

**The Carle Foundation
IRB Policy 501**

Subject	Vulnerable Populations		
Approval	Dec 2006	Review	Jun 2009
Scope	These policies and procedures apply to all research under the jurisdiction of the IRB.		
Purpose	To provide guidance for research involving vulnerable populations.		

Statement of Policy

1. Certain populations may be prone to be vulnerable to the consequences of participation in a research study. This vulnerability may be either through limited self-determination capacity or through exposure to external undue influence. The extent of protection afforded should depend upon the risk of harm, the likelihood of benefit, and the ability of the individual to make reasoned decisions. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.
2. Potentially vulnerable groups may include:
 - a. Prisoners
 - b. Children
 - c. Pregnant women and fetuses
 - d. Cognitively impaired subjects
 - e. Other vulnerable groups

Specific Policies

1. Prisoners

- a. All research involving prisoners must be reviewed by the Carle IRB and will be reviewed in accordance with Subpart C of the federal regulations found at 45 CFR 46.301 through 45 CFR 46.306.
- b. This policy applies whenever any human subject in a research protocol becomes a prisoner at any time during the protocol, *e.g.*, after the research has commenced. This is necessary because it is unlikely that review of the research and the consent document contemplated the constraints imposed by the possible future incarceration of the subject.
 - If a subject becomes a prisoner after enrollment in research, all research interactions and interventions with, and obtaining of identifiable private information about, the subject must cease. The Investigator is responsible for reporting this situation in writing to the IRB immediately. If the Investigator believes, based on his or her medical judgment, that it is in the best interest of the incarcerated subject to continue in the study, the Investigator shall so advise the IRB Chair in writing, describing with specificity the reason for such a continuation of intervention. If the IRB Chair (or member designated by the Chair, if the Chair is not a physician) concurs that it is in the best interest of the subject to continue an intervention, the Chair may, in writing, agree to such continuation until the IRB can review the protocol at the next convened IRB meeting.
 - At the earliest opportunity after receiving the Investigator's notice or otherwise becoming aware of the prisoner status of a subject, the IRB should review the protocol again with a prisoner representative as a member of the IRB. The IRB should take special consideration of the conditions of the subject being a prisoner.
 - After review, the IRB can either (a) approve the involvement of the prisoner-subject in the research in accordance with this policy or (b) determine that this subject must be withdrawn from the research.
 - Additionally, the IRB should confirm that, when appropriate, the informed consent process includes information regarding situations when subsequent incarceration may result in termination of the subject's participation by the Investigator.

2. Children

- a. The special vulnerability of children makes consideration of involving them as research subjects particularly important in the deliberations of the IRB. All research involving children must be reviewed by the Carle IRB and will be reviewed in accordance with Subpart D of the federal regulations found at 45 CFR 46.401 through 45 CFR 46.409.
- b. **Parental Consent.** Children may be subjects of research only if informed consent is obtained from the parents or legal guardian. The IRB will determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered not reasonably available.

Specific Policies (cont.)

The regulations provide that the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 (minimal risk research) or 45 CFR 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) [45 CFR 46.408(b)]. Where research is covered by 45 CFR 46.406 and 45 CFR 46.407, and permission is to be obtained from parents, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child [45 CFR 46.408(b)].

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with state law, for clinical investigations to be conducted under 21 CFR 50.51 or 50.52. Where clinical investigations are covered by 21 CFR 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with state law.

Permission by parents or guardians must be documented in accordance with and to the extent required by 21 CFR 50.27. Participation of children in clinical investigations that are wards of state is governed by 21 CFR 50.53, 50.54 and 50.56.

- c. **Assent of Children.** The IRB must determine that adequate provisions are made for soliciting the assent of children when, in the judgment of the IRB, the children are capable of providing assent (21 CFR 50.55). In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate. When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

Children over the age of 7 can agree to participate in the research and provide written assent. Assent forms should be provided based on reasonable age ranges for comprehension. When the research offers the child the possibility of a direct benefit that is important to the health or well being of the child, and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary. Additionally, in such circumstances a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion.

- d. **Waiver of Assent.** The assent of the child is not a necessary condition for proceeding with the clinical investigation if the IRB determines:
- That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or
 - That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.
 - Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:
 - The clinical investigation involves no more than minimal risk to the subjects;
 - The waiver will not adversely affect the rights and welfare of the subjects;
 - The clinical investigation could not practicably be carried out without the waiver; and
 - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

3. Pregnant Women, Fetuses and Neonates

- a. Pregnant women or fetuses prior to delivery may be involved in research if the conditions listed at 45 CFR 46.204(a) through 45 CFR 46.204(j) are met.
- b. After delivery, neonates of uncertain viability and nonviable neonates may be involved in research if all of the conditions listed at 45 CFR 46.205(a) are met.
- c. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by federal regulations unless the additional conditions listed at 45 CFR 46.205(b) are met.
- d. After delivery, a nonviable neonate may not be involved in research covered by federal regulations unless all of the additional conditions listed at 45 CFR 46.205(c) are met.
- e. A neonate, after delivery, that has been determined to be viable is a child as defined by 45 CFR 46.402(a) and may be included in research only to the extent permitted by and in accordance with the requirements of 45 CFR 46 subparts A and D.
- f. Research involving, after delivery, the placenta, the dead fetus, or fetal material.

Specific Policies (cont.)

- 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.
- If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent regulations apply.

