Grand Valley State University Human Research Review Committee	
Title: *Assessing Risks to Vulnerable Participants [Pre-Revised Common Rule Version]*	
Section: 720a.	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: 03/28/2018 Revised by IRBPPC: 11/04/2024	Approved by the RIO/HRPA: 09/23/2011 Revisions Approved: 09/10/2013 Approved by the AIO/RIO: 4/16/2018 Approved by the IO: 12/13/2024
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Related documents: 710: *Assessing Risk to Research Participants* *730: Collection, Management and Security of Research Information* *G-1: Guidance on Research Involving Vulnerable Populations* *G-5: Guidance on Assessing Risk Using Magnitude of Harm in Categorizing Risk Level* *G-6: SACHRPP Guidance on Assessing 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.

- *Note:* See Additional Guidance section below for clarification on analytic vs. category models of risk.

Procedures

1. Special considerations for vulnerable populations

    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.

        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. How should a study that involves pregnant women walking a mile without resting be classified as to risk?

i. Within any of the 13 vulnerable populations (see pg. 6), a research procedure or intervention may pose greater than minimal risk to some individuals but not to others. For example, walking for a mile without resting may be greater than minimal risk for persons with breathing problems, but minimal risk for those without such problems. In such cases, the assessment of risk assigned to the overall study is that which is appropriate for the most vulnerable members of the target population. Thus, such a study would be classified as greater than minimal risk if it is reasonable to presume that at least some participants are likely to have or to develop breathing problems even if they have not been previously diagnosed with breathing problems, and even if no participant actually develops such problems in the study.

On the other hand, if all potential participants are initially screened for breathing and other problems, and all are determined to be in very good or excellent health, the study may be assessed as minimal risk *for the population under study*, despite all participants being members of a subjectively "vulnerable" population. Thus, if the pregnant participants are screened for hypertension and breathing problems before participating, the study may be classified as minimal risk because the pregnant women are not deemed "vulnerable" in the relevant sense, despite being members of a recognized "vulnerable" population.

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

2. Pregnant Women, Fetuses and Neonates

Research related risks to this population are those that are directly or indirectly connected to the medical condition of being pregnant. Taking a survey about personal career interests is a minimal risk activity for anyone, including pregnant persons. Taking a new medication for acne may be minimal risk for non-pregnant adults but greater than minimal risk for pregnant adults because it is unknown what effects the medication may have on the woman's fetus.

3. Prisoners

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).

4. Minors

If research involving a minor 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.

5. Significantly Disadvantaged Persons

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

Additional Guidance

1. Defining Minimal Risk to Prisoners

a. 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.

ii. *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)

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

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

b. 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].

c. Approval of research proposals involving prisoners currently is based on a subjective (category) model of risk rather than an objective (analytic) model. Further, there is no

category for exempt research involving prisoners in the federal regulations, and the definition of risk is different in the Food and Drug Administration (FDA) regulations than the Department of Health and Human Services (DHHS) regulations pertaining to prisoners. [See Background section of this policy.]

2. Differing Approaches to Assessing Risk

a. The general regulations of the DHHS at 45 CFR 46 and the FDA at 21 CFR 56, identify vulnerable participants as persons who belong to one or more of 8 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.

Contra, 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).

Finally, 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."]

3. Problematic Language of 45 CFR 46.204 Concerning Pregnant Women as Research Participants

a. When initially issued, subpart B of the federal regulations sought to protect pregnant women involved in research through maximal reduction of risks by disallowing participation in any research that was not aimed at improving pregnancy safety or outcomes. The difficult restriction occurs at regulation 45 CFR 46.204 which states in part:

i. Pregnant women of fetuses may be involved in research if all of the following conditions are met:
… (d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit to both the pregnant woman and the fetus, or

no prospect of direct benefit to the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

AND

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

AND …

(g) For children as defined in 406.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

b. This language has three problematic effects, which is why GVSU has not included the provisions of subpart B in its federal wide assurance.

   i. It renders a woman who is pregnant ineligible to participate in research in which she has an interest and which poses no known risk to her or to her fetus but which is unrelated to her pregnancy or the health of her fetus.
   ii. It denies a woman who is pregnant from participating in research that holds the prospect of direct benefit to her fetus but who has a conflicted relationship, or no relationship, with the father of her fetus, but the father does not consent.
   iii. It requires a woman who is pregnant but not yet 18 years of age to secure the permission of her parents or legal guardians in order for her to participate in research that holds the prospect of direct benefit to herself. However, she may assent to research on her fetus without her parent's permission.

Background

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, 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 (minors). As noted below there are twelve total 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 HRRC has identified a thirteenth group, those in relationships of significantly unequal authority to the researcher. This policy is intended to apply to members of all thirteen populations.

3. Note: the federal wide assurance held by GVSU does not include the additional protections in subparts B, C and D. However, under its own authority it routinely requires compliance with those protections in its review and approval processes and researchers should anticipate this when submitting protocol proposals.

4. The thirteen populations are:

   1-3: Pregnant women, fetuses and neonates (additional protections in 45 CFR 46 subpart B)
   4: Prisoners (additional protections in 45 CFR 46 subpart C)
   5: Minors (additional protections in 45 CFR 46 subpart D)
   6-8: Persons who are significantly disadvantaged due to social, economic or educational circumstances including the sensory & mobility challenged, the poor, and the illiterate
   9: Persons with diminished decision making capacity (e.g. developmentally delayed or cognitively impaired)
   10: Racial minorities
   11: The very ill
   12: Institutionalized persons
   13: 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.