Additional Regulatory Protections for Children as Research Participants

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Additional protections for children as research subjects

45 CFR 46, Subpart D and 21 CFR 50 FDA

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.

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U.S. Department of Health and Human Services

IRB Duties

45 CFR 46.403

- 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***
- 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)

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U.S. Department of Health and Human Services

Federal Regulations Defining Risk in Research

Minimal Risk

The probability and magnitude of harm or discomfort anticipated ***in the research*** are not greater in and of themselves than those ***ordinarily encountered in daily life*** of the general population or during the performance of routine physical or psychological examinations or tests

Greater than Minimal Risk

The probability and magnitude of harm or discomfort anticipated in the research risks are more than minimal risk, but not significantly greater.

The IRB will consider additional risks to the participant such as psychological, physical, legal, social and economic harm.

The IRB will also consider if the targeted population requires additional protections because they are vulnerable such as – children, cognitively impaired, economically disadvantaged, prisoners etc.

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,

IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of **one** parent or guardian

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

- PI will collect information about the child's medical history from EPIC, measure height and weight, and ask the child to complete four questionnaires asking about their health, digestive symptoms, and quality of life.
- Participants will need to download an app onto their phone for future QOL questions.
- Risks are minimal - survey questions, time commitment, breach of confidentiality
- Only one parental signature is required
- A separate assent form was created for children 11-17
- Expedited Review level, IRB deemed study a ***Risk level 1***

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

- Research in which the IRB finds that 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

- The risk is justified by the anticipated benefit to the subjects

- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches

- Permission of a single parent and assent of the child (if applicable) are required

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 about 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

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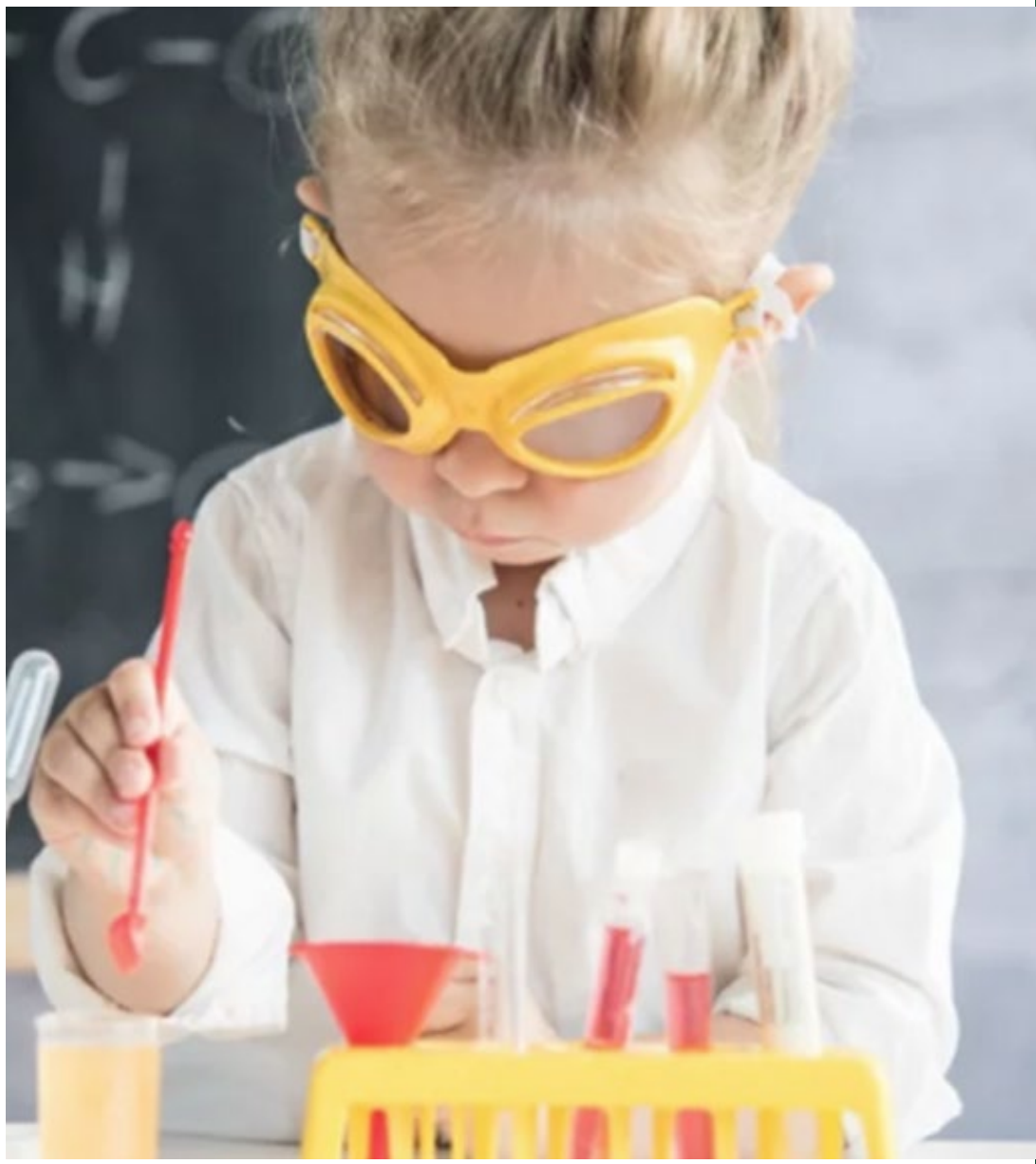
Pediatric Risk Level II - 46.405 Greater than Minimal Risk with a Prospect for Direct Benefit

