Grand Valley State University Institutional Review Board (IRB)	
Title: *Assessing Risks to Vulnerable Participants*	
Section: 720.	This policy and procedure supersedes those previously drafted
Approved by HRRC: 9/13/2011 Revised: 09/10/2013 Reviewed: 10/28/2014 Revised by HRRPPC: 04/24/2018 Revised by IRBPPC: 9/29/2020	Approved by the RIO/HRPA: 09/23/2011 Revisions Approved: 09/10/2013 Approved by the AIO/RIO: 05/23/2018 Approved by AIO/RIO: 10/2/2020
Effective Date: 10/02/2020	
Related documents: *710: Assessing Risk to Research Participants* *730: Collection, Management and Security of Research Information* *G-5: Guidance on Assessing Risk Using Magnitude of Harm in Categorizing Risk Level* *G-6: Guidance on Assessing Minimal Risk*	

Policy

The decision to participate in research should be informed by a description of risk based on the *objective (analytic) risk model rather than the subjective (category) model*. Participants' decision to enroll in research should be well informed and free from coercion and undue influence. The minimal standard for decision is that which can be reasonably accomplished under the circumstances of deliberate and intentional decision making by competent persons acting in the best interests of the participants and the general social welfare. The IRB shall endeavor to acknowledge what, if any, special accommodations may be required to protect the research study population while also avoiding stereotyping any individuals or groups.

Procedures

1. Minimal Risk for the general research population is defined in the federal regulations as: *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.* [45 CFR 46.102(j), and 21 CFR 56.102(23)(i)].

2. Five populations have been provided specific additional protections in the three subparts to the federal regulations at 45 CFR 46: B (pregnant women, fetuses & neonates); C (prisoners); and D (children). As noted below there are specific populations identified as vulnerable in the federal regulations, Office of Human Research Protections (OHRP) guidance, and various advisory groups to the Secretary of DHHS. The IRB has identified an additional group, those in relationships of significantly unequal authority to the researcher. This policy is intended to apply to members of all of these specific populations.

3. The specific vulnerable populations may include:

    - Prisoners (additional protections in 45 CFR 46 subpart C)
    - Children (additional protections in 45 CFR 46 subpart D)
    - Persons who are significantly disadvantaged due to social, economic or educational circumstances including the sensory & mobility challenged, the poor, and non-readers
    - Persons with diminished decision-making capacity (e.g. developmentally delayed or cognitively impaired)

- Racial minorities
- The very ill
- Institutionalized persons
- Persons in independently unequal authority relationships to the researcher, e.g. students in research conducted by their course instructors, athletes in research conducted or supported by their coaches, and employees in research conducted or supported by their employer.

4. In support of the federal regulations, additional guidance is provided for two specific vulnerable populations:
    a. Prisoners
        i. "Prisoner" means any involuntary confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. [45 CFR 46.303(c)]

        ii. Assessing research related risks to research participants who are prisoners in prison is especially challenging due to the difficulty of assuring uncoerced, voluntary participation. Federal regulations specify that research involving prisoners has additional required protections and restrictions on permitted goals and intent of the study. See Guidance section below and *Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*, subpart C: 45 CFR 46.306 (a) (i-iv).

        iii. Defining Minimal Risk to Prisoners
            1. Minimal risk for prisoners involved in research is defined slightly differently than for non-prisoners in the federal regulations. In addition, additional restrictions and protections are specified:

                a. *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.* [45 CFR 46.303(d)]. ("Discomfort" is not a listed harm for prisoners, but is for non-prisoners.)

                b. *The risks involved in research are commensurate with risks that would be accepted by non-prisoner volunteers* [45 CFR 46.305(a)(3)];

                c. *The study presents no more than minimal risk and no more than inconvenience to the subjects* [45 CFR 46.306(a)(2)];

            2. The permitted research categories include the effects of incarceration, health conditions specifically affecting prisoners, and other narrow areas. In its 2006 report, *Ethical Considerations for Research Involving Prisoners*, the Institute of Medicine (IOM) argued for changing to a risk-based assessment of vulnerability as a more useful and appropriate strategy than the category approach. This would allow some studies containing greater than minimal risk, provided there is sufficient potential benefit to the individual. The

consensus report also acknowledges that much research involving prisoners now takes place outside current federal regulations, to which the Department of Justice's Bureau of Prisons and state prison authorities are not signatory agencies. The IOM panel called for Congressionally mandated uniform guidelines and a national oversight system for all human research programs that enroll prisoners. The SACHRP went further and proposed that legislation setting standards for prisoners should extend to all human subject research, including independently funded studies that fall outside the boundaries of the Common Rule [45 CFR 46].

