

SOP: SC 501 Version No.: 06 Effective Date: 12/6/10	VULNERABLE POPULATIONS	Supersedes Document Dated: 7/1/08
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Steering Committee approved 10/17/11

1. POLICY

All research studies that include enrollment of vulnerable populations must meet certain criteria under federal and state law before the IRB can approve such research studies. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity, wholly or in part, because of illness, mental disability, or circumstances that severely restrict liberty. willingness to volunteer in a research study may be unduly influenced by the expectation (whether justified or not) of benefits associated with participation. Some persons are in need of extensive protection, even to the point of excluding them from activities that may harm them. Other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. Indeed, some types of research may, in and of themselves, create a vulnerable group – that is, the subjects lose their autonomy or are exposed to unknown risks. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations. The central issue for the IRB to consider is whether the potential subject's ability to exercise free choice is limited in some way. Potentially vulnerable groups may include:

- Prisoners
- Children
- Pregnant women, fetuses and neonates
- Decisionally incapacitated
- Non-English speaking subjects
- Nursing home residents or others living in institutional settings
- Patients in emergency situations

Specific Policies

Terms used in this policy, but not defined herein shall have the meanings set forth in the Glossary.

1.1. Prisoners

1.1.1. Definitions

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A. "Prisoner" is defined by HHS regulations at 45 CFR part 46.303(c) as "any individual involuntarily 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."

B. Parolees who are detained in residential treatment (i.e. residing in a treatment center) as a condition of parole (which is an alternative to incarceration in a penal institution) are Prisoners, for purposes of research taking place within that facility. However, persons living in the community and sentenced to court-supervised monitoring or treatment, regardless of whether they are described as parolees or probationers, are not Prisoners. Persons wearing monitoring devices are generally not considered to be Prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. OHRP may be contacted when questions arise about research involving these populations.

C. The definition of minimal risk for research involving Prisoners can be found at 45 CFR 46.303(d). This definition, promulgated in 1978, differs from the definition of minimal risk in subpart A of 45 CFR 46. See 45 CFR 46.102(i).

For research involving Prisoners, the definition of minimal risk is "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."

1.1.2. Prisoners who Participate in Research

A. For review of research involving Prisoners by the convened Aurora IRB, the Primary Reviewer takes the IRB through the determinations in SC 501-A to determine whether the research can be approved and to make all other required determinations. The Aurora IRB provides protocol -specific determinations justifying each regulatory determination to the RSPP staff taking minutes, and the RSPP staff document in the minutes the regulatory determinations and protocol-specific findings justifying those determinations.

B. For review of research involving Prisoners using the expedited procedure, the reviewer uses SC 501-A to determine whether the research can be approved and to make all other required determinations. The reviewer documents on the review form (SC 501-A) the regulatory determinations and protocol-specific findings justifying those determinations.

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1.1.3. When Subjects Become Prisoners During a Research Protocol

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.

A. If a subject becomes a prisoner after enrollment in research, the investigator is responsible for reporting this situation to the RSPP office immediately on a Significant New Findings report (RR 403-F) per policy RR 403.

B. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until all of the requirements of subpart C of the DHHS regulations have been satisfied with respect to the relevant protocol. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chair may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

C. 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 Aurora IRB, in conjunction with the other requirements of this policy. The IRB should take special consideration of the conditions of being a Prisoner.

D. Upon this review, the Aurora 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.

E. Additionally, the Aurora IRB should confirm that, when appropriate, the informed consent process includes information regarding when subsequent incarceration may result in termination of the subject's participation by the investigator without regard to the subject's consent.

1.1.4. The Aurora Facility where the research is to be conducted must certify to the Secretary of HHS in a form and manner prescribed by the Secretary that the federal requirements have been satisfied by the Aurora IRB.

1.2. Children

1.2.1. Definitions

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“Children” means 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.

In Wisconsin, “children” are generally those persons under the age of 18 years.

In Wisconsin, emancipated minors are not subject to Subpart D of 45 CFR 46 and are consented as adults. Emancipated minors include individuals under 18 years of age who are or have been married, who have given birth or who have been freed from the care, custody and control of their parents with little likelihood of returning to the care, custody and control prior to marriage or prior to reaching the age of majority. [Wis. Stat. 48.375(2)(e), 765.02(2), 880.04(1), 895.037(1)(c), 54.46(6)].

In Wisconsin, non-emancipated minors may consent to certain treatment or procedures without parental permission.

“Guardian” means an individual who is authorized under applicable law to consent on behalf of a child to general medical care, specifically including, in FDA regulated research, when general medical care includes participation in research.

Under Wisconsin law, in addition to a parent, a court-appointed “guardian” for an unemancipated child under the age of 18 has the authority to consent to major medical, psychiatric and surgical treatment. [Wis. Stat. 48.023(1)].

1.2.2. Rationale for Research Involving Children

Enrolling children in research studies presents especially difficult considerations for IRBs. Arguments for including children in research are:

- A. Children differ markedly from adults, and therefore, these models cannot substitute as alternatives to testing in children.
- B. Lack of appropriate research in children will increase their risk of harm from exposure to practices and treatments untested in this population. In addition, new therapies could not be developed for diseases that specifically affect children.

1.2.3. IRB Considerations

- A. For review of research involving children by the convened Aurora IRB, the Primary Reviewer takes the Aurora IRB through the determinations in SC 501-B to determine whether the research can be approved and to make all

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other required determinations. The Aurora IRB provides protocol specific determinations justifying each regulatory determination to the RSPP staff taking minutes, and the RSPP staff document in the minutes the regulatory determinations and protocol specific findings justifying those determinations.

