
- Explaining why the research could not otherwise be conducted
- Issuing an apology

If possible, researchers should debrief the subjects while they still have an opportunity to withdraw their data should they feel offended and not wish to continue participation or have their data excluded.

D. How to Acquire SBR Consent

1. The statement "there are no risks" should not be used. Although some SBR might have no physical risks, it is always necessary to consider whether there is a possibility (even if not a high likelihood) of emotional/psychological risk, loss or breach of confidentiality, or stigmatization.
2. Describe the content of questions, interview topics, etc., and give specific examples of the most personal, sensitive, or distressing questions that will be asked. Sometimes it is appropriate to reassure subjects that there is no "right" or "wrong" answer.
3. State that subjects have the right to refuse to answer any question for any

reason. This statement should not impute to subjects a specific sensitivity or emotional state (for example, it should not say, "You have the right to skip any questions that make you uncomfortable").
4. It may be difficult to advise subjects about emotional distress without increasing the likelihood of experiencing it. This is a judgment call that needs careful consideration in wording of consent forms.
5. If recordings are used, the consent should state that subjects have the right to review and delete recordings that will be kept indefinitely or shared outside of the research team.
6. If focus groups are used, subjects should be reminded that the identities of fellow subjects and the information exchanged are confidential.

5. On Records and HIPAA Laws

Before collecting information from records for research purposes, a researcher should consult with:

- The Institutional Review Board/Independent Ethics Committee (IRB/IEC) at his/her organization to determine the type of review required (if any); and
- The applicable administrator at the organization where the actual records are owned or maintained to ensure ability to access them for research purposes.

In addition, the researcher needs to determine if there are other regulations affecting the record-review. Examples include the Health Insurance Portability and Accountability Act's (HIPAA) Privacy Rule for medical records research, or the Family Educational Rights and Privacy Act (FERPA) for student education records.

A. Privacy

Privacy can be defined in terms of having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) or information about oneself with others. In the context of research, privacy risk pertains primarily to the methods used to obtain information about subjects.

B. Confidentiality

Confidentiality pertains to the actual handling of the personal information once it

is obtained. In other words, now that the researcher has obtained private information, how will it be used, stored, and reported in a way that is consistent with the manner under which it was originally obtained from the individual? Information from public records, and information obtained under a relationship of trust, as in the doctor-patient relationship, will require different considerations for protecting confidentiality.

The risks of breach of confidentiality associated with records-based research are necessarily tied to the sensitivity of the requested information. If the information is recorded without any identifiers, the sensitivity of the information is less of a concern. If the information is both identifiable and sensitive, methods to protect confidentiality must be carefully considered by the researcher, and approved by the IRB/IEC. Therefore, in considering the research hypothesis, the researcher must assess how important it is to be able to associate the individual with his/her information.

a. De-Identification

Whenever possible, and to the greatest extent possible, only de-identified or anonymous information should be recorded. Assuming the research cannot be conducted anonymously, the following questions speak to protection of the collected information. Based on a researcher's answers, an IRB/IEC **(not the International Electrotechnical Committee but rather an Independent Ethics Committee)** will carefully assess whether possible risks from breaches of confidentiality have been minimized:

- What kind of identifiable information (if any) will be collected?
- Who will have access to the identifiable information?
- Where will the identifiable information be kept?
- What kinds of codes or encryption will be used to separate research data from subject identifiers?
- How will limitations on access be ensured?
- How will research staff be trained about privacy and confidentiality?
- How long will identifiable information or linkages to personal identifiers be kept?
- For data being transmitted physically and/or electronically, what encryption methods will be used?
- What procedures will be used for disposal/destruction of identifiers and

research documents, once no longer required?

b. Certificate of Confidentiality (CoC)

i. These are automatic for NIH-funded studies

ii. Once issued, a CoC prohibits disclosure of research data by the researcher if requested to do so through civil, criminal and other types of legal proceedings, and also prohibits disclosure to any other person not connected with the research, unless certain conditions are met (for example, request is made with consent of the subject).

iii. Requirements: Specifically, the research data in question must constitute identifiable, sensitive information, defined as "information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research and

a. Through which an individual is identified; or
b. For which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual."

C. On Records-based Research

Do the activities meet the federal definition of "human subjects research?"

If yes:

- Is the research eligible for exemption from the federal regulations?

  If no:

  - Is the research eligible for expedited review under the federal regulations?