3. Approval of research proposals involving prisoners currently is based on a subjective (category) model of risk rather than an objective (analytic) model. The definition of risk is different in the FDA regulations than the DHHS regulations pertaining to prisoners. [See **Background** section of this policy, supra. And also see http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm]

iv. While there is no specific category for exempt research involving prisoners in the federal regulations, it is permissible to review research involving prisoners under the exempt categories as long as the research is aimed at involving a broader subject population that only incidentally involves prisoners.

b. Children

i. "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. [45 CFR 46.402(a)]

ii. If research involving a child aged participant is greater than minimal risk based on the analytic model of risk, but includes the prospect of direct benefit to the participant, the degree of risk must be justified by the type and degree of anticipated benefit.

iii. The DHHS regulations identify four categories of research involving children as subjects:

1. Research not involving greater than minimal risk to the children [45 CFR 46.404]. To approve this category of research, the IRB must make and document the following determinations:

a. The research presents no greater than minimal risk to the children; and

b. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research [45 CFR 46.405]. To approve this category of research, the IRB must make and document the following determinations:

a. The risk is justified by the anticipated benefits of the research;

b. The relation of the anticipated benefits to the risk presented in the study is at least as favorable to the subjects as that provided by available alternative approaches; and

c. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

3. Research involving greater than minimal risk and no prospect of direct benefit to the individual children involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition [45 CFR 46.406]. To approve this category of research, the IRB must make and document the following determinations:

    a. The risk of the research represents a minor increase over minimal risk;

    b. The intervention or procedure presents experiences to the child 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 subject's disorder or condition which is of vital importance for the understanding of amelioration of the disorder or condition; and

    d. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

4. Research the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children [45 CFR 46.407].

    a. If the research is federally funded or subject to compliance with FDA regulations, the IRB cannot approve such research, but instead, may refer the protocol to HHS and/or FDA for review and approval.

    b. If the research is not federally funded or subject to compliance with FDA regulations, the IRB can approve the research after making and documenting the following determinations:

        i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children;

ii. The research will be conducted in accordance with sound ethical principles; and

iii. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

c. The IRB may, at its discretion, require additional review and approval from institutional officials as a condition of IRB protocol approval.

iv. For research involving children, the IRB must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risk and potential benefits, the IRB should consider the circumstances of the children to be enrolled in the study (e.g., their health status, age, ability to understand what is involved in the research), as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole.

c. Significantly Disadvantaged Persons

i. Persons significantly disadvantaged due to social, economic or educational circumstances including the sensory and mobility challenged, the poor, and non-readers may require additional protections of their interests and welfare before allowing them to enroll in research studies.

ii. Researchers planning or anticipating significantly disadvantaged persons to be enrolled in their research should describe planned procedures for minimizing any possible objective (analytic) risks to the participants.

Guidance

1. Objective (Analytic) Risk vs. Subjective (Category) Risk
   a. How should the risk to participants in a research study that includes walking a mile without resting be classified? It depends on who the participants are.

      i. The definition of risk is generally understood on either the objective (analytic) risk model or a subjective (category) model. An objective or analytic model identifies risk as present/possible to all participants based on particular physical circumstances and processes integral to the research procedures itself. Walking without resting for a mile on level ground has inherent physical risk to all participants because of the nature of the activity. It is generally considered within the routine activities of daily living for most normal adults, and therefore generally classified as minimal risk.

      ii. In contrast, a subjective or category model identifies risk as present/possible to some persons but not to others, based on specific characteristics of the persons themselves. Walking without resting for a mile on level ground may be assessed as greater than minimal risk for specific groups of persons, e.g. persons over a certain age, or who have specific physical conditions such as hypertension (high blood pressure).

b. A helpful analysis of assessing research related risk is available from the Secretary's Advisory Committee on Human Research Protections (SACHRP).

2. Differing Approaches to Assessing Risk
   a. The general regulations of the Department of Health and Human Services (DHHS) at 45 CFR 46 and the Food and Drug Administration (FDA) at 21 CFR 56, identify vulnerable participants as persons who belong to one or more of the following categories: Women; Human fetuses; Neonates; Prisoners; Children; Persons with physical handicaps or mental disabilities, or disadvantaged economically or educationally. *The Belmont Report* also describes racial minorities, the very ill, and the institutionalized as vulnerable.

   b. In contrast, the *National Bioethics Advisory Committee* (NBAC) and a 2006 Institute of Medicine Report both recommend an analytic or functional approach to addressing vulnerability rather than the category approach used by the DHHS and FDA. Thus, prisoners would be classified as vulnerable only if known to have diminished or impaired mental abilities rather than residing in a particular environmental (prison) context. The NBAC identified six traits of vulnerability that may "interfere with an individual's ability to protect themselves in research especially during the informed consent process." The vulnerability traits are: Cognitive or communicative; Institutional; Deferential; Medical; Economic; Social. Further, an NBAC commissioned background paper used 6 concepts of vulnerability: cognitive, juridic, deferential, medical, allocational, and infrastructural see: *Vulnerability in Research Subjects: A Bioethical Taxonomy*, (Kipnis, 2000).

   c. In addition to identifying a research study population as vulnerable vis-a-vis a particular research study, the "risks" can refer to two quite different things: (1) chances of incurring harm that specific individuals are willing to undertake in order to achieve some desired goal; or (2) the inherent conditions that make a situation dangerous *per se*. The IRB is responsible for evaluating risk only in the second sense. It must then judge whether the anticipated benefit, either of new general knowledge or of improved health for the research participants, justifies inviting any person to undertake the identified risks. The IRB disapproves research in which the risks are judged unreasonable in relation to the anticipated benefits. [*See also* IRB Guidebook, Chapter 5, Section A, "Overview: Social Policy Experimentation."] http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm