206.1 What is “Risk”? 

Risk in the context of human participant research refers to the combination or the probability and magnitude of some future harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary independently and result in risks that range from “high” to “low” depending on whether they are more (or less) likely to occur, and whether the potential harm is more (or less) serious.

Minimal risk means that 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 of during the performance of routine physical or psychological examinations of tests.41

When following Department of Defense requirements, the definition of the minimal risk based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” must not be interpreted to include the inherent risks certain categories of research participants face in their everyday life. See GUIDE 617: Other Federal Agencies—Additional Requirements for additional regulations, funding agency requirements and guidance on risk (and minimal risk) applicable to specific situations or populations (e.g., children, prisoners).

206.2 Minimizing Risk in Human Participant Research

There are multiple steps to minimize risk in human participant research. Both the Investigator and the IRB have the responsibility to ensure risks are minimized and reasonable relative to the anticipated benefits before a research secures approval.

Identifying Potential Risk and Analyzing Level of Risk (Investigator)

The Investigator documents in the Protocol/Proposal Application information that would allow the IRB to conduct an analysis of the risks and potential benefits on a particular research study:

- Purpose of the research.
- Scientific or scholarly rationale for conducting such research.
- Research procedures including procedures already performed for treatment or diagnostic purposes.
- Potential risks to participants.
- Procedures for protecting against or minimizing potential risks, including risks to confidentiality and privacy.
- When requesting changes to the research, the Modification Request form includes description of the proposed changes and potential impact on the level of risks to participants.

41 45 C.F.R. § 46.102(i); FDA 21 C.F.R. § 56.102(i)
In an Initial Application, Modification or a Continuing Review submission, the Investigator indicates level of risk (little to no risk, minimal risk, greater than minimal risk) to participants by declaring the review type on their submission (exempt, expedited, full-board).

**Ensuring Risks are Minimized (IRB Determination)**

The IRB considers the overall level of risk to participants in reviewing the proposed research in accordance with the conditions described in 45 C.F.R. §§ 46.111(a)(1-7), 21 C.F.R. 56.111(a)(1-7) and the ethical principles outlined in the Belmont Report. The IRB utilizes its armory of scientific and scholarly expertise, and seek consultants when expertise is needed, to critically assess the research when reviewing risks to participants.

The IRB must determine that risks (or burden to participants) are minimized before approving a research. This includes:

- Ensuring that the proposed research has sound (scientific and scholarly) research design and purpose;\(^\text{42}\);  
- The research does not expose participants to unnecessary risks;\(^\text{43}\); and  
- When appropriate, the research uses procedures that are already being performed on the participants for diagnostic or treatment purposes.\(^\text{44}\).

Appropriate plans to minimize risk to participants may include having an adequate data monitoring plan, coding data to protect confidentiality of participant information, or providing medical or psychological resources to participants as a potential consequence of involvement in the research. If risks are not minimized, the research will not be approved as written.

The IRB also considers the professional qualifications and resources (including time, equipment, support services) of the research personnel to protect participants and minimize potential harm. Research personnel must receive appropriate training, and clinicians involved in the research must maintain the professional credentials and/or licenses appropriate to their role in the research.

**Anticipated Benefits (Investigator)**

The application requires that the Investigator includes information about the potential benefit(s) to participants (if any), and how the knowledge gained may benefit the participants, future participants or society. Compensation for participation is not considered a benefit.

The Investigator must explain how these potential benefits to the participant or society outweigh the risks inherent in the research.

**Potential Risks vs. 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.\(^\text{45}\)

\(^{42}\) 45 C.F.R. § 46.111(a)(1)(i), 21 C.F.R. § 56.111(a)(1)(i)  
\(^{43}\) ibid.  
\(^{44}\) 45 C.F.R. § 46.111(a)(1)(ii), 21 C.F.R. § 56.111(a)(1)(ii)  
\(^{45}\) 45 C.F.R. § 46.111(a)(2), 21 C.F.R. § 56.111(a)(2)
The IRB bases its risk/benefit analysis on the information provided by the Investigator 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. It does not consider long-term 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 otherwise receive if they do not participate in the research.46

### 206.3 Data and Safety Monitoring

When appropriate, the IRB must determine that the research plan includes adequate provisions for monitoring the data to ensure the safety of research participants, prior to approval of the research.

