Special Protections for Children as Research Subjects

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Children in Research

Understanding the regulations governing participation of children in research is vital.

Children are neither legally nor developmentally capable of consenting to their own treatment or participation in research.

No one can consent for an individual other than that person. As a result, a proxy, such as a parent, must provide permission in lieu of consent and children who are deemed capable, must provide their assent.

A person who has not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

21 CFR 50.3 CFR 46.402

The State of Vermont and the UVM IRB consider anyone under 18 to be a child.

Who is considered a child?

CFR 46.402- Definitions of Children in Research

(a) Children are 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.

(b) Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) Parent means a child's biological or adoptive parent.

(e) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

The Common Rule includes Subpart D: additional protections for children as research subjects

- Because children cannot protect their own interests, they are considered vulnerable in the research context.
- Children may be particularly vulnerable to undue influence and coercion due to the significant influence that parents and other authority figures (e.g. teachers, doctors) have over this population.
- Children should be included in research only when their participation is necessary to answer the research question and not out of convenience.

The Common Rule includes Subpart D: additional protections for children as research subjects

- Subpart D establishes risk - benefit categories for research involving children.
- Only research that fits into one of the 3 categories may be approved by an IRB
- A 4th category requires the approval of the Secretary of the Department of Health and Human Services. (UVM has never been presented with this type of research)

Pediatric Risk Level 1 - 45 CFR 46.404 Minimal Risk

- research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of **one** parent or guardian

“Multicenter study of patient-reported gastrointestinal symptoms in people with Cystic Fibrosis”

- One study visit, the PI will collect information about the child’s medical history, measure height and weight, and ask the child to complete four questionnaires asking about their health, digestive symptoms, and quality of life. Download an app onto their phone to ask future questions on QOL.
- Risks are minimal.
- Uncomfortable questions, time commitment, breach of confidentiality
- Only one parental signature is required
- A separate assent form was created for children 11-17.

Pediatric Risk Level II - 46.405:
Greater than Minimal Risk with a Prospect for Direct Benefit

Research offers a prospect for direct benefit when there is a reasonable and plausible expectation based on prior research, pre-clinical data or other basis that participants will receive a meaningful, clinical benefit.

The IRB applies a similar risk-benefit assessment process to research in this category as a clinician and patient would for other types of clinical decision-making, namely that the proposed participation offers benefits that outweigh the probability and magnitude of harm.

Permission of a **single** parent and assent of the child (if applicable) are required for research approved under #46.405

“A Phase III, Randomized, Double Blind, Placebo Controlled Study of AeroVanc for the Treatment of Persistent Methicillin Resistant Staphylococcus Aureus Lung Infection in Cystic Fibrosis Patients”

- Objectives of the study are to learn more about the effectiveness and safety of a new powder form of vancomycin, called AeroVanc, that can be used with a reloadable capsule inhaler in patients with cystic fibrosis who have a chronic methicillin-resistant Staphylococcus aureus (MRSA) lung infection
- Participants will receive either AeroVanc or placebo to be taken by inhaler twice daily in 28-day on/off dosing cycles for 24 weeks
- Study visits will include blood draws, sputum or throat swab collection, physical exams, and procedures such as spirometry and electrocardiograms

Pediatric Risk Level II - 46.405:
Greater than Minimal Risk with a Prospect for Direct Benefit

- More than minimal risk study
- Risks include: cough, increased mucus, bronchospasm, and allergic reactions like rash, itching, and difficulty breathing.
- Benefits include: potential improvement of lung function
- Only one parental signature is required
- A separate assent form was created for children 11-17.

Pediatric Risk Level III - 46.406:
Greater than Minimal Risk Without Prospect for Direct Benefit

If the research activity or a component of the research is purely for research purposes and is not for the participants direct benefit, the IRB can only approve the research if the risks are not more than a minor increase above Minimal Risk.

Since the meaning of the definition of minimal risk is controversial, so is the definition of minor increase. It is the investigator's responsibility to provide the IRB with as much information as possible about the probability and magnitude of all possible harms from the procedure or intervention.

Permission of **both** parents and assent of the child (if applicable) are required for research approved under §46.406.

Pediatric Risk Level III - 46.406:
Greater than Minimal Risk Without Prospect for Direct Benefit

- intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding of the subjects' disorder or condition;
- adequate provisions are made for soliciting assent of the children and permission of both their parents

Perception of Physical Exertion in Healthy Weight and Obese Adolescents: A Pilot Study

- The study included 40 children ages 13-18 years. 20 normal weight, 20 healthy weight
- 2 testing sessions including body composition measures, physiological measures, submaximal and maximal treadmill exercise, and nutrition and physical activity questionnaires.
- DEXA x-ray scan percentage of fat, lean body mass and bone mineral density in the study participants
- Even though the amount of radiation the children are exposed to is small, with any exposure to radiation there are potential risks. The risk to children may be increased compared to adults because of developing organs. For example, adolescent female breast tissue is much more sensitive to radiation, and the adolescent male and female reproductive organs are also more sensitive to radiation exposure.

Pediatric Risk Level IV - 45 CFR 46.407
Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

- If the IRB does not believe that a proposed research activity fits any of the three categories, but that it does present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB may forward that proposed activity to the HHS Secretary for review under conditions identified in section 407 of the regulations.

- UVM has never had a proposed protocol of this nature

Child Assent

An child’s affirmative agreement (verbally or written) to participate in research obtained in conjunction with permission from the child’s parents or legally authorized representative.

Child Assent

- Assent is typically conducted with children 11 – 17 .
- The assent of a child ***is not*** a necessary condition for proceeding with the research if the IRB finds that the capability of some or all of the children is so limited that they cannot be reasonably 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.
- Permission of the parents/guardians is still a requirement.