4. Cognitively Impaired Subjects

Cognitively Impaired Subjects include those individuals having a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests. Although there are no federal regulations specifically written to address the needs of this vulnerable group, the IRB will generally follow the recommendations governing the conduct of research in children and of specific recommendations made by the National Commission.

- General Assumption of Competence.** As a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent unless there is evidence of serious mental disability that would impair reasoning or judgment. Even those who do have a diagnosed mental disorder may be perfectly able to understand the matter of being a research volunteer, and quite capable of consenting to or refusing participation. Mental disability alone should not disqualify a person from consenting to participate in research; rather, there should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.
- Evaluation of Mental Status of Subjects.** In the case of research involving subjects who may be cognitively impaired, the investigator must propose adequate procedures for evaluating the mental status of prospective subjects to determine whether they are capable of consenting. Determination of capacity to consent or inability to withdraw may be made through a standardized measure and/or consultation with another qualified professional in accordance with the level of risk and the prospect of benefit. When appropriate, the patient's physician or other health care provider may be consulted. The investigator must explain and the IRB must determine whether procedures for evaluating the mental status of subjects are appropriate both to the subject population and the nature of the proposed research.
- Selection of Subjects.** Research involving individuals with diminished capacity to consent should have a direct relationship to their illness or condition. Particular attention should be paid to institutionalized individuals, as issues of dependence and coercion may be factors that may compromise the voluntary nature of their participation in research. For this reason, subjects should be recruited from among noninstitutionalized populations whenever possible.
- Risk Determination.** Generally the IRB will follow the recommendations of the National Commission when determining the degree of risk and its impact on the approvability of a research protocol in cognitively impaired subjects as follows:
 - A minor increase over minimal risk may be permitted in research involving those institutionalized as mentally disabled, but only where the research is designed to evaluate an intervention of foreseeable benefit to their care.
 - For research that does not involve beneficial interventions and that presents more than minimal risk, the anticipated knowledge sought should be of vital importance for understanding or eventually alleviating the subject's disorder or condition.
- Limiting Risks.** Investigators should include a description of appropriate psychological or medical screening criteria to prevent or reduce the chances of adverse reactions to the therapeutic and research procedures. When appropriate, IRBs might want to require that other health care providers be consulted to ensure that proposed research procedures will not be detrimental to ongoing therapeutic regimens. Specific diagnostic, symptomatic, and demographic criteria for subject recruitment should be described in the research proposal.

Any plan to hospitalize subjects or extend hospitalization for research purposes should be justified by the investigator. The effects of separation from supportive family or friends, of disruption in schooling or employment, and the question of responsibility for bearing any additional costs should be carefully considered. Methods for assuring adequate protections for the privacy of the subjects and the confidentiality of the information gathered should also be described by the investigator.

Specific Policies (cont.)

- f. **Informed Consent.** Under Illinois law, the patient or the patient's guardian, spouse, parent, or authorized agent may consent to the patient's participation in research if the patient is unable to consent; it may be necessary to consult with legal counsel concerning who may serve as the patient's authorized agent. If someone other than the patient consents, the assent of the prospective subject should be required. An advocate or consent auditor may be appointed to ensure that the preferences of potential subjects are elicited and respected. If a cognitively impaired adult subject objects to participate in a research study, that decision should be binding, except when the individual's participation is specifically authorized by a court of law, the intervention is expected to provide a direct health benefit to the subject, and the intervention is available only in the context of the research. This is in keeping with the National Commission's recommendation that "despite the fact that consent may be obtained from a legally authorized representative or guardian, the feelings and expressed wishes of an incompetent person should still be respected".

Studies involving subjects who are decisionally impaired may take place over extended periods. The IRB will consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. In particular, the IRB may require that Investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB will consider whether, and when, it should require a reassessment of decision-making capacity.

5. **Other Vulnerable Groups.** Although federal regulations list vulnerable groups, other vulnerable groups may include mentally impaired persons, employees of the Institution, Sponsor or Investigator, terminally ill patients, disadvantaged individuals, and the very elderly. The IRB will determine special protections for these groups on a case-by-case basis, taking into account the risks and benefits and other protections afforded by institutional policies and state and federal law.

- a. **Subjects in "Treatment IND" Studies.** Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications that have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. IRBs must ensure that potential subjects are fully aware of the risks involved in participation.

The IRB will also pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs, to ensure equitable selection and the involvement in research of vulnerable populations, particularly the economically disadvantaged persons [see 21 CFR 56.111(a)(3)]. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. The stated purpose of the Treatment IND exemption is to facilitate the availability of promising new drugs to desperately ill patients while obtaining additional data on the drug's safety and effectiveness. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB will need to balance this interest against the possibility that unless the Sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval. In approving a Treatment IND, the IRB requires the following additional information:

- A copy of the approval of the Treatment IND by the FDA;
- A certification that all known and possible adverse events, whether considered to be significant or not, have been described in the informed consent;
- A certification that the population which the Investigator plans to enroll the Treatment IND meets statutory and regulatory requirements for inclusion in the Treatment IND;
- A certification from the Sponsor that the amount charged for the test article reflects only costs of the drug's manufacturer, research, development and handling;
- A certification from the Sponsor that clinical trials on the test article are underway and continue unimpeded and the Sponsor will actively pursue marketing approval of the drug with "due diligence."

Reference

45 CFR 46 [Subparts A, B,C and D]

Approval On File

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