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**Definitions**

**Risk:** The probability of harm (physical, psychological, social, legal, or economic) occurring as a result of participation in a research study. Both the probability and the magnitude of possible harm may vary from minimal to significant. The Federal regulations only define “minimal risk.”

**Minimal Risk:** A risk is considered to be minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

**Benefit:** A valued or desired outcome; although these terms may appear straightforward, evaluations of risk and benefit are made more complex both by the subtle distinctions between therapeutic and research activities, and by evaluations of actual risks in the lives of normal and vulnerable classes of subjects (i.e., prisoners, children, cognitively impaired individuals, etc.)
9.1 Steps to Minimizing Risk

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These policies and procedures are based on: Common Rule 45 CFR 46.111(a) (1),(2); FDA 21 CFR 56.111(a)(1),(2); When reviewing the application submitted by the Principal Investigator (PI), the IRB analyzes levels of risk, ensures risks are minimized, and ensures risks are reasonable relative to anticipated benefits, before approving the proposed research.

Investigators submitting research proposals for IRB review should understand that the IRB is responsible for assessing the possible risks vs. anticipated benefits, if any, of research as one of its primary functions. In addition, once risks and benefits have been assessed, the IRB is responsible for ensuring that the risks of study participation are minimized to the greatest extent possible, while the benefits of study participation are maximized.

Identifying Potential Risks (PI Input)

When considering risks, the IRB considers only those risks associated with the research, i.e., physical, psychological, social, legal, emotional. Investigators should be aware that risks would include immediate risks of study participation, risks of randomization (especially to placebo groups in medical and pharmaceutical research), risks of breach of confidentiality, and risks of long term effects.

For biomedical research (primarily medical and pharmaceutical research) the IRB is required to determine and differentiate between the risks associated with the research and the risks associated with standard diagnostic or therapeutic interventions or therapies subjects would undergo regardless of participation in research. The IRB does not establish or determine what constitutes “standard of care.” It is important for investigators to clearly distinguish procedures which they consider are “standard of care” from those which are conducted solely for research purposes in the protocol and the informed consent form.

Minimal Risk

Much of the IRB review process is governed by the concept of “minimal risk.” Assignment of research for expedited review, approval of waiver of consent, and the conduct of research involving vulnerable research populations may be dependent upon whether the research places subjects at minimal risk or greater than minimal risk (significant risk).

Physical Risks

Some research presents risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation (especially those which result from medical procedures, drug research or device research) may result in permanent injury to subjects. For all research with the potential to do physical harm investigators are encouraged to think through all risk possibilities, however rare they may seem, so that they can be resolved quickly and effectively to minimize harm to subjects. By clearly detailing procedures to address situations of physical harm, the IRB can be assured that the investigator has made efforts to minimize physical risks to the greatest extent possible.

Psychological Risks

Some research has the potential to cause undesired changes in thought processes and emotion including episodes of depression, confusion, and hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem. As is the case with physical risks, these effects are usually transient. For all research with the potential to cause psychological
harm investigators are encouraged to think through all risk possibilities, however rare, so that a course of action can be planned to quickly and effectively minimize the distress to subjects. By clearly detailing procedures to address situations of psychological harm, the IRB can be assured that the investigator has made efforts to minimize psychological risks to the greatest extent possible.

Social, Legal and Economic Risks
Some research proposals involve the handling of sensitive information which may result in injury to subjects through a breach of confidentiality. These breaches may result in embarrassment within a subject’s business or social group, loss of employment, or criminal prosecution. The IRB is especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior, and illegal activities. For these situations investigators should clearly detail strong precautions to ensure that the research does not cause social, legal or economic risks to the subjects.

Research may also pose direct economic risk to study subjects. Procedures billed to insurance companies may require a significant co-payment on behalf of subjects, insurance companies may refuse to pay for “investigational” therapies, subjects may be responsible for transportation costs, and subjects may lose wages during research participation. Investigators should attempt to minimize economic costs to subjects. If the research may involve additional actual costs to individuals, the anticipated costs should be described to subjects during the consent process.

Ensuring Risks Are Minimized (IRB Determination)
The IRB considers the overall level of risk to participants in evaluating the proposed research in accordance with the conditions outlined in 45 CFR 46.111(a)(1-7), 21 CFR 56.111(a)(1-7) and the ethical principles outlined in the Belmont Report. Furthermore, the IRB may consult with additional experts as needed. [45 CFR 46.111(a)(1)(i), 21 CFR 56.111 (a)(1)(i)]

When assessing risks and benefits, the IRB is required to:
1. identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in the research;
2. determine that the risks will be minimized to the fullest extent possible;
3. identify the probable benefits to be derived from the research;
4. determine that the risks are reasonable in relation to the benefits to subjects, if any, and the importance of the knowledge to be gained;
5. assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;
6. determine intervals for periodic review (no greater than annually), and, where appropriate, determine that adequate provisions are in place for monitoring the data collected and, if the subjects are likely to be members of vulnerable populations, determine that appropriate additional safeguards are in place to protect the rights and welfare of these subjects.

The IRB examines the research plan, including research design and methodology, to determine that there are no inherent flaws that would place research participants at unnecessary risk. This includes the risk that research lacking in statistical power may not lead to meaningful results. Appropriate safeguards can also minimize risk to participants, for example: having an adequate data monitoring plan, or protecting confidentiality by using coded data. If risks are not adequately minimized, the protocol will not be approved as written.

The IRB also considers the professional qualifications and resources (including time, equipment, support services) of the research team to protect participants and minimize potential harm. Research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges.
Potential Risks v. Anticipated Benefits (PI Input)
The Protocol Application requires that the PI describe the potential benefit(s) that may be gained by participants, and how the knowledge gained may benefit the participants, future participants or society. The PI must explain how these potential benefits to the participant or society outweigh the risks inherent in the research.

Potential Risks v. Anticipated Benefits (IRB Determination)
The IRB determines whether the risks of the research are reasonable in relation to the anticipated benefits (if any) to research participants and the importance of the knowledge that may reasonably be expected to result. [45 CFR 46.111(a)(2), 21 CFR 56.111(a)(2), 38 CFR 16.111(a)(2)]

The IRB bases its risk/benefit analysis on the information provided by the PI and by the expertise of its members and consultants who utilize the most current information about the risks and benefits of the interventions involved in the research.

The IRB considers only those risks that result from the research, and does not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research. The IRB does not consider those risks and benefits that participants would receive even if not participating the research. [45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2)]

9.2 Data Monitoring Plan

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<td>The IRB has and follows written policies and procedures for reviewing the plans for data and safety monitoring, when applicable, and determines that the data and safety monitoring plan provides adequate protection for participants.</td>
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To approve research, the IRB must determine that, where appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of research participants. (45 CFR 46.111(a)(6), 21 CFR 56.111(a)(6), 38 CFR 16.111(a)(6))

Many studies (e.g., if more than minimal risk) need a Data and Safety Monitoring (DSM) Plan:
- The DSM Plan must be commensurate with the level of risk, size and complexity of the study.
- The DSM Plan might need to include a DSMB or DMC (a data safety monitoring board, or committee – the terms are generally used interchangeably): for example, a DSMB or DMC may be required as part of the monitoring plan by NIH, FDA, other sponsors, or the IRB.

PIs are required to describe a Data Monitoring Plan, if applicable, on the Protocol Application.
- Chapter 15- discusses PI responsibilities
- Data Monitoring Committees - FDA March 2006 “Guidance for Clinical Trial Sponsors”

Data Monitoring Plans and Data Monitoring Committees – NIH and NCI policies:
- NIH: Policy for Data and Safety Monitoring
- NIH: Further Guidance On Data And Safety Monitoring For Phase I And Phase II Trials
- NCI: Data and Safety Monitoring Guidelines: Essential Elements
IRB Review of the Data Monitoring Plan
The IRB primary reviewer and Compliance Auditor review the proposed Data Monitoring Plan, and the administration and composition of the monitoring entity, when applicable. If additional expertise is needed, the IRB will seek input from persons with appropriate knowledge.

Continuing Review; Timeframe for Reporting Data Monitoring Findings to the IRB
It is not the role of the IRB to perform data monitoring, but to ensure that appropriate monitoring is taking place, and to review reports from the monitoring entity.

The IRB must ensure that the conditions satisfied in order for initial IRB approval of the research are still satisfied at continuing review. These include, but are not limited to, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for participants. Thus, the PI must include in the continuing review application the outcomes of data and safety monitoring including, any unanticipated problems, and any new information pertaining to the research - either from the research itself or from other sources, which have occurred since the previous IRB review. The amount of detail required depends on the type of research being conducted. In many cases, an appropriate summary would be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

In addition, periodic (usually annual) reports from the monitoring entity are submitted by the PI to the IRB at continuing review. (When a monitoring entity is used, the IRB conducting continuing review of the research may choose to rely on a current statement from the monitoring entity indicating that it has and will continue to review study-wide adverse events, interim findings, and any recent literature that may be relevant to the research.)