Child Assent Process Overview

- The process of asking a child to participate in research should be carefully planned and implemented, using age-appropriate language and methods, for any child who is considered capable of understanding and providing assent. This process should include a clear explanation (verbally, and in written form when applicable) that conveys:

- what the study is about;
- why the child is eligible/being invited to participate in the study;
- procedures the child will be expected to take part in;
- potential risks and/or discomforts to the child;
- potential benefits to the child or society;
- that the child is completely free to choose whether or not to participate, and may withdraw at any time without negative consequences;
- an invitation to ask questions at any time; and
- names and contact information (phone numbers, email addresses) of whom to contact with questions.

Waiver of Assent

The regulations for waiver of assent are contained in Subpart D which enumerates the special protections for children in research.

There are three ways in which the IRB can waive assent for some or all of the subjects.

Waiver of Assent Criteria - #1

45 CFR 46.408

Some or all of the children aren't capable of providing assent:

- The default age for assent at UVM is age 11 so if all subjects will be younger than 11 years, then the requirement for assent may be waived.
- The research may be complicated or the subject population may have limitations which make the likelihood that they can comprehend the research sufficiently to provide assent.

The research must:

(1) holds out the prospect for direct benefit to the child,

(2) the benefit is important for the child's health and

(3) the benefit is only available in the research. This usually means that the investigational agent(s) are only available in the context of the research.

- All three conditions must be met;
- The most frequent use of this waiver is for clinical trials of investigational drugs or devices for life-threatening conditions such as treatment of cancer

Waiver of Assent Criteria - #2

Research is approved under 21 CFR 50.52 or 45 CFR 46.405

Waiver of Assent Criteria - #3

The research meets the criteria for Waiver of Consent under 45 CFR 46.116(d)

- Waiver of assent may be requested along with waiver of consent. The most frequent example for this waiver is for studies that are limited to the retrospective review of records.
- Waiver of assent may also be requested in situations where consent (parental permission) will be obtained. For example, it may not be practicable for the investigator to obtain the assent of the child for a telephone survey.

Children in State Custody (wards of the state, Foster Care)

- The Vermont Department of Children and Families (DCF) is the legally authorized agency able to grant permission for participation in research for children in their custody.
- The decision of whether to grant permission for research is made on a case-by-case basis by DCF and consent is provided by an appropriate representative of DCF.
- If a child has begun research procedures with the consent of a parent but is subsequently placed in the custody of DCF while undergoing research interventions, ***consent must be sought again from the appointed advocate for the child at DCF in order to continue participation in the research***.

EMANCIPATED MINOR

According to Vermont Statute, an emancipated minor means a minor who:

a. has entered into a valid marriage

b. is on active duty with any of the armed forces of the United States of America; or

c. has been, by a court of law, ordered emancipated.

- In certain limited circumstances, it may be appropriate to allow an emancipated minor to consent to participate in a research study in the absence of the permission of a parent or legal guardian if the minor has the sufficient capacity to consent to the procedures involved in the research study.
- Each situation is judged on a case-by-case basis.

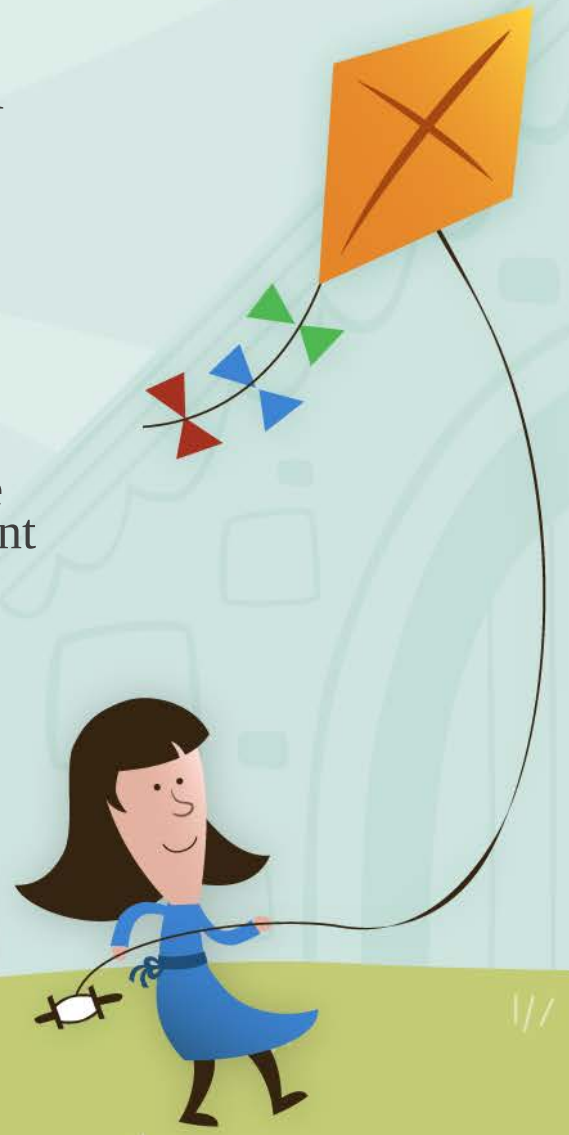
Children Reaching Legal Age of Consent While Enrolled in a Study

Consent is an ongoing process!

When a child who was enrolled in research with parental permission subsequently reaches the legal age of consent the researcher should obtain the informed consent for the now-adult subject for any ongoing interventions.

The prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject.

Refer to our Continued Participation after Reaching Age of Majority (DOCX)



Questions?