B. For review of research involving children using the expedited procedure, the IRB Reviewer uses SC 501-B to determine whether the research can be approved and to make all other required determinations. The IRB Reviewer documents on the review form (SC 501-B) the regulatory determinations and protocol specific findings justifying those determinations.

1.3. Pregnant Women, Fetuses and Neonates

1.3.1. Research Involving Pregnant Women, Live Fetuses, and Neonates

A. For review of research involving pregnant women, fetuses, and neonates by the convened Aurora IRB, the Primary Reviewer takes the Aurora IRB through the determinations in SC 501-C to determine whether the research can be approved and to make all other required determinations. The Aurora IRB provides protocol specific determinations justifying each regulatory determination to the RSPP staff taking minutes, and the RSPP staff document in the minutes the regulatory determinations and protocol specific findings justifying those determinations.

B. For review of research involving pregnant women, fetuses, and neonates using the expedited procedure, the IRB Reviewer uses SC 501-C to determine whether the research can be approved, and to make all other required determinations. The IRB Reviewer documents on the review form (SC 501-C) the regulatory determinations and protocol-specific findings justifying those determinations.

1.3.2. Research involving, after delivery, the placenta, the dead fetus, or fetal material.

A. 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. In addition, any Investigator who intends to conduct research using a placenta, dead fetus, or fetal material should contact the FDA to determine whether an IND needs to be held.

B. If information associated with material described in Section 1.3.2.A above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those

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individuals, those individuals are research subjects and all pertinent regulations apply

1.4. Mentally Ill, Developmentally Disabled, Alcohol or Drug Abusers

1.4.1. State law has additional requirements for prospective research subjects who are receiving treatment for mental illness, developmental disabilities or alcohol or drug abuse as an inpatient. The Aurora IRB must meet the following requirements before approving such research studies:

A. The Aurora IRB must have one member who satisfies Section 1.2.1(v) of Policy OR 201 when reviewing the research study.

B. The Aurora IRB must designate a consent monitor who is authorized to: validate the informed consent process (to ensure voluntary enrollment); and terminate participation by subjects immediately upon any violation of the subject’s rights under Wis. Stat. §51.61 or upon the subject’s withdrawal of consent.

C. The Aurora IRB must consider also the requirements under federal and state law related to release of private health information set forth in Policy HI 1201.

D. The Aurora IRB must ensure that a psychiatrist licensed in the State of Wisconsin has assessed the prospective subject prior to his/her enrollment in the study, and that such psychiatrist is listed as a sub-investigator in the protocol.

1.5. Other Vulnerable Groups

Although federal regulations list vulnerable groups, other potentially vulnerable groups which are not set forth above may include mentally impaired persons, employees of the Sponsor, Investigator, or institution, members of a group with hierarchical structure (e.g., students and members of the armed forces), minority groups, unemployed, homeless, nomads, refugees, educationally or economically disadvantaged, terminally ill patients, patients suffering from an incurable disease, and the very elderly. The Aurora 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.

1.6. Subjects in “Treatment IND” or “Treatment IDE” Studies

Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving

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medications or devices which 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 risks involved. IRBs must ensure that potential subjects are fully aware of the risks involved in participation.

IRBs should also pay particular attention to Treatment INDs and IDEs in which the subjects will be charged for the cost of the drugs or devices. The question here is one of equitable selection and the involvement in research of vulnerable populations, particularly 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 and Treatment IDE exemption is to facilitate the availability of promising new drugs and devices to desperately ill patients while obtaining additional data on the test article's safety and effectiveness. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. IRBs will need to balance this interest against the possibility that, unless the sponsor can charge for the drug or device, it will not be available for treatment use until it receives full FDA approval [See also OHRP IRB Guidebook Chapter 3].

1.7. Decisionally Incapacitated Subjects.

Refer to Policy IC 702 for the Aurora IRB policy on inclusion of decisionally incapacitated adults into research.

2. SCOPE

These policies and procedures apply to all research studies submitted to the Aurora IRB in which vulnerable subjects may be enrolled.

3. APPLICABLE REGULATIONS, GUIDELINES AND STANDARDS

The Belmont Report

45 CFR 46: Subparts B, C, D

45 CFR 46.122, 305(c)

21 C.F.R. 50

21 CFR 56.111, 107, 50

Wis. Stat. §51.30

Wis. Stat. §51.61

Wis. Stat §155.10

Wis. Admin Code HFS 92

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Wis. Admin. Code HFS 94

OHRP IRB Guidebook

FDA Information Sheets

E11 Clinical Investigation of Medicinal Products in Pediatric Populations

ICH Harmonized Tripartite Guidelines: EG Guideline for good clinical practice, 1 May 1996

OPRR Reports, Number 94-01 dated April 25, 1994

OHRP Guidance on Written IRB Procedures Dated January 15, 2007

OHRP Guidance on the Involvement of Prisoners in Research Dated May 23, 2003

Executive Directive 36, dated April 1994 from the State of Wisconsin Department of Corrections

CBER letters to Sponsors/Researchers - Fetal Cellular or Tissue Products In Human Clinical Studies November 30, 2002

AAHRPP Standard II-4, Elements II.4.A. and II.4.B.

4. REFERENCES TO OTHER APPLICABLE SOPS

SOP 201

SOP 402

SOP 403

SOP 701

SOP 702

SOP 1201