    If no:

    - Does the records-based research need review by the full/convened IRB/IEC?

      Must be yes!

Record-based research may be exempt from federal regulation if:

- The information is existing (on the shelf) at the time the exemption is requested; and
- The information sources are publicly available (any person can obtain the data), or the information is recorded by the researcher in such a manner that subjects cannot be identified (directly or through identifiers linked to the subjects). Although the researcher may actually see identifiers while reviewing the data set, he/she cannot record any of them in any research record, or data collection instrument

OHRP recommends that researchers **do not determine** if their research qualifies as exempt. Rather, the organization should **designate** an applicable institutional official (or the **IRB**/IEC) to **conduct this review**. Organizations may have internal rules and policies in addition to the federal regulations that will determine whether to grant the exemption.

If the records review activity constitutes human subjects research, and doesn't qualify for exemption, it will then be subject to federal regulations. However, it may qualify for expedited review if the research activity:

- Poses no more than minimal risk of harm or discomfort to the subjects; and
- Is described in one of the expedited review categories (OHRP 1998): Records-based research that is eligible for expedited review generally falls under Category 5, "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)."

D. HIPAA Laws: Protected Health Information (PHI)

Under the US Health Insurance Portability and Accountability Act (HIPAA), PHI that is linked based on the following list of 18 identifiers must be treated with special care:

1. Names
2. All geographical identifiers smaller than a state, except for the initial three digits of a zip code if, according to the current publicly available data from the U.S. Bureau of the Census: the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000
3. Dates (other than year) directly related to an individual
4. Phone Numbers
5. Fax numbers
6. Email addresses
7. Social Security numbers
8. Medical record numbers
9. Health insurance beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web Uniform Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger, retinal and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code **except the unique code assigned by the investigator to code the data**

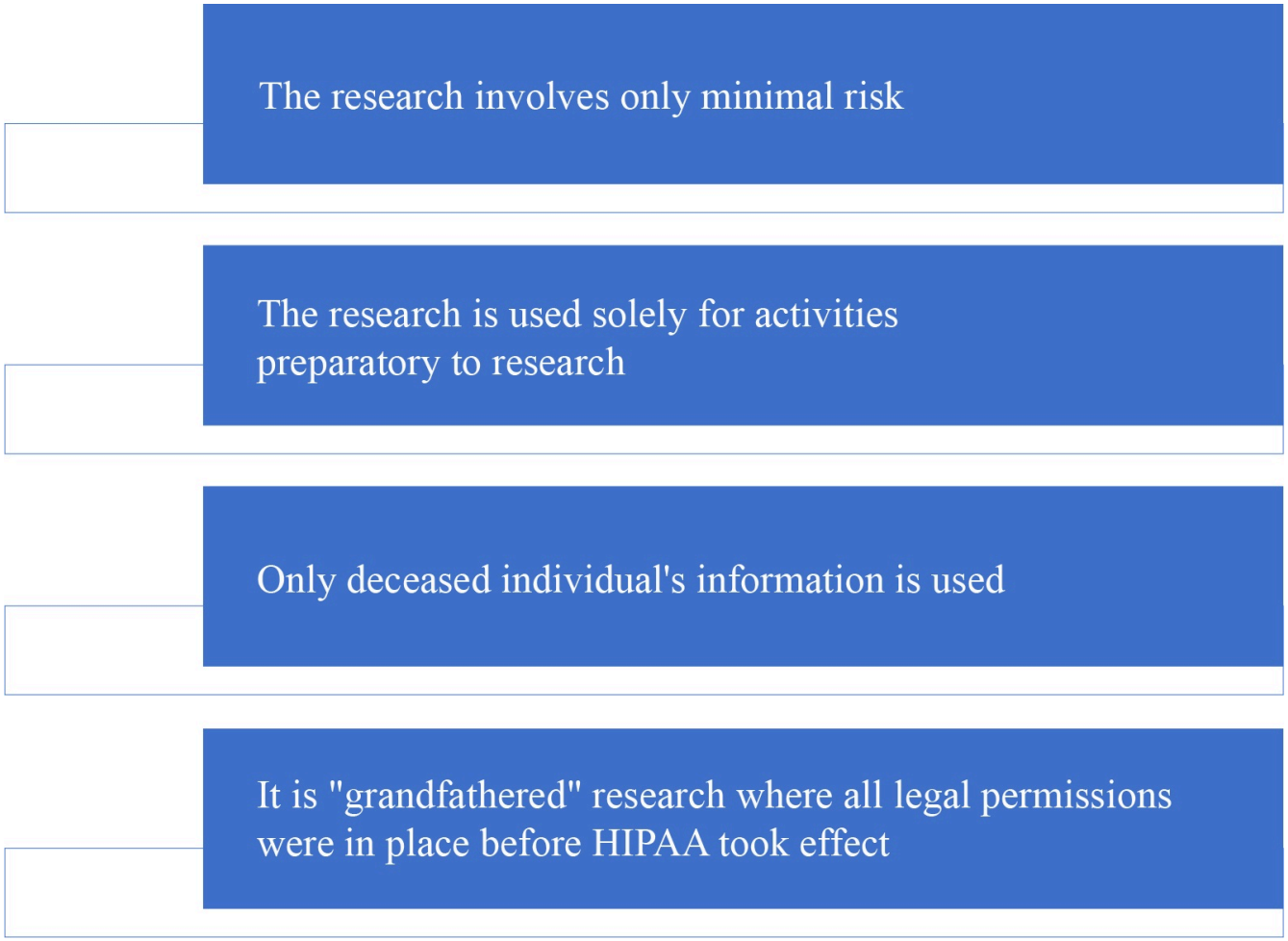
PHI may be de-identified by:

1. The removal of 18 specific identifiers listed above (Safe Harbor Method)

2. Obtain the expertise of an experienced statistical expert to validate and document the statistical risk of re-identification is very small (Statistical Method).

De-identified data is coded, with a link to the original, fully identified data set kept by an honest broker. Links exist in coded de-identified data making the data considered indirectly identifiable and not anonymized. Coded de-identified data is not protected by the HIPAA Privacy Rule, but is protected under the Common Rule. The purpose of de-identification and anonymization is to use health care data in larger increments, for research purposes. Universities, government agencies, and private health care entities use such data for research, development and marketing purposes.

HIPAA allows for research-related access to individuals' identifiable health data without authorization under certain circumstances:



E. HIPAA Laws: Limited Data Set Provisions

A limited data set under HIPAA is a set of **identifiable** healthcare information that the HIPAA Privacy Rule permits covered entities to share with certain entities for research purposes, public health activities, and healthcare operations without

obtaining prior authorization from patients, if certain conditions are met.

In contrast to de-identified protected health information, which is no longer classed as PHI under HIPAA Rules, a limited data set under HIPAA is still identifiable protected information. Therefore it is still subject to HIPAA Privacy Rule regulations.

A HIPAA limited data set can only be shared with entities that have signed a data use agreement with the covered entity. The data use agreement allows the covered entity to obtain satisfactory assurances that the PHI will only be used for specific purposes, that the PHI will not be disclosed by the entity with which it is shared, and that the requirements of the HIPAA Privacy Rule will be followed.

The data use agreement, which must be accepted prior to the limited data set being shared, should outline the following:

- Allowable uses and disclosures
- Approved recipients and users of the data
- An agreement that the data will not be used to contact individuals or re-identify them
- Require safeguards to be implemented to ensure the confidentiality of data and prevent prohibited uses and disclosures
- State the discovery of improper uses and disclosures must be reported back to the covered entity
- State that any subcontractors who are required to access or use the data also enter into a data use agreement and agree to comply with its requirements.

In all cases, the HIPAA minimum necessary standard applies when consent is not given, and information in the data set must be limited to only the information necessary to perform the purpose for which it is disclosed.

The following items are allowable in a limited dataset provided those dealing with the data are under a Data Use Agreement compliant with HIPAA Laws:

- **City**
- **State**
- **ZIP Code**
- **Elements of dates**
- **Other numbers, characteristics, or codes not listed as direct identifiers**

A data use agreement is the means by which covered entities obtain satisfactory assurances that the recipient of the limited data set will use or disclose the PHI in the data set only for specified purposes. Even if the person requesting a limited data set from a covered entity is an employee or otherwise a member of the covered entity's workforce, a written data use agreement meeting the Privacy Rule's requirements must be in place between the covered entity and the limited data set recipient.