- 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
- Full Committee Review level, IRB deemed study a ***Risk level II***



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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.

- The intervention or procedure is likely to yield generalizable knowledge about the participants disorder or condition

- *Permission of both parents* and assent of the child (if applicable) are required

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. Radiation was not for treatment but solely for research purposes.
- Both parents required to consent
- Full Committee Review, IRB deemed study a ***Risk level III***

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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

UVM has never had a proposed protocol of this nature

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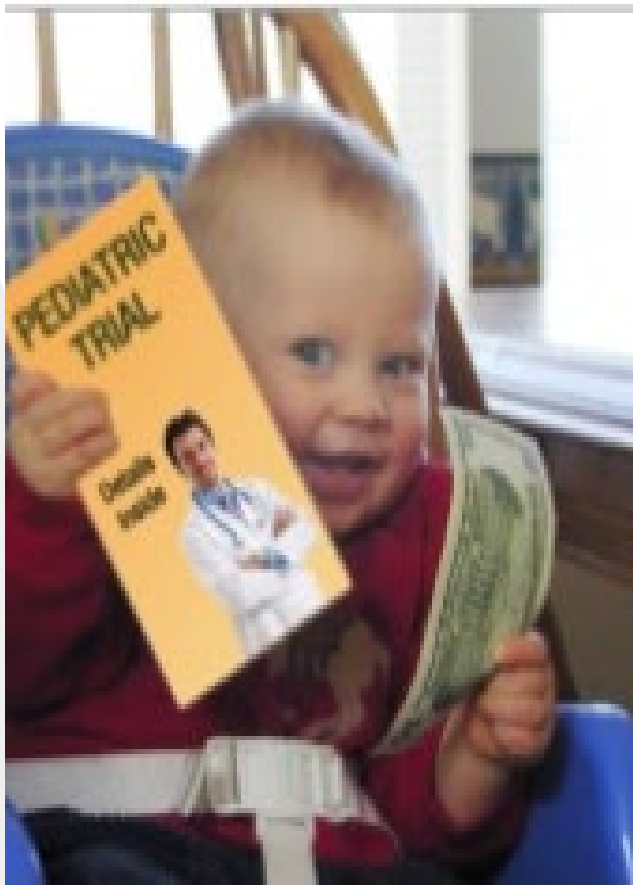
Child Assent

- A child's affirmative agreement (verbally or written) to participate in research obtained in conjunction with consent from the child's parents or legally authorized representative.
- Research assent at UVM is typically conducted with children 11 – 17 .
- Assent *can be waived* if the IRB finds the capability of some, or all 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.
- Consent of the parent/guardian is ***always*** a requirement.



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Child Assent Process

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)

The IRB has 2 child assent templates for researchers to use.

- 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.

