

CARILION CLINIC INSTITUTIONAL REVIEW BOARD

Standard Operating Guidelines

Title: 3.6: Reviews Requiring Special Consideration: VULNERABLE POPULATIONS	
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Primary Sponsor: Human Research Protections Office	Approved By: Director of the Human Research Protections Office

Objective:

To define vulnerable populations and to note additional approval criteria and safeguards that must be met prior to Institutional Review Board (IRB) approval of research involving vulnerable populations.

General Description:

Certain groups of human subjects are considered particularly vulnerable in a research setting. 45 CFR 46.111(b) states that subjects considered vulnerable and therefore likely to coercion or undue influence include children, prisoners, individuals with impaired decision making capacity, or economically or educationally disadvantaged persons. In reviewing research studies, the Carilion IRB will ascertain that the inclusion of the vulnerable population(s) is adequately justified and that safeguards are implemented to minimize risks unique to each population.

Procedure:

Each research study is evaluated for inclusion of possible vulnerable populations. The IRB must determine which of the following categories of research would involve:

- The research does not involve more than minimal risk to the subject
- The research is likely to benefit the subject directly, even though the risks are considered to be more than minimal
- The research involves greater than minimal risk with no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition

The Carilion IRB will then make a determination whether the specific approval criteria are met and required safeguards are planned prior to approving the study. This determination will be documented in the minutes.

No standard safeguards or approval criteria exist for research that targets other vulnerable populations (students, employees, etc.). Therefore, for any other vulnerable populations, the investigator must propose additional safeguards and the Carilion IRB will determine whether those safeguards are adequate. The Carilion IRB may, depending on circumstances of the study, determine that subjects beyond those proposed by the investigator are also vulnerable and may dictate additional safeguards.

Children

All pediatric research subjects, defined as subjects under the age of 18, should be fully informed about a research study, in language appropriate for their age, maturity, and previous experiences, whether assent is to be requested or not. This information can be provided verbally and should include all tests and procedures to be performed, frequency of interventions, duration of participation in the study, risks, discomforts, and potential benefits. The child should be encouraged to ask questions, all of which should be answered. Please see SOG 5.2: Informed Consent Process: Components of Informed Consent Form, Waiver of Informed Consent and Waiver of Documentation of Informed Consent for further information.

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 and 45 CFR 46.407 only if such research is related to their status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards (45 CFR 46.409).

The IRB membership will include at least one member who is knowledgeable about or experienced in working with children. The Carilion IRB will defer to Virginia law regarding the informed consent requirements for prospective child subjects who qualify as emancipated children by law.

Investigators must obtain informed consent from subjects who were enrolled in research as children but have now reached the age of majority. Consent to continue in the research must be documented by having subjects sign a consent form for continued participation at the next study or clinic visit after becoming the official, legal consent authority for themselves. If subjects are undergoing any research procedures or interventions, a current, approved version of the consent form must be used. If, however, all research procedures or interventions have been completed and the subject is in long-term follow-up involving data collection only, an addendum to consent for continued data collection may be used following IRB review and approval.

Prisoners

At this time the section on prisoners is included for informational purposes only. The Carilion IRB does not have the required expertise to oversee this type of research.

Depending on the research procedures, considerations will be made to manage participation in the event of a subject currently enrolled in research overseen by the Carilion IRB becoming incarcerated. The IRB must be notified and arrangements may be made to have the subject removed from the research.

The term prisoner refers to any individual who is involuntarily confined or detained in a penal institution; sentenced under a criminal or civil statute; detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution; and detained pending arraignment, trial or sentencing. This also applies to current subjects who suddenly become incarcerated. Regulations do not differentiate between detention, jail or prison.

The principal investigator indicates on the application if the enrollment of prisoners is anticipated. If the study is not initially approved to recruit prisoners, then the investigator may not enroll a prisoner. For ongoing research studies, investigators notify the IRB immediately upon becoming aware of a current subject's incarceration, and all interactions, interventions and collection of protected health information (PHI) cease until requirements of Subpart C have been satisfied for the research. Exception: The investigator may assert to the IRB that it is in the best interest of the subject to remain in the research while incarcerated and the IRB Chair, or designee, may determine that the subject may continue while the requirements of Subpart C are satisfied.