For research (e.g., if more than minimal risk) that requires a Data and Safety Monitoring Plan (DSMP):
- The DSMP must be commensurate with the level of risk, size and complexity of the study.
- The DSMP may need a Data Safety Monitoring Board (DSMB).

Investigators must include a discussion of the DSMP, if applicable, on the Protocol Application.

For guidance, see:

- 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

### IRB Review of the Data and Safety Monitoring Plan

The IRB primary reviewer reviews the proposed DSMP, and the administration and composition of the monitoring entity, when applicable. External experts are consulted when needed to assist with the review.

### Reporting DSMP Outcomes

Investigators are expected to submit all reportable findings from the DSMB to the IRB within the prescribed timeframe. See SOP 116: Reporting and Reviewing Unanticipated Problems.

Investigators must also including in the continuing review application the outcomes of data and safety monitoring including a summary of adverse events, 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. This includes audit, inspection, multi-center trial, and DSMB reports.

46 45 C.F.R. § 46.111(a)(2), 21 C.F.R. § 56.111(a)(2)
206.4 Risks to Vulnerable Populations

The IRB takes into special consideration the Common Rule and FDA regulations in protecting the welfare of vulnerable participants (i.e., children, pregnant women and neonates, and prisoners) involved in research.

To approve research involving vulnerable populations, the IRB must determine, as applicable, that additional safety measures have been placed to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as:

- Pregnant women, human fetuses, or neonates (45 C.F.R. 46 Subpart B)
- Prisoners (45 C.F.R. 46 Subpart C),
- Children (45 C.F.R. 46 Subpart D; 21 C.F.R. 50 Subpart D),
- Individuals with mental disabilities,
- Economically or educationally disadvantaged persons, or
- Socially marginalized persons.

Reviewing Research Involving Vulnerable Participants

When reviewing research involving vulnerable participants, the IRB considers the following elements in the protocol or proposal:

- Method of recruitment and enrollment of participants (i.e., use of exclusion/inclusion criteria; informed consent process; coercion and undue influence; confidentiality of data).
- Group characteristics (e.g., economic, social, physical, and environmental conditions)
- Participant selection to prevent over-selection or exclusion of certain participants based on perceived limitations or complications associated with including those participants.
- Application of state or local laws regarding decision-making abilities of potentially vulnerable populations (e.g., age of majority for providing consent).
- Procedures for assessing and ensuring participants’ capacity to understand and provide consent or assent.
- Any other additional safety measure necessary to protect potentially vulnerable populations.

Pregnant Women, Fetuses and Neonates

Under 45 C.F.R. part 46, subpart B, special protections are provided for research involving pregnant women, fetuses and neonates. Research involving women who are or may become pregnant shall receive special attention because of additional health concerns for pregnant women and because of the need to avoid unnecessary risk to the fetus.

Subpart B requires that research involving pregnant women, fetuses, and neonates shall involve the least possible risk. Those engaged in the research may have no involvement 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.
Each of the four following conditions has their own requirements and IRB determinations:

1. **Research Involving Pregnant Women or Fetuses.** No pregnant women may be involved as a research participant unless either of the following conditions are met:
   a. The purpose of the research 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
   b. The risk to the fetus is minimal.

   **Consent:** 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.

2. **Research Involving Human Fetuses.** For research directed at human fetuses:
   a. The purpose of the research needs to meet the health needs of the individual fetus and shall be conducted in a way that minimize risk; OR
   b. The research will pose no more than minimal risk to the fetus, and the purpose of the research activity is to ascertain important biomedical information that is unobtainable by other means.

   **Consent:** The mother and the father are legally competent and have provided consent, unless the father is not reasonably available or the pregnancy resulted from rape.

3. **Research Involving Viable Neonates.** A neonate, after delivery, that has been determined to be viable is considered a “child” and may be included in research only to the extent permitted by and in accordance with the requirements of subparts A and D of 45 C.F.R. part 46.

4. **Neonates of Uncertain Viability.** Neonates of uncertain viability may not be involved in research unless one of the following conditions applies:
   a. There is no added risk to the neonate and the purpose of the research is to obtain important biological information that cannot be obtained by other means; OR
   b. The purpose of the activity is to enhance the probability of survival of the individual neonate.

   **Consent:** Research involving neonate of uncertain viability is allowed only if either parent or the parent’s legally authorized representative provides their consent.

5. **Nonviable Neonates.** Nonviable neonates maybe not be involved in research unless all of the following are met:
   a. The vital functions of the neonate are not artificially maintained;
   b. Experimental activities that would of themselves terminate the heartbeat or respiration are not used; AND
   c. The purpose of the research is development of important biomedical information that cannot be obtained by other means.

   **Consent:** 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. Consent by a parent’s legally authorized representative is not permitted.

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47 45 C.F.R. § 46.204.
Prisoners

Under 45 C.F.R. part 46, subpart C, special protections are provided for research involving prisoners. The incarceration could affect the Prisoners' ability to make a truly voluntary decision on whether to participate as subjects in research. To protect prisoners' rights and welfare, the Investigator and the IRB shall take extra measures to meet the ethical and regulatory requirements on research involving prisoners.

Definition of minimal risk in research involving prisoners is different from minimal risk in research involving individuals from the general population. Minimal risk specific to prisoners is measured by the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. 48

When reviewing research that involves prisoners, the IRB must include at least one member who was a prisoner, or is a prisoner representative with appropriate background and experience to serve in that capacity, except that, where a particular research project is reviewed by more than one IRB, only one IRB needs to satisfy this requirement. 49 Examples of such members are former or present prisoners, prisoner psychologists, prison social workers, or prison chaplains.50 A majority of the IRB, excluding prisoner members, must not be associated with the prisons involved51 (see Section 202.2: IRB Member Composition and Structure).

Except certain types of epidemiologic research, research involving prisoners must be in one of the following four categories52:

1. Research on the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
2. Research on prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
3. Research on conditions particularly affecting prisoners as a class provided that the study may proceed only after the Secretary of HHS has consulted with appropriate experts; or
4. Research on practices, innovative or accepted, which have the intent and reasonable probability of improving the health or well-being of the participant.

Certain types of epidemiologic research conducted or supported by HHS does not need to be in one of the above four categories listed under 45 C.F.R. § 46.306(a)(2).53 But the epidemiologic research must meet the following requirements before it may proceed:

1. The sole purposes of the research are:
   (a) to describe the prevalence or incidence of a disease by identifying all cases, or
   (b) to study potential risk factors associated with a disease, and

48 45 C.F.R. § 303(d).
49 45 C.F.R § 46.304(b).
50 OHRP IRB Membership Video.
51 45 C.F.R. § 304(a).
2. the institution responsible for the conduct of the research certifies to OHRP that an IRB:
   (a) approved the research and made the findings under 45 C.F.R. § 46.305(a)(2)–(7); and
   (b) determined and documented that:
       (i) the research presents no more than minimal risk and no more than inconvenience to the
           prisoner-subjects, and
       (ii) prisoners are not a particular focus of the research.

   See GUIDE 629: Research Involving Vulnerable Populations for more information about research involving prisoners. See SOP 124: Research Involving Prisoners for procedures in reviewing and reporting research involving prisoners.

Children

If research involves children, the IRB follows subpart D of 45 C.F.R. part 46 in its review of the research, except when the research is regulated only by FDA.54

Only the following four categories of research involving children are allowed:

1. Research Not Involving More than Minimal Risk. If the IRB finds that the research involves no more than minimal risk to children, the IRB may approve the proposal only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.55

2. Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit. If the IRB finds that more than minimal risk to children is presented by a research intervention or procedure that holds out the prospect of direct benefit to the individual subject, or by a monitoring procedure that is likely to contribute to the individual subject’s well-being, the IRB may approve the research only if it finds that:
   (a) the risk is justified by the anticipated benefit to the subjects;
   (b) the ratio of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
   (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.56

3. Research Involving Greater than Minimal Risk and Presenting No Prospect of Direct Benefit. If the IRB finds that more than minimal risk to children is presented by a research intervention or procedure that does not hold out the prospect of direct benefit to the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the individual subject, the IRB may approve the research only if the IRB finds that:
   (a) the risk represents a minor increase over minimal risk;
   (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   (c) the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is vitally important for the understanding or amelioration of the subjects’ disorder or condition; and
   (d) adequate provisions are made for soliciting assent of the children and permission of their

55 45 C.F.R. § 46.404.
56 45 C.F.R. § 46.405.
4. **Research Not Otherwise Approvable but Presenting an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children.**

For more information on research involving children, see [GUIDE 629: Research Involving Vulnerable Populations](#).