The Privacy Rule requires a data use agreement to contain the following provisions:

- Specific permitted uses and disclosures of the limited data set by the recipient consistent with the purpose for which it was disclosed (a data use agreement cannot authorize the recipient to use or further disclose the information in a way that, if done by the covered entity, would violate the Privacy Rule).
- Identify who is permitted to use or receive the limited data set. Stipulations that the recipient will:
    - Not use or disclose the information other than permitted by the agreement or otherwise required by law.
    - Use appropriate safeguards to prevent the use or disclosure of the information, except as provided for in the agreement, and require the recipient to report to the covered entity any uses or disclosures in violation of the agreement of which the recipient becomes aware.
    - Hold any agent of the recipient (including subcontractors) to the standards, restrictions, and conditions stated in the data use agreement with respect to the information.
- Not identify the information or contact the individuals

If a covered entity is the recipient of a limited data set and violates the data use agreement, it is deemed to have violated the Privacy Rule. If the covered entity providing the limited data set knows of a pattern of activity or practice by the recipient that constitutes a material breach or violation of the data use agreement, the covered entity must take reasonable steps to correct the inappropriate activity or practice. If the steps are not successful, the covered entity must discontinue disclosure of PHI to the recipient and notify HHS.

Section 164.512 of the Privacy Rule also establishes specific PHI uses and

disclosures that a covered entity is permitted to make for research without an Authorization, a waiver or an alteration of Authorization, or a data use agreement. These limited activities are the use or disclosure of PHI preparatory to research and the use or disclosure of PHI pertaining to decedents for research.

For more see:
https://www.hhs.gov/hipaa/for-professionals/faq/limited-data-set/index.html

6. FDA Regulated Research (only applies for devices / drugs)

A. Investigational New Drug (IND) Approval

a. Research involving a drug or biologic that has not yet reached the marketplace or that studies a new use of the marketed product requires an IND per 21 CFR 312 (Investigational New Drug Application 2014)
b. This is sent to the FDA in accordance with Federal Regulations
c. Determination is dependent upon:
    - Data from prior animal or human testing
    - Methods of manufacturing
    - Plans for testing and reporting significant toxicities
    - A well-developed clinical research plan that minimizes risks to

the subjects

Researchers may want to use an approved product in the context of clinical studies. When the principal intent of the product's investigational use is to develop information about safety or efficacy, an IND may be required. However, the clinical investigation of a marketed drug does not require an IND if the following conditions are met:

- The data will not be used to support a new indication, new labeling, or change in advertising.
- The research does not involve a route of administration/dosage level or subject population that significantly increases the drug product's risks of harm.
- The research is conducted in compliance with Institutional Review Board (IRB) review and informed consent requirements.
- The research is conducted in compliance with requirements for promotion and sale (21 CFR 312.2[b] [Investigational New Drug Application 2014]).

B. Investigational Device Exemption (IDE) Approval

A medical device is any healthcare product that does not achieve its primary intended purpose by a chemical interaction or by being metabolized.

Manufacturers who wish to market a new medical device may need to submit a pre-market notification to the FDA. Some medical devices are exempt from the pre-market approval process. If the device is not exempt, FDA at 21 CFR 807.81(a)(1) (Establishment Registration 2014) determines whether the device is substantially equivalent to similar devices marketed before the 1976 amendment. These devices are often referred to as **510k** devices (see 21 CFR 807.92). If the new device is not substantially equivalent, the company may need to demonstrate safety and efficacy in a pre-market approval application, which could include clinical trials.

By definition, a study with a **Significant Risk (SR) device** poses more than minimal risk to the human subjects and requires full IRB review. A SR device presents a potential for serious risk to the health, safety, or welfare of the subject and it:

- Is intended to be implanted into a human;
- Is used in supporting or sustaining human life;
- Is of substantial importance in diagnosing, curing, mitigating, or treating

disease, or otherwise prevents impairment of human health; or
- Otherwise presents serious risk to health, safety, and welfare of a subject (21 CFR 812.3[m] [Investigational Device Exemptions 2014]).

A **Non-Significant Risk (NSR)** device, by default, does not meet the criteria of significant risk. It is considered to have an approved IDE application (that is, no application is filed with the FDA), and is studied without FDA oversight if the sponsor complies with certain FDA requirements such as monitoring, record keeping, and properly labeling the investigational device. The IRB must agree that the study meets the criteria for non-significant risk. The clinical trial of a NSR device requires IRB approval, informed consent, and proper study monitoring and it must meet all other regulatory compliance requirements.

C. Informed Consent Waivers

In life-threatening conditions involving an individual person where requirements for an exception from informed consent are met. More specifically, FDA regulations (21 CFR 50.23) permit exception from informed consent in life-threatening situations where:

a. The researcher, with the concurrence of another physician not participating in the clinical investigation, believes and certifies in writing that the situation for the human subject is life-threatening and necessitates the use of a test article (that is, an investigational drug, device, or biologic).
b. The subject and/or legally authorized representative (LAR) is unable to communicate consent. The FDA (Protection of Human Subjects 2014) indicates that a LAR is:
c. “An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."
d. There is insufficient time to obtain consent.
e. No alternative exists that will provide an equal or better chance of saving the subject's life.

The FDA permits exception from informed consent requirements for planned emergency research (21 CFR 50.24). Unlike the exception noted in 21 CFR 50.23, the activities described in 21 CFR 50.24 are associated with an IRB-approved

research study that involves research in emergencies. According to the FDA (Protection of Human Subjects 2014), emergency research are investigations [that] involve human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who, because of their condition (e.g., traumatic brain injury) cannot provide consent. The research must:

a. Have the prospect of direct benefit to the patient.
b. Must involve an investigational product.
c. The product, in order to be effective, must be administered before informed consent from the subject or the subject's LAR can be obtained.
d. There is no reasonable way to identify prospectively individuals likely to become eligible for participation.

Exception from Informed Consent Requirements for Emergency Research

On 24 July 2017, the FDA issued guidance that they will not object if an IRB approves a waiver or alteration of consent for a no more than minimal risk clinical investigation if the IRB determines that (FDA 2017):

- The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3[k] or 56.102[i]) to subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

D. Emergency Device Use

Researchers and IRBs may be confronted with the need to use an unapproved investigational drug or device on a human subject in an emergency situation. In these circumstances, review by a convened IRB may not be feasible because of the problem's emergent nature. When this happens attention must be given to the

IND/IDE requirements, informed consent, and IRB procedures. ***Please note:***

- Regulations at 21 CFR 50.23 cover unplanned emergency use
- Regulations at 21 CFR 50.24 cover planned emergency research

Emergency use is the use of an investigational drug or device with a human subject in a life-threatening situation, or in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval. Life-threatening means that the likelihood of death is high unless an intervention interrupts the process. It also applies to a condition that is immediately and severely debilitating and that causes irreversible morbidity (such as, blindness or paralysis) per 21 CFR 56.102(d) (Institutional Review Boards 2014).

If an individual subject does not meet the criteria for an existing research plan, or an approved research plan does not exist, the usual procedure is for the physician to contact the manufacturer and determine if the drug can be made available for an "emergency use" under the company's IND. If there is no IND, the FDA per 21 CFR 312.36 (Investigational New Drug Application 2014), may authorize the manufacturer to allow the drug to be used in advance of an IND submission.

In addition, if the company agrees to provide the product, the physician can contact the FDA, explain the situation, and obtain an emergency IND to permit the drug's shipment.

If there is no IDE, the physician may use the device and notify FDA of its use after the fact. The physician should obtain both an independent assessment from another physician and informed consent from the subject, before emergency use of the device occurs.

In an emergency use situation, the FDA at 21 CFR 56.104(c) (Institutional Review Boards 2014) permits an exemption from prior review and approval by an IRB. For emergency use of devices, concurrence of the IRB chair is required before the use takes place. However, individual organizations may have a variety of policies to handle this situation. For example, the researcher may be required to notify the IRB office when emergency use is being considered. HHS regulations do not prohibit a researcher from using any investigational or approved drug or device in an emergency situation for the subject's clinical care, but they do not consider information collected to be research data. FDA does consider this to be a research use and wants the data reported to them. IRB review and approval is required in all

circumstances if the researcher wishes to use the data for research purposes.

> **AFTER AN INVESTIGATIONAL DRUG OR DEVICE HAS BEEN USED IN AN EMERGENCY**
>
> **Subsequent use of the investigational product at the organization should have prospective IRB review and approval. If the IRB was not notified before the investigational drug or device was used in an emergency situation, the IRB should be notified per organizational policy or within five working days (Protection of Human Subjects 2014). The FDA and sponsor should be notified as necessary.**

Further information on emergency use of investigational devices can be found at the FDA's *Guidance on IDE Policies and Procedures*.