For review of research with prisoners:

- The IRB membership must include an individual with appropriate background and experience to serve as a prisoner representative, by nature of having experience or a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner. In addition, the majority of the IRB membership (exclusive of prisoner members) has no association with the prison(s) involved, apart from their membership on the board.
- When the IRB reviews research involving prisoners, the prisoner or prisoner representative is present as a voting member.
- The prisoner representative is present during the review of initial applications, continuing reviews, modifications, adverse events, and other reviews that may be applicable.
- An expedited review process can be used if appropriate to the research and only minimal risk as defined for the prisoner population is evident. If the expedited review process is used to review research involving prisoners, the prisoner representative of the IRB must be one of the designated reviewers.
- Exempt review does not apply to research with prisoners.

Only research studies meeting one of four categories described below may be approved to include prisoners as research subjects:

- Studies of 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 minor inconvenience to the subjects.
- Studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than minor inconvenience to the subjects
- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after DHHS has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research; or
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after DHHS has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice in the Federal Register of the intent to approve such research.

In addition to the other responsibilities described in the section for use of prisoners, the IRB can only approve research studies if it finds that:

- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers
- Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research study
- The information is presented in a language and reading level that is understandable to the participant population
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole, and
- Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provisions have been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Individuals with Impaired Decision Making Capacity – please see SOG 5.3: Informed Consent Process: Use of Legally Authorized Representative and SOG 5.6 Informed Consent Process: Decision Making Capacity Assessment for Adults

Economic or Educationally Disadvantaged

The Department of Health and Human Services indicates that certain populations may require additional protections because they are economically or educationally disadvantaged.

Prospective subjects may have an economic vulnerability when they have the cognitive capacity to consent but are disadvantaged in the distribution of social goods and services such as income, housing or health care. There is a chance that the subject's distributional disadvantage could be exploited. For example, offers of large sums of money as payment for participation or access to free health care services for conditions not related to the research could lead some prospective subjects to enroll when otherwise they would not do so.

Educational disadvantage (including illiteracy) may be addressed by ensuring the consent documents are written in language that is easily understandable to participants. The possibility of illiteracy or limited reading skills must be taken into consideration. The material in the consent form should be read to the research participant and the consent process witnessed.

The IRB will safeguard all subject's rights and welfare by making sure that any possible coercion or undue influence is eliminated (e.g., compensation that is not commensurate with risk, discomfort, or inconvenience involved, or recruiting in institutional settings where voluntary participation might be compromised).

Individuals of Child Bearing Potential, Pregnant Individuals and Fetuses

The revised Common Rule 45 CFR 46 (2018) no longer classifies pregnant individuals as vulnerable. The Carilion IRB adheres to the regulatory requirements of 45 CFR 46, Subpart B, which states that pregnant individuals or fetuses may be involved in research only if the conditions outlined in the regulations are met. These conditions include scientific appropriateness, acceptability of potential risks and benefits, compliance with the additional informed consent provisions, absence of any inducements (monetary or otherwise) to terminate a pregnancy, and confirmation of the independence of the researchers from the decisions related to pregnancy termination and/or any decisions related to the determination of viability of a neonate.

Pregnant individuals should not be excluded from any phase of research unless the science of the project or the health of the subject will be compromised. Regarding clinical drug research, Phase I, II and III trials should have the proportion of pregnant individuals in the study that reflects the proportion of individuals in the population who will receive the drug when it is marketed, and should enroll numbers adequate to detect clinically significant sex differences in drug metabolism and response.

Pregnant women or fetuses may not be involved as participants in a human clinical research project unless:

- the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus, or
- if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means and any risk is the least possible for achieving the objectives of the research.

For a full list of all requirements, please refer to [45 CFR 46 Subpart B](#) § 46.204.

The informed consent of both the father and mother is needed unless:

- The research holds out the prospect of direct benefit for the pregnant individual
- 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
- The identity or whereabouts of the father cannot reasonably be ascertained
- The father is not reasonably available
- The pregnancy resulted from rape or incest

There are also specific requirements for research involving Neonates listed in 45 CFR 46, Subpart B. For detailed information, please refer to the last section of this document.

Other Vulnerable Groups

Vulnerable subjects include individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation. Vulnerable subjects can also be individuals who may be unduly influenced by a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy,

dental and nursing students; subordinate hospital and laboratory personnel; employees of the pharmaceutical industry and members of the armed forces. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, refugees, those incapable of giving consent and cognitively impaired subjects.