### Individuals with Diminished Decision-Making Capacity

When research involves individuals with psychiatric, cognitive, or developmental disorders, or who are substance abusers, the predominant ethical concern is that their disorders may compromise their decisional capacity, i.e., their capacity to understand the presented information and their ability to make a reasoned decision. Also, many of those individuals are residents of institutions responsible for their care and treatment. Institutionalization may further compromise their ability to exercise free choice.

Research involving persons with diminished capacity shall bear a direct relationship to their condition or circumstances.

### UH Students and Employees

Students and employees[^58] at UH and other facilities under the purview of the IRB are considered vulnerable participants mainly because of the risk of coercion and undue influence.

Students may volunteer out of a belief that doing so will place them in good favor with faculty such as better grades, recommendations, or employment, or that failure to participate will negatively affect their relationship with the Investigator or faculty in general such as seeming “uncooperative” or not being part of the scientific community.

Employee participation raises questions about the ability of employees to exercise free choice because employees are likely to view their employers as authority figures to whom they must show deference. Employees may also fear that a decision to participate could affect performance evaluations or job advancement even if it is only the employee’s perception, or refusal to participate may result in a loss of benefits.

Safeguards will be placed to reduce or minimize undue influence or coercion when recruiting and enrolling participants who are students or employees.

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[^57]: 45 C.F.R. § 46.406.
[^59]: See 45 C.F.R. § 46.113; 21 C.F.R. § 56.113.
The IRB may decide to suspend or terminate a protocol or proposal for any of the following reasons including but not limited to:

(a) When an Investigator does not comply with the IRB requirements, the Regulations, or both; or
(b) When the study poses unexpected serious harm to research participants. This category includes suspension or termination on an urgent basis.
   (i) Suspension or termination on an urgent basis means that a study poses imminent high risk to participants such that it becomes necessary to immediately suspend or terminate the study.
   (ii) The Director or the IRB Chair is authorized to suspend or terminate a study on an urgent basis.

Who Is Authorized to Suspend or Terminate a Study?

The Director, the IRB Chair, and the IRB are authorized to suspend a previously approved research. Only a convened IRB may terminate a previously approved research. The Institutional Official may also suspend a study, but must provide strong justification for the decision. The Institutional Official does not have the authority to terminate a study, but may request to the convened IRB that a study be terminated if there is reason for termination.

Voluntary Suspension or Termination

The sponsor or the Principal Investigator (PI) of a study may voluntarily decide to suspend or terminate the study due to various reasons, including but not limited to:

   (a) an unanticipated problem,
   (b) serious noncompliance, or
   (c) continuing noncompliance.

If this occurs, the PI must notify the HSP in writing no later than three (3) working days after the suspension or termination, describing

   (a) the steps taken or to be taken to protect the welfare of currently enrolled participants, and
   (b) corrective actions, if appropriate, to address the cause for the suspension or termination.

This report will be reviewed at a convened IRB meeting. After reviewing the report, the IRB will decide whether to officially suspend or terminate the IRB approval.

Reporting Suspension and Termination of IRB Approval

The HSP staff fulfills the regulatory reporting requirements on suspension and termination no later than two (2) months after the IRB’s decision to suspend or terminate IRB approval, including reporting to federal agencies as appropriate.

See SOP 109: Suspension or Termination of Research for procedures for suspending or terminating IRB approved research protocols or proposals.
Protecting Participants Who May Be Affected by IRB Action

If the suspension or termination will affect participants in the research (e.g., requires withdrawal of participants), the IRB may require additional actions, taking into consideration the impact on the participants’ health and safety. This shall occur before the suspension or termination, when it is feasible and delay will not compromise participants’ welfare. Actions the IRB may require include, but not limited to:

- Require the Principal Investigator to submit proposed procedures for any withdrawal of participants.
- Allowing participants to continue with the research (e.g., continuing treatment of investigative drug) if the IRB determines that it is in the best interests of the participants
- Requiring IRB review and approval of any PI correspondence material to participants about the IRB action
- Requiring the reassignment of a new PI to the research