E. Sponsor / PI Responsibilities

A sponsor may be an individual, a private company, or other organization that is responsible for the initiation and conduct of a study involving a drug, device, or biologic. Researchers who design and conduct their own studies assume this responsibility in addition to their role as researcher. Often these are called "investigator-initiated" studies. The sponsor's responsibilities include:

- Selecting clinical researchers qualified by training and experience.
- Informing and qualifying researchers by obtaining their commitment to supervise the study, follow the research plan, and obtain consent.
- Monitoring the study’s conduct by auditing documentation and conducting site visits.
- Completing regulatory filings related to the IND or IDE, adverse events, amendments or revisions, progress reports, withdrawal of IRB approval, and final reports.
- Controlling the distribution, tracking, and dispensation of the regulated products.

F. Researcher Responsibilities

- Ensuring IRB approval for the study is obtained before any subjects are enrolled.

- Ensuring that informed consent is obtained in accordance with FDA regulations.
- Ensuring that the investigation is conducted according to the investigational plan and applicable regulations.
- Administering the drug or using the device only in subjects under the researcher's supervision or under the supervision of a recognized sub-researcher.
- Maintaining adequate records of the dispensation of the drug or device.
- Returning unused materials at the end of trial.
- Preparing and maintaining adequate case histories and signed informed consent documents.
- Maintaining correspondence with the IRB and the sponsor to make sure that both have reviewed research plan amendments, recruitment materials, and Investigator’s Brochures.
- Retaining records in accordance with regulations.
- Providing progress, safety, final, and financial disclosure reports.
- Notifying the sponsor if IRB approval is withdrawn.
- Comply with International Council for Harmonisation (ICH) guidelines, if applicable

7. Adverse Events and Unexpected Problems

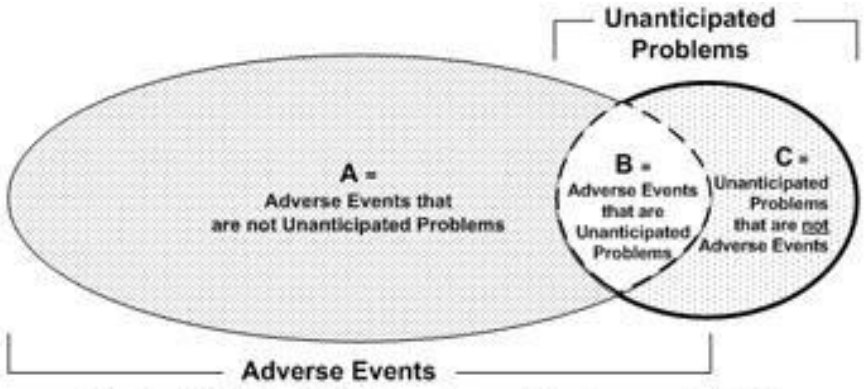
Many researchers and IRBs are concerned about both adverse events and unanticipated problems. It is important to remember that not all adverse events are considered unanticipated problems.

Adverse Event:

> Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

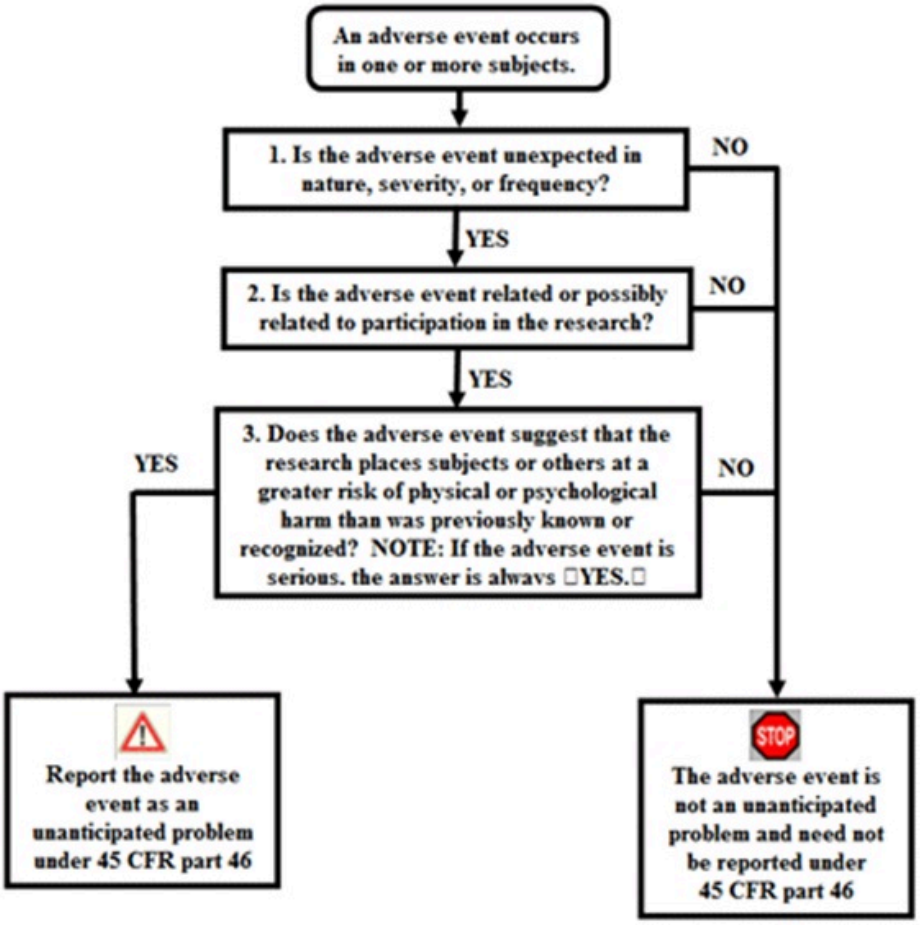
Unanticipated Problem:

Only adverse events that are also unanticipated problems need to be reported to the IRB.



Under 45 CFR part 46: Do not report A, Do report (B+C)

Adverse events are harms that befall subjects in research while unanticipated problems involve risks to subjects or others. If the research unexpectedly increases the risk of harm to individuals other than the research subjects (such as, family members or the community), it is an unanticipated problem.



Other examples of unanticipated problems include (FDA 2009b):

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as, angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A serious adverse event that is described or addressed in the Investigator's Brochure, research plan, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).
- Any other adverse event or safety finding (for example, based on animal or epidemiologic data) that would cause the sponsor to modify the Investigator's Brochure, research plan, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

In Closing:

Adverse events are, by definition, events that cause harm to subjects. Unanticipated problems are events that increase risk to subjects. Risk is not harm; it is the possibility of harm. An event could increase the risk of harm to subjects without actually harming any subjects. Such an event would be an unanticipated problem and reportable. This is an important concept that could easily be misunderstood by a researcher, who then might fail to report it to the IRB.

Unanticipated Problems meet all three criteria:

- Unexpected
- Related or possibly related to participation in the research
- Places **subjects or others** at a greater **risk** of harm

<table>
<tr><td colspan="4">Reporting Unanticipated Problems</td></tr>
<tr><td colspan="2">OHRP</td><td colspan="2">FDA</td></tr>
<tr><td>From</td><td>To</td><td>From</td><td>To</td></tr>
<tr><td>Researcher</td><td>IRB</td><td>Researcher</td><td>IRB and sponsor</td></tr>
<tr><td rowspan="2">IRB</td><td rowspan="2">OHRP, other federal Agencies and other organizational offices as directed by written procedures</td><td>Multicenter trial sponsor</td><td>Researchers, IRBs, FDA</td></tr>
<tr><td>IRB</td><td>FDA, OHRP if appropriate, and other organizational offices as directed by written procedures</td></tr>
</table>

Both OHRP and FDA regulations require that IRBs maintain written procedures ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head (such as, OHRP or FDA) of any unanticipated

problems involving risks to subjects or others. Written procedures should provide a detailed description of the procedure to report an unanticipated problem to the IRB and the information that must be contained in the report. OHRP (2007) suggests the procedures should include:

1. The type of information that is to be included in reports of unanticipated problems.
2. A description of which office(s) or individual(s) is responsible for promptly reporting unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency heads (or designees), and OHRP.
3. A description of the required timeframe for accomplishing the reporting requirements for unanticipated problems.
4. The range of the IRBs possible actions in response to reports of unanticipated problems.

Written procedures should also include detailed information regarding IRB review of reports of unanticipated problems and any internal reporting requirements for the IRB to follow, such as to the institutional official or a regulatory affairs unit within the organization.

FINALLY, this document does NOT constitute Human Subjects Research certification and ALL THOSE READING ARE RESPONSIBLE FOR THEIR OWN KNOWLEDGE AND CERTIFICATION OF THE NECESSARY MATERIALS TO PROPERLY CONDUCT RESEARCH.