Following is a brief summary of potentially vulnerable groups:

Cognitive or Communicative Vulnerability

Prospective subjects who are insufficiently able to understand information, deliberate and make decisions about whether to participate in a proposed research study have cognitive or communicative vulnerability. These subjects may be vulnerable in this way for one of three reasons:

- Capacity-related cognitive vulnerability – such as young children, or adults with cognitive impairments that affect decision-making, may lack capacity to make informed choices
- Situational cognitive vulnerability – these people do not lack capacity, but are in situations that do not allow them to exercise their capacity effectively, such as stressful emergencies
- Communicative vulnerability – subjects who speak or read different languages than the study investigators, so standard informed consent procedures will not suffice. They do not lack capacity but are in situations that do not allow them to exercise their capacity effectively.

Institutional Vulnerability

Subjects with the cognitive capacity to consent but are subject to the formal authority of others who may have independent interests in whether the prospective subject agrees to enroll in research may be subject to institutional vulnerability. This includes prisoners, enlistees in the military and college students when they are required to be research subjects for course credit or when such participation could affect their grades. There may be a risk that the subordinated status of these individuals will be exploited. (Also see the sections on prisoners and students.)

Medical Vulnerability

This category concerns potential subjects who have serious health conditions for which there are no satisfactory standard treatments (e.g., metastatic cancer or rare disorders). Seriously ill individuals are often drawn to research because they or their physicians believe it is the best alternative to standard treatment. It can be difficult for subjects to weigh the risks and benefits associated with the research. This type of vulnerability increases the risk that informed consent might be based on misunderstanding potential benefits or might be motivated by a desire to find a treatment. It also increases the chance of these subjects being exploited because they have unreasonable expectations about the benefits or investigators mislead them about risks and benefits.

Social Vulnerability

Prospective subjects may have a social vulnerability when they have the cognitive capacity to consent but belong to undervalued social groups. Social vulnerability is a function of the social

perception of certain groups, which includes stereotyping and can lead to discrimination. The perceptions devalue members of such groups, their interests, their welfare, or their contributions to society. These social perceptions are pervasive and often insidious and can affect persons' conceptions of certain groups.

The IRB will consider whether a potential subject's ability to exercise free choice is limited in some way, and if so, what types of special protections are required for these vulnerable populations.

Students/Staff of the Principal Investigator (PI)

In addition to conducting research in accordance with federal regulations involving research, projects that are utilizing students as subjects must also meet the requirements of The Family Educational Rights and Privacy Act (FERPA) (34 CFR 99). FERPA is a federal law that protects the privacy of student education records. It applies to all schools that receive funds under an applicable program of the U.S. Department of Education.

FERPA gives parents certain rights with respect to their children's education records. These rights transfer to the student when the student reaches the age of 18 or attends a school beyond the high school level. In addition to having certain rights to inspect and review a student's education records, parents or eligible students must provide written permission prior to the release of information from a student's education record. This includes information that is to be provided from education records to researchers.

PIs intending to recruit students or staff to participate in a research study should ensure that the recruitment plan minimizes the perception of undue influence or coercion, as these populations are vulnerable to perceived pressures to appear cooperative of the PI, colleagues, the research, and/or the institutions involved in the research. The recruitment plan should assure potential participants that their relationship with the researchers and their grade, standing, employment, status, etc. are not dependent on and will not be otherwise affected by their decision to participate in a study. When research participation is a course expectation, when extra credit or course credits are offered for participation, or when recruitment occurs in a classroom, students must be informed of non-research alternatives involving comparable time and effort to fulfill the course requirements or to obtain the credit to minimize the possibility of undue influence. Students cannot be penalized for refusing to participate in research as all research participation must be voluntary, according to federal regulations.

Prior to approving a research project involving student records, the IRB will need assurance from the researcher that the requirements of FERPA have been met. For more information, please go to <http://www.ed.gov/policy/gen/guid/fpco/ferpa/index.html>

Specific Requirements for Research Involving Viable or Nonviable Neonates or Neonates of Uncertain Viability

For Neonates of uncertain viability and Nonviable Neonates to be included in any research project, strict Federal Guidelines must be followed. A full list of those guidelines can be found by viewing [45 CFR 46, Subpart b § 46.205.](#)

Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in the research only to the extent permitted by and in accord with the requirements of

the pre-2018 Requirements or the 2018 Requirements, as applicable, and [45 CFR 46, Subpart D](#). Additional Protections for Children Involved as Subjects in Research. Please refer to the Children Section of this document.

Additional Considerations for Research involving, after delivery, the placenta, the dead fetus or fetal material.

- Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

For Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, refer to [45 CFR 46, Subpart b § 46.207](#)