Whether the method of monitoring is by PI oversight or from the establishment of a DSMB, the IRB can tailor a specific timeframe for future reporting of data monitoring findings to the IRB. The IRB can set the date of continuing review for the protocol as being less than the maximum of a year, if they determine that interim reporting of data monitoring information will serve to better protect participants. Alternatively, the IRB can request a report after a specific number of participants are enrolled or after a serious adverse event has been reported.

9.3 Risks to Vulnerable Populations

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<td>II.4.A</td>
<td>The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.</td>
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The IRB is cognizant of the vulnerable nature of many participants. Food and Drug Administration (FDA) regulations and the Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable participants. In order to approve research involving vulnerable populations, the IRB must determine, where appropriate, that additional safeguards have been included to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as:

- Children (45 CFR 46 Subpart D; 21 CFR 50 Subpart D),
- Prisoners (45 CFR 46 Subpart C),
- Pregnant women, human fetuses, or neonates (45 CFR 46 Subpart B),
- Persons with mental disabilities, or
- Economically or educationally disadvantaged persons
The IRB includes among its members persons who are knowledgeable about and experienced in working with vulnerable participants. (45 CFR 46.107(a); 21 CFR 56.107(a)). When a research study involves a vulnerable population not otherwise covered by these policies, the IRB takes steps to evaluate whether additional safeguards have been included in the research to protect the rights and welfare of participants. See also Chapter 12.2 for consent procedures for vulnerable populations.

Considerations in Reviewing Research involving Vulnerable Participants

The IRB considers the following elements of the research plan when reviewing research involving vulnerable participants:

**Strategic issues** that involve inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.

**Group characteristics**, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable participants.

**Participant selection to prevent over-selection or exclusion** of certain participants based on perceived limitations or complexities associated with those participants. For example, it is not appropriate to target prisoners as research participants merely because they are a readily available “captive” population.

**Application of state or local laws** that bear on the decision-making abilities of potentially vulnerable populations. State statutes (as discussed in Chapter 12) often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.

**Procedures** for assessing and ensuring participants’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable participants, the IRB verifies that such procedures are a part of the research plan. In certain instances, it may be possible for investigators to enhance understanding for potentially vulnerable participants. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a participant advocate, interpreter for hearing-impaired participants, translation of informed consent forms into languages the participants understand, and reading the consent form to participants slowly and ensuring their understanding paragraph by paragraph.

**Need for additional safeguards** to protect potentially vulnerable populations. For example, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

**Children**

**Children**: Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

- The IRB follows the requirements of the DHHS regulations at 45 CFR 46, Subpart D and FDA regulations at 21 CFR Part 50, Subpart D in reviewing protocols involving children. The IRB makes the findings and determinations required by the DHHS and FDA regulations related to the risks before allowing research involving children to proceed. See Chapter 12.2 for consent requirements for research involving children participants.

See guidances:
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• Additional Protections for Inclusion of Children in Research (OHRP)
• Additional Safeguards for Children in Clinical Investigations (FDA)

Prisoners

Prisoner: Any individual involuntarily confined or detained in a penal institution. This includes individuals:

• sentenced to such an institution under a criminal or civil statute,
• detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution,
• detained pending arraignment, trial, or sentencing.
• DHHS details special protections for research involving prisoners, who due to their incarceration may have a limited ability to make truly voluntary and un-coerced decisions about whether or not to participate as participants in research.
• [45 CFR 46, Subpart C]. The IRB will apply the standards of Subpart C to all prisoner research, whether or not DHHS-supported.

DHHS-supported research: The IRB must certify to the Secretary (of DHHS), via the Office for Human Research Protections (OHRP) that it has reviewed and approved the research under 45 CFR 46.305; additionally, the Secretary (through OHRP) must determine that the proposed research falls within permissible categories [45 CFR 46.306(a)(2)]. If biomedical or behavioral research is conducted or supported by DHHS, approval must be obtained from the Secretary of DHHS (through OHRP) before commencing research.

Note: OHRP discourages expedited review of any research involving prisoners as participants.

Non-DHHS-supported research: Certification to OHRP is not required; the IRB substitutes a comparable risk assessment measure in place of the review and approval by the Secretary of DHHS.

Refer to guidance Additional Protections for Prisoners in Research for:

• Special requirements regarding IRB composition and additional duties
• Categories of permissible research
• Other requirements pertaining to DHHS-supported research
• IRB required findings.

In order to consider research involving prisoners, the IRBs must:

• Ensure a majority of its members are not otherwise associated with the prison(s) involved in the research, and
• Include a prisoner or a prisoner advocate, who can adequately represent the interests of the prisoners, unless the research has already been reviewed by an IRB that included a prisoner advocate.

When a previously enrolled research subject becomes a prisoner and the relevant research protocol was not reviewed and approved by the IRB (under 45 CFR 46, Subpart C) the PI should promptly notify the IRB of this event through the IRB Amendment Form. The PI should state that all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-participant will cease until the requirements of Subpart C have been satisfied with respect to the relevant protocol, unless the PI asserts that it is in the best interests of the participant to remain in the research study while incarcerated, in which case the IRB Chair may determine that the participant may continue to participate in the research until the requirements of Subpart C are satisfied. Upon receipt of notification that a previously enrolled research participant has become a prisoner, the IRB should promptly re-review the protocol in accordance with the requirements of Subpart C if the PI wishes to have the prisoner participant continue to participate in the research.
DHHS Conducted or Supported Epidemiologic Research Involving Prisoners as Subjects

Under certain conditions DHHS conducted or supported epidemiologic research may be approvable by the Secretary of DHHS, as outlined in the Federal Register Vol 68 No.119, June 20, 2003.

Decisionally Impaired Participants

The IRB reviews the risk-benefit analysis including the possibilities of coercion and undue influence, and must determine whether such participants should be recruited and whether support mechanisms, such as surrogate consent, are appropriate. See Chapter 12.2 for more information on the consent process, and criteria for including decisionally impaired participants in research.

Pregnant Women, Human Fetuses, and Neonates

The Department of Health and Human Services (DHHS) details special protections for research involving pregnant women, human fetuses, and neonates. [45 CFR 46, Subpart B.]

Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent, in accordance with the guidance Additional Protections for Research Involving Pregnant Women, Fetuses, and Neonates.

In general, Subpart B requires that research involving pregnant women, human fetuses, and neonates should involve the least possible risk. Persons engaged in the research may have no part in the timing, method, or procedures used to terminate the pregnancy, or to determine the viability of the fetus. No inducements may be offered to terminate a pregnancy.

Four separate conditions, each with their own requirements and IRB determinations, apply to research with pregnant women, human fetuses, and neonates:

**Research Involving Pregnant Women.** No pregnant women may be involved as a participant in research unless either of the following conditions applies: The purpose of the activity is to meet the health needs of the mother, and the fetus is placed at risk only to the minimum extent necessary to meet such needs; OR the risk to the fetus is minimal. The mother and the father must be legally competent and provide consent, unless the purpose of the research is to meet the health needs of the mother, or the father is not reasonably available, or the pregnancy resulted from rape.

**Research Directed at Human Fetuses.** The IRB must find that: the purpose of the research is to meet the health needs of the individual fetus and shall be conducted in a way that will minimize risk; OR the research will pose no more than minimal risk to the fetus, and the purpose of the activity is to ascertain important biomedical knowledge that is unobtainable by other means. These activities are permitted only if the mother and father are legally competent and have given their informed consent, unless the father is not reasonably available or the pregnancy resulted from rape.

**Research Involving Neonates.** For research involving neonates, the IRB must distinguish between viable and non-viable neonates. Viable is defined in the regulations as being able to survive to the point of independently maintaining a heartbeat and respiration, given the benefit of available medical therapy. If the neonate is viable, it is considered a “child” and may be involved in research to the extent permissible under 45 CFR 46, Subpart D, which is discussed later in this chapter.

- **A non-viable neonate** may not be involved in research unless all of the following conditions apply: The vital functions of the neonate are not artificially maintained; experimental activities that would of themselves terminate the heartbeat or respiration are not employed; AND the purpose of the research is development of important biomedical knowledge that cannot be obtained by other means. Research involving a non-viable neonate is permitted only when both parents have given their informed consent, unless one parent is not
reasonably available or the pregnancy resulted from rape or incest. In the case of non-viable neonates consent by a parent’s legally authorized representative is not allowed.

- **A neonate of uncertain viability** may not be involved in research unless one of the following conditions applies:
  
  There is no added risk to the neonate and the purpose of the research is to obtain important biological knowledge that cannot be obtained by other means; OR the purpose of the activity is to enhance the probability of survival of the individual neonate. Research involving a neonate of uncertain viability is permitted only if either parent or the parent’s legally authorized representative gives their permission.

**Non-pregnant women of reproductive potential**

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

**Other Potentially Vulnerable Participants**

The context of the research is an important consideration for the IRB when reviewing research that involves other potentially vulnerable participants such as research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of participants and the IRB takes such considerations into account. Nevertheless, research involving these participants is socially important for understanding and eventually improving adverse health and general well-being in these populations.