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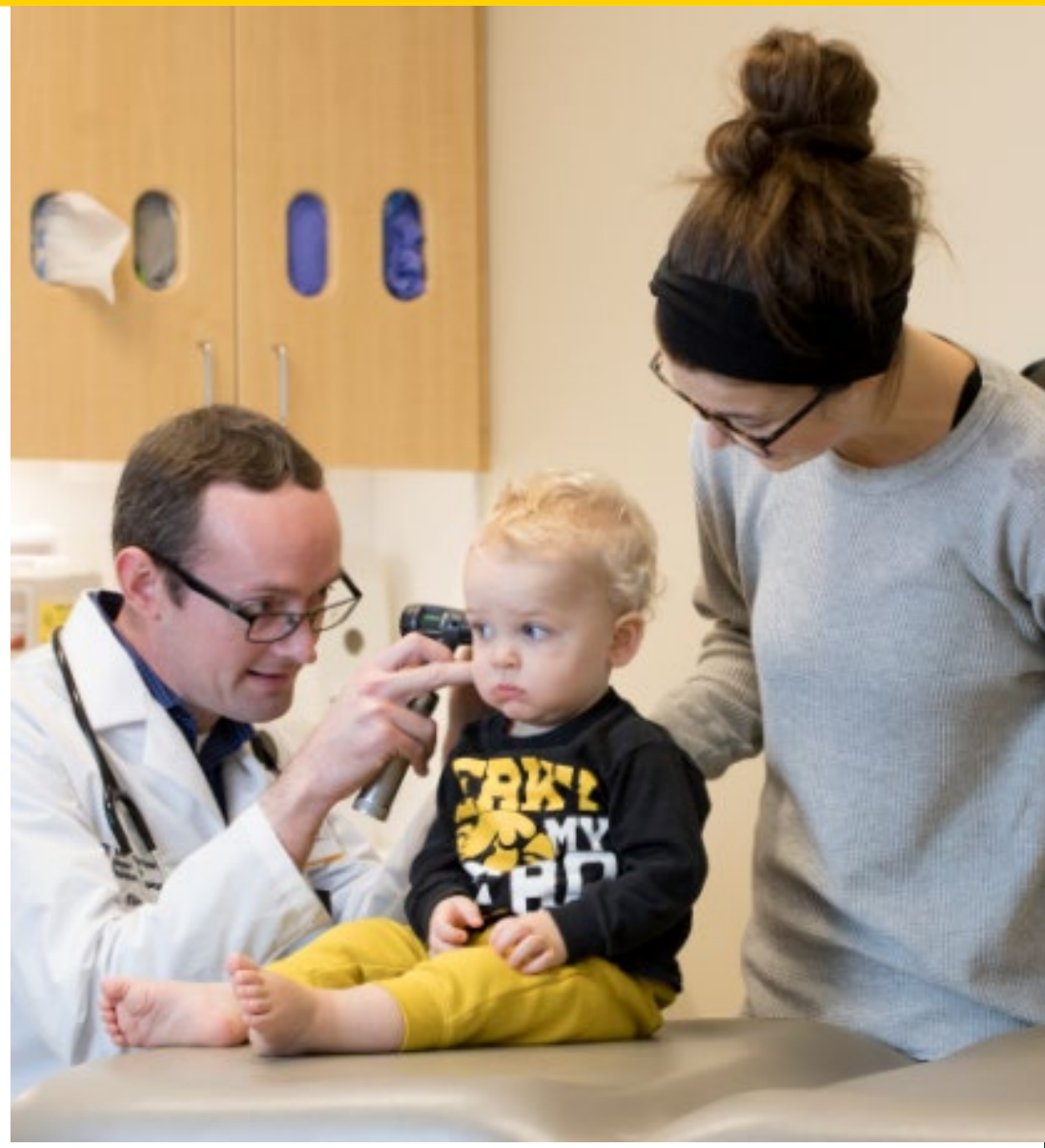
Waiver of Assent Criteria - #1
45 CFR 46.408

IRB criteria - All the children are not 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)

Justifications - 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



Waiver of Assent Criteria - #2
Research is approved under 21 CFR 50.52 or 45 CFR 46.405

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

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.

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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, exempt 4iii

- 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

- 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***.
- Pediatric Risk Level III protocols can not have children in state custody enrolled.

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)

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PI Guidance & Education Materials

PI Checklist for New Studies - A list of questions for researchers to consider while working your way through the IRB submission process

UVM IRB Templates – Protocol, consent and data management forms required for review

UVM Policy & Procedures – search this document to access federal and local research regulations and polices that may affect your research. CRTL F on the page

Guidance Materials Required for UVMClick Submissions - Outlines the materials investigators should assemble and include with their applications for IRB review or Determination of Exemption

UVMClick User Guides – Step-by-step directions on how to submit and navigate the Click software platform for protocol submission to the IRB.

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Questions?