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| DEPARTMENT: Clinical Operations Group – Research | POLICY DESCRIPTION: IRB Required Additional Protections For Vulnerable Subjects/Children |
| PAGE: 1 of 6 | REPLACES POLICY DATED: 3/1/12, 9/1/13 |
| EFFECTIVE DATE: February 22, 2019 | REFERENCE NUMBER: COG.IRB.009 (formerly CSG.IRB.009) |
| APPROVED BY: Ethics and Compliance Policy Committee | |

SCOPE: This policy pertains to all Company-affiliated facility-run Institutional Review Boards (IRBs).

PURPOSE: To provide guidance for IRBs regarding protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, or other persons deemed by the IRB as needing additional protections. The IRB must also ensure that it has adequate representation on the Board to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

IRBs must review the regulations referenced in the reference section of this policy to understand the requirements pertaining to potentially vulnerable subject populations.

POLICY:

The IRB reviews the following elements for research involving vulnerable subjects:

1. The investigators must not over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available “captive” population.
2. IRBs must be knowledgeable about applicable federal, state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research-related procedures, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research-related procedures.
3. Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring each subject’s capacity, understanding, and informed consent and assent. When weighing the decision of whether to approve or disapprove research involving vulnerable subjects, the IRB must look to see that such procedures are part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.

The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions, or that a mental status examination be performed to determine decision-making capacity.

| | |
|--|---|
| DEPARTMENT: Clinical Operations Group – Research | POLICY DESCRIPTION: IRB Required Additional Protections For Vulnerable Subjects/Children |
| PAGE: 2 of 6 | REPLACES POLICY DATED: 3/1/12, 9/1/13 |
| EFFECTIVE DATE: February 22, 2019 | REFERENCE NUMBER: COG.IRB.009 (formerly CSG.IRB.009) |
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PROCEDURE:

1. **Pregnant Women, Fetuses and Human in Vitro Fertilization**

Research involving pregnant women and fetuses should involve the least possible risk. The IRB must document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. The IRB must be familiar with the specific federal laws located at 45 CFR 46 Subpart B pertaining to the following conditions:

- a. Research involving pregnant women;
- b. Research directed towards the fetus *in utero*;
- c. Research involving the fetus *ex utero*; and
- d. Research involving dead fetuses, fetus material, or placenta.

It is important to note that these regulations serve as a guideline for all research as appropriate (but without reporting obligation to OHRP) except they are legally required if the research is conducted or supported by DHHS or otherwise falls under the jurisdiction of Subpart B of the Common Rule (45 CFR 46); or

Additionally, the IRB should be familiar with the following special considerations:

- a. National Commission for the Protection of Human Subjects recommendations concerning abortions; and
- b. The President's Council on Bioethics recommendations concerning Stem Cell Research.

2. **Research Involving Prisoners**

Research involving prisoners requires special considerations. Prisoners may have a limited ability to make truly voluntary and un-coerced decisions about whether or not to participate as research subjects. Research expected to involve prisoners as participants should not be subjected to expedited review.

The IRB must be familiar with the specific federal laws located at 45 CFR 46 Subpart C pertaining to review of research on prisoners. It is important to note that these regulations serve as a guideline for all research as appropriate (but without reporting obligation to OHRP) except they are legally required if: the research is funded by DHHS or otherwise falls under the jurisdiction of Subpart C of the Common Rule (45 CFR 46); or

Any IRB conducting a review under 45 CFR 46 Subpart C must be knowledgeable of the Subpart C requirements regarding having a prisoner's representative as a voting member as well as how to submit a "Subpart C Certification" to HHS.

3. **Children Involved as Subjects in Research**

IRBs are required to classify (as a whole or classify each individual arm of a research protocol) all non-exempt research with children as subjects into one of four categories. This classification

| | |
|--|---|
| DEPARTMENT: Clinical Operations Group – Research | POLICY DESCRIPTION: IRB Required Additional Protections For Vulnerable Subjects/Children |
| PAGE: 3 of 6 | REPLACES POLICY DATED: 3/1/12, 9/1/13 |
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must be documented. IRBs are then only permitted to approve three of those four categories without special permissions from federal authorities. The three categories that IRBs can approve and their requirements are:

- a. **Research not involving greater than minimal risk to the children.** To approve this category of research, the IRB must make the following determinations (45 CFR 46.404, 21 CFR 50.51):
 - i. the research presents no greater than minimal risk to the children; and
 - ii. adequate provisions are made for soliciting the assent of the children and the permission of at least one parent/guardian.

- b. **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.** To approve research when more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, the IRB must make the following determinations (45 CFR 46.405, 21 CFR 50.52):
 - i. the risk is justified by the anticipated benefits to the subjects;
 - ii. the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and
 - iii. adequate provisions are made for soliciting the assent of the children and the permission of at least one parent/guardian.
 - iv. [Note: placebo arms of studies do not fit this criteria and must be classified elsewhere.]

- c. **Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.** To approve research when more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, the IRB must make the following determinations (45 CFR 46.406, 21 CFR 50.53):
 - i. the risk of the research represents a minor increase over minimal risk;
 - ii. 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;

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|--|---|
| DEPARTMENT: Clinical Operations Group – Research | POLICY DESCRIPTION: IRB Required Additional Protections For Vulnerable Subjects/Children |
| PAGE: 4 of 6 | REPLACES POLICY DATED: 3/1/12, 9/1/13 |
| EFFECTIVE DATE: February 22, 2019 | REFERENCE NUMBER: COG.IRB.009 (formerly CSG.IRB.009) |
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- iii. 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 or amelioration of the disorder or condition; and
 - iv. adequate provisions are made for soliciting the assent of the children and the permission of both parent/guardians unless one is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child.
 - v. [Note: "healthy children" arms of studies do not fit this criteria and must be classified elsewhere.]
4. The fourth category of research (**Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children**) requires a special level of DHHS and/or FDA review beyond that provided by the IRB if federally-funded. This category is research that the IRB believes does not meet the conditions of 1.a, 1.b or 1.c above, 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, 21 CFR 50.54). In this situation, in order to approve the research, the IRB must refer the protocol to DHHS, OHRP and/or FDA for review as appropriate to their jurisdiction over the research. The research may proceed only if the Secretary of DHHS/FDA, or his or her designee, approves the research.
5. **Assent & Waiver of Assent**
 Assent of the child, regardless of the age, is required unless waived by the IRB. The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall 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 research under a particular protocol, or for each child, as the IRB deems appropriate. 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 research 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 research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with federal/state regulations and the relevant policy.
6. **Parental Permission and Waiver of Parental Permission**
 In addition to the provisions for waiver of assent, with the exception of FDA governed clinical investigations (where waiver of parental permission is not allowed except for meeting the criteria for Emergency Use and/or Planned Emergency Research, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian

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|--|---|
| DEPARTMENT: Clinical Operations Group – Research | POLICY DESCRIPTION: IRB Required Additional Protections For Vulnerable Subjects/Children |
| PAGE: 5 of 6 | REPLACES POLICY DATED: 3/1/12, 9/1/13 |
| EFFECTIVE DATE: February 22, 2019 | REFERENCE NUMBER: COG.IRB.009 (formerly CSG.IRB.009) |
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permission is not a reasonable requirement to protect the subjects, the IRB may waive parental or guardian consent. Note that parental permission is required unless waived by the IRB. Examples may include research involving older adolescents and treatment for which they may, under applicable state law, consent on their own behalf (e.g., treatment for sexually transmitted diseases or drug abuse). In other research (e.g., research on child abuse or neglect), there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. The IRB may waive the consent requirements provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Children who are wards of the state or any other agency, institution, or entity can be included in research categorized in certain classes designated above (specifically either "Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition" or "Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children") only if such research is:

- a. Related to their status as wards; or
- b. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

In addition to the above, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. The advocate need not be present for nor are they required to cosign the informed consent. They only need to be knowledgeable of the child's participation in the study.

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|--|---|
| DEPARTMENT: Clinical Operations Group – Research | POLICY DESCRIPTION: IRB Required Additional Protections For Vulnerable Subjects/Children |
| PAGE: 6 of 6 | REPLACES POLICY DATED: 3/1/12, 9/1/13 |
| EFFECTIVE DATE: February 22, 2019 | REFERENCE NUMBER: COG.IRB.009 (formerly CSG.IRB.009) |
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7. Research Involving Decisionally-Impaired Subjects

Decisionally-impaired individuals are those who have a (temporary or permanent) diminished capacity for judgment and reasoning due to psychiatric, organic, developmental, or other disorder (whether temporary or permanent) that affects cognitive or emotional functions. Other individuals who may be considered decisionally-impaired, with limited decision-making ability, are individuals under the influence or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

There are no regulations specific to research involving decisionally-impaired persons. As with all research subjects the IRBs must carefully consider whether additional safeguards should be added to the proposed research to provide additional protection for these subjects.

Numerous articles to assist an IRB in the efforts to protect human research subjects with decisional impairment are found in recent publications. Examples of these documents may be found at <http://bioethics.gov>.

REFERENCES:

1. IRB Related Definition and Common Acronyms Policy, [COG.IRB.001](#)
2. Clinical Operations Group Research Policies in the COG.IRB series (COG.IRB.001 through COG.IRB.011)