1.0 POLICY

1.1 Background

1.1.1 “Children” are persons who have not attained the legal age for consent to treatments or procedures involved in research and clinical investigations under the applicable law of the jurisdiction in which the research will be conducted. Children are a vulnerable population. [45 CFR §46.602 (a)] [21 CFR§ 50.3]

1.1.2 Note that under Alabama law the legal age of majority at which people can consent to research is 18 unless there are specific circumstances. See Guidance Document on Alabama law.

1.1.3 Investigators wishing to include persons younger than 18 should consider whether a waiver of parental permission or a waiver of documentation of informed consent is appropriate.

1.1.4 Because of their unique vulnerability, the involvement of children in research and clinical investigations makes their consideration particularly important in the deliberations of the IRB. At the same time, the IRB recognizes the importance of conducting scientifically sound and ethically designed studies with this population.

1.1.5 Two factors support the involvement of children in research.

1.1.5.1 Children differ markedly from both animals and adults, and therefore these models cannot substitute as alternatives to testing in children.

1.1.5.2 Lack of appropriate research in children will increase their risk of harm from exposure to practices and treatments untested within this population. Also, new therapies could never be developed for diseases or conditions that specifically affect children.

1.1.6 The involvement of children in research requires investigators to justify their use, describe special effort to reduce their risk, obtain permission from one or more parents or guardians, and, often assent from the child.

1.1.6.1 Assent” means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. [45 CFR §46.602 (b)] [21 CFR§ 50.3(n)]

1.1.7 Other regulations may apply to research with children. For instance, research with school age children may be subject to Department of Education rules such as FERPA and the Protection of Pupil Rights Amendment (PPRA) which identify categories of protected information for survey responses and give certain rights to students and
parents. See GUIDANCE: Family Educational and Privacy Rights Act (FERPA) and GUIDANCE: US Department of Education/No Child Left Behind Guidance. The Environmental Protection Agency also has special regulations for research involving children (40 CFR 26.304). Investigators are expected to be aware of and demonstrate conformity to these additional requirements.

1.2 Policy

1.2.1 The University of Alabama IRBs' membership shall include persons who can serve as advocates for children.

1.2.2 The University of Alabama IRBs does allow research with children to be considered for exempt status or expedited review with adequate justification.

1.2.3 The University of Alabama IRB shall review research involving children in accordance with federal and state regulations, principles of sound design, and consideration of children’s special needs within the context of each application.

1.2.4 Research involving children requires the IRB to consider the following within a pediatric population:

1.2.4.1 Determination of Probable Risks and Associated Discomforts

1.2.4.1.1 Procedures that usually present no more than minimal risk to a healthy child include urinalysis, obtaining small blood samples, EEG's, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests.

1.2.4.1.2 The assessment of the probability and magnitude of the risk, however, may be different in sick children, and may vary depending upon the diseases or conditions the participants have. For example, obtaining blood samples from a hemophiliac child may present more than minimal risk to the child. On the other hand, the IRB may consider that children suffering from chronic illnesses, who are accustomed to invasive procedures, are placed at minimal risk by their involvement in similar research procedures, in contrast to those children who have not had such experiences. The IRB must also consider the extent to which research procedures would burden any child, regardless of whether the child is accustomed to the proposed procedure.

1.2.4.1.3 Procedures that exceed the limits of minimal risk may be difficult to define in the abstract, but should not be too difficult to identify on a case-by-case basis. Riskier procedures might include the biopsy of internal organs, spinal taps or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress or directed at groups at risk of violent or self-destructive behaviors may also exceed minimal risk levels.

1.2.4.1.4 As with adults, children may experience psychological, social, or economic risks and threats to privacy. Stigmatic conditions, "labeling" a child by virtue of participation in a research group (e.g., aggressive child, failing academically, HIV+), substance abuse, illegal behaviors, and genetic tests
and findings are circumstances that investigators and IRB must consider if relevant to the application.

1.2.4.2 Determination of Possible Benefits:

1.2.4.2.1 When assessing potential benefits of research intervention, the IRB considers the differences in health status among potential participants. For example, a potential participant might be a normal, healthy child, or a child who has been exposed to a disease or a toxin (e.g., meningococcus or lead) where it is known that a percentage of the children exposed will actually experience untoward consequences. A child may also be in an early stage of disease, e.g., an HIV-infected child, or may actually suffer from disease or other significant medical condition. Thus, the IRB must take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

1.2.5 Wards of the State

1.2.5.1 The special protections for children set forth in Subpart D include additional limitations on some research involving children who are wards of the state or any other agency, institution or entity.

1.2.5.2 Where the research involves greater than minimal risk to the participants with no prospect of direct benefit to individual participants (45 CFR 46.406), or requires HHS Secretarial approval (45 CFR 46.407), the research must be either related to their status as wards, or else be conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as participants are not wards (45 CFR 46.409).

1.2.5.3 The IRB requires the appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as a guardian.

A. The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

B. One individual may serve as advocate for more than one child.

C. The advocate must be an individual who has the background and experience to act in the best interest of the child for the duration of the child’s participation in the clinical investigation.

D. The advocate must not be associated in any way (other than the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian.

1.2.6 The IRB is particularly concerned with the involvement of HIV-infected children who are in foster care, but who are also not wards. Many of these children are from racial or ethnic minorities. The IRB gives special attention to groups of children such as these who, while they need special protections, should not be denied the opportunity to participate in research that may potentially benefit them.
1.2.7 When institutionalized children are involved in research, the IRB does not allow the institutionalized children to be included as participants simply because of their availability to the investigator.

1.2.8 Classification of Risk

1.2.8.1 Federal regulations require the IRB to classify research involving children into one of four categories and to document the discussions of the risk and benefits on the research study. Minutes must document how the research protocol meets the required criterion for the particular category of risk and benefit:

1) Research that does not involve greater than minimal risk.

2) Research involving greater than minimal risk, but presenting the prospect of direct benefit to individual participants. Research in this category is approvable provided that (a) the study risks are justified by the anticipated benefit to the participant, and (b) the risk/benefit ratio is at least as favorable as any available alternative approach.

3) Research involving greater than minimal risk with no prospect of direct benefits to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition. Research in this category is approvable, provided that (2) the risk represents only a minor increase over minimal risk; (b) the intervention or procedure present experiences to participants that are reasonably commensurate with those inherent in their actual medical, dental, psychological, social, or educational settings; and the intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition that is of vital importance for understanding or ameliorating that disorder or condition.

4) Research that is not otherwise approvable under 45 CFR 46.404, 405, or 406 or 21 CFR 50.1 but which presents an opportunity to understand, prevent or alleviate serious problem affecting the health or welfare of children. (45 CFR 46.407)

1.2.8.2 If the IRB finds that a study falls into category 4 above and the research is governed by DHHS, such research may only be conducted if:

1.2.8.2.1 The IRB finds that the research represents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children, and:

1.2.8.2.2 The Secretary of DHHS, consulting with a panel of experts in pertinent disciplines, and following opportunity for public review and comment, determines either:

1. The research does in fact satisfy 45 CFR 46.404, 405, or 406, or:
2. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children;

3. The research will be conducted in accordance with sound ethical principles; and

4. Adequate provisions will be made for soliciting the assent of children and the permission of their parents or guardians.

1.2.8.3 If the IRB finds that a study falls into Category 4 and the research is governed by the FDA, such research may only be conducted if:

1.2.8.3.1 The IRB finds that the clinical investigation represents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children, and:

1.2.8.3.2 The Commissioner of Food and Drugs, consulting with a panel of experts in the applicable field or discipline (for example, science, medicine, education, ethics, or law) and a period for public review and comment, determines either:

1. The clinical investigation does in fact satisfy the conditions of 21 CFR 50.51., 52, and 53 as applicable, or

2. That the following conditions are met:

   A. The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children;

   B. The clinical investigation will be conducted in accordance with sound ethical principles; and

   C. Adequate provisions will be made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 21 CFR 50.55.

1.2.9 Parental Permission

1.2.9.1 Children may be participants of research only if informed consent/active parental permission is obtained from the parents or their legal guardian. The federal regulations state that permission from both parents is required but empowers IRBs to consider investigator requests to obtain consent from only one parent. The IRB determines whether the permission of both parents is necessary, and the conditions under which one parent may be considered not reasonably available.

1.2.10 Assent of Children
1.2.10.1 The IRB determines 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 (21 CFR 50.55).

1.2.11 Waiver of Assent

1.2.11.1 The assent of the child is not always a necessary condition for proceeding with the clinical investigation. The IRB may determine that assent is not necessary.

1.2.12 Research Conducted Outside the State of Alabama

1.2.12.1 Research or clinical investigations involving children conducted outside of Alabama, whether or not the principal investigator is from the University of Alabama, shall adhere to the applicable laws of the jurisdiction in which the research is conducted, regarding the legal age of consent and any other laws affecting the proposed research.

1.2.13 Responsibility

1.2.13.1 The Vice President for Research is ultimately responsible for this policy. Enabling parties include the Office of Research Compliance staff, the IRB chairs or designees, IRB members, investigators, and professors supervising student investigators.

2.0 PROCEDURE

2.1 Screening and Educational Guidance

2.1.1 The principal investigator submits the IRB application stating that the research will involve the use and participation of children and FORM: Application for Research With Children, which focuses on ethical and regulatory issues pertaining to the conduct of research involving children.

2.1.2 If the research involves children with another category of vulnerability (e.g., the children are cognitively impaired or are prisoners) the investigator completes the supplementary forms for research with those populations.

2.1.3 If the research sponsor has special requirements for protection of children, the investigator describes how those requirements will be met.

2.1.4 Upon receipt of the IRB review application, ORC staff will conduct a preliminary screening to determine whether the proposed research study involves the use of children as study participants. Subsequently, the ORC staff will provide (as necessary or requested) appropriate regulatory or educational materials applicable to children as vulnerable subjects for guidance during the IRB review.

2.1.5 The ORC, IRB chair, or designee will request a consultant review if it is determined additional expertise is needed during the Initial Full Review, Expedited Initial Review, or the Continuing Review process.
2.1.6 The ORC staff will verify that a member with expertise in research on children as a vulnerable population will be present at the convened IRB meeting or will submit comments in writing in advance of the IRB meeting. A consultant or other designated representative may also attend the convened IRB meeting or provide comments in writing.

2.2 Review Process

2.2.1 The IRB will review the application and determine whether the study protocol includes the enrollment and participation of children and whether appropriate safeguards have been considered and are in place.

2.2.2 As applicable and in addition to application elements required for all full board reviews, the IRB will consider and/or acquire information for special consideration of the following elements when reviewing research involving vulnerable children:

2.2.2.1 Inclusion/Exclusion criteria

2.2.2.2 Over-selection or exclusion of certain groups based upon perceived limitations

2.2.2.3 Recruitment and incentive strategies, including any possibly coercive inducements to children or parents/guardians

2.2.2.4 Degree of risk, risk minimization, and risk-benefit balance (Section 1.2.7)

2.2.2.5 Whether the children’s assent is desirable and if so, the adequacy of the assent plan (developmentally appropriate, includes elements of consent, obtained at an appropriate time in the consent process and in appropriate setting).

2.2.2.6 Specific laws governing the State of Alabama application to children which may have a bearing on the final approval of the research protocol (emancipated individuals, legally authorized representatives, age of majority for research consent, etc.)

2.2.2.7 Conformity to any special sponsor requirements for the protection of children.

2.2.2.8 Special requirements of federal funding agencies for studies conducted with their support.

2.2.2.9 The IRB will follow all relevant federal/state regulations or guidelines and internal IRB policies regarding vulnerable populations, in reviewing and approving research with children, because the involvement of children may involve other vulnerable populations (e.g., the children’s mothers are prisoners or the children are mentally disabled). These regulations and policies include:

2.2.2.9.1 Pregnant Women, Fetuses, and Human In-Vitro Fertilizations (45 CFR 46, Subpart B);

2.2.2.9.2 Research Involving Prisoners (45 CFR 46, Subpart C);
2.2.2.9.3 Research Involving Children (45 CFR 46, Subpart D; 21 CFR 50, Subpart D; and US Department of Education, Subpart D);

2.2.2.9.4 Research Involving Mentally Disabled Individuals;

2.2.2.9.5 Research Involving University of Alabama Students.

2.2.2.10 Any other aspects of the application that have implications for children as a vulnerable population.

2.2.3 Whether approval for one year is adequate or whether the project should be approved for less than one year, based on the nature of the research and the level of risk involved.

2.2.4 Whether the study should be flagged for routine post-approval monitoring based on the nature of the research and the level of risk involved.

2.2.5 The IRB will consider and deliberate each response indicated on the IRB application form applicable to research involving vulnerable subjects and the Form: Application for Research with Children. IRB approval will also document whether the IRB members acknowledge and agree with the description of all safeguards and risk assessments contained within the protocol as submitted by the Principal Investigator or what changes are required. ORC staff will document all discussions of controverted issues within IRB convened meetings in the minutes.

2.2.6 ORC staff will document in the minutes, specific findings or IRB determinations in accordance with IRB policy. The IRB does not need to reconsider pre-determined subjects during continuing reviews, unless changes to the protocol dictate otherwise.

3.0 REFERENCES

The Belmont Report
45 CFR 46: Subparts A, B, C, D
45 CFR 46.101, 46.115 (B), 46.116, 46.122
21 CFR 50: Subpart D 50.51, 50.52, 50.53, 50.54, 50.55, 50.56.
21 CFR 56.111
ORHP Guidance on Special Protections for Children as Research Subjects
ED: 34 CFR 98.4

4.0 RELATED SECTIONS

FORM: Application for Research Involving Children
GUIDANCE: Alabama Law on Children, Minors, Consent, and Other Research-Related Topics
GUIDANCE: A Pediatric Research “Assent” Decision Matrix
GUIDANCE: Examples of Assent Forms
GUIDANCE: US Department of Education/No Child Left Behind Guidance
POLICY: Waivers of Consent/Parental Consent
GUIDANCE: FERPA