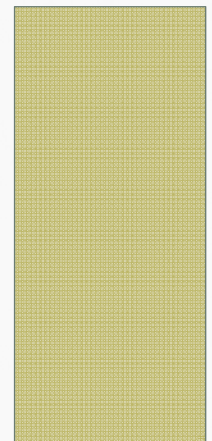


FAQ'S FROM PEDIATRIC INVESTIGATORS

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AGENDA

- Review the categories of research involving children
 - what are the differences
 - which one is special and why
- Identify the most frequently asked questions from Pediatric Investigators
- Informed Consent
- Review of the basics
- Complaints
- Q & A

DEFINITION OF CHILDREN

- The human subject research regulations define “children” as persons who have not attained the legal age for treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (45 CFR 46.402(a)).



Categories of Research Involving Children

WHAT ARE THE CATEGORIES FOR RESEARCH INVOLVING CHILDREN AND WHY ARE THEY IMPORTANT?

- Category 1 (45 CFR 46.404/21 CFR 50.51)
- The research poses no more than minimal risk to children.
- Examples include: retrospective chart review, standardized measures, buccal or nasal swabs, blood draws that do not exceed the lesser of 50mls or 3mls per kg in an eight week period and is not collected more frequently than twice per week.

WHEN MAY THE IRB APPROVE RESEARCH UNDER CATEGORY 1?

- The IRB may approve the research only if the IRB finds that adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians.

WHAT ARE THE CATEGORIES FOR RESEARCH INVOLVING CHILDREN AND WHY ARE THEY IMPORTANT?

- Category 2 (45 CFR 46.405/21 CFR 50.52)
- The research poses greater than minimal risk to children and includes an intervention or procedure that **DOES hold out the prospect of a direct benefit** for the individual child OR a monitoring procedure that is likely to contribute to the child's well-being.
- Examples include: trials of investigational or FDA approved drugs for chronic conditions and life-threatening diseases, which have been shown to be effective or equivalent to currently available treatment.

WHAT ARE THE CATEGORIES FOR RESEARCH INVOLVING CHILDREN AND WHY ARE THEY IMPORTANT?

- Category 2 (45 CFR 46.405/21 CFR 50.52)
- Informed consent **SHOULD** be obtained from both parents unless one parent is deceased, unknown, incompetent, or is not reasonable available, or when only one parent has legal responsibility for the care and custody of the child.

WHEN MAY THE IRB APPROVE RESEARCH UNDER CATEGORY 2?

- The IRB may approve the research **only if** the IRB finds that:
 - 1. The risk is justified by the anticipated benefit to the children;
 - 2. The relation of the anticipated benefit to the risk is at least as favorable to the children as that presented by available alternative approaches; and
 - 3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians.

WHAT ARE THE CATEGORIES FOR RESEARCH INVOLVING CHILDREN AND WHY ARE THEY IMPORTANT?

- Category 3 (45 CFR 46.406/21 CFR 50.53)
- The research poses greater than minimal risk to children and includes an intervention or procedure that **DOES NOT** hold out the prospect of a direct benefit for the individual subject OR a monitoring procedure that is likely to contribute to the well-being of the subject, BUT is likely to yield generalizable knowledge about the subject's disorder or condition.
- Examples of research which pose greater than minimal risk with no prospect of direct benefit: bone marrow obtained for genetic testing or future research related to disease; extending sedation time to obtain additional MRI research data for non-clinical purposes.

WHAT ARE THE CATEGORIES FOR RESEARCH INVOLVING CHILDREN AND WHY ARE THEY IMPORTANT?

- Category 3 (45 CFR 46.406/21 CFR 50.53)
- Informed consent **MUST** be obtained from both parents unless one parent is deceased, unknown, incompetent, or is not reasonable available, or when only one parent has legal responsibility for the care and custody of the child.

WHEN MAY THE IRB APPROVE RESEARCH UNDER CATEGORY 3?

- The IRB may approve the research only if the IRB finds that:
 - 1. The risk represents a minor increase over minimal risk;
 - 2. The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - 3. The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition; and
 - 4. Adequate provisions are made for soliciting assent of the children and permission of their parents or legal guardians

CATEGORY 3

- *IRB FAL language:*
 - *With respect to the enrollment of children, the Committee determined the permission of both parents/legal guardians is required unless one parent is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. **If both parent/guardian signatures are not obtained in any case, documentation of the rationale should be retained with the signed consent form.** The Committee also determined assent must be obtained from the child. **For children ages 12 years and younger, the investigator may determine on a case-by-case basis whether it is appropriate to obtain a signature, based on the age, maturity and psychological state of the child.***

WHAT ARE THE CATEGORIES FOR RESEARCH INVOLVING CHILDREN AND WHY ARE THEY IMPORTANT?

- Category 4 (45 CFR 46.407/21 CFR 50.54)
- The proposed research does not meet the requirements of Category 1, 2, or 3.

WHEN MAY THE IRB APPROVE RESEARCH UNDER CATEGORY 4?

- The IRB may approve the research only if:
 1. The IRB 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;

WHEN MAY THE IRB APPROVE RESEARCH UNDER CATEGORY 4?

- 2. If Federally funded, the Secretary of the Department of Health and Human Services (DHHS), after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
 - a. That the research in fact satisfies the conditions of categories 46.404, 46.405, or 46.406; or
 - b. The following:
 - i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - ii. The research will be conducted in accordance with sound ethical principles; and
 - iii. Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians, as set forth below in Section III.

WHEN MAY THE IRB APPROVE RESEARCH UNDER CATEGORY 4?

- 3. For non-Federally funded research meeting 45 CFR 46.407, the IRB must conduct the review with a panel of experts and provide an opportunity for public review and comment.

DOES ANYTHING CHANGE IF THE CHILD IS A WARD OF THE STATE?

- Wards of the State (45 CFR 46.409)
- When children as wards of the State are involved in research under 45 CFR 46.406, or 407, the IRB must require appointment of an individual to act on behalf of the child as a guardian or in loco parentis.
- The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the research. In addition, the advocate may not be associated in any way with the Investigator's or the guardian organization.

ARE THERE DIFFERENCES FOR THE CATEGORIES OF EXEMPTION WHEN RESEARCH INVOLVES CHILDREN?

- Yes – 45 CFR 46.101(b)(2) is different.
- The only research activities involving children that may fall under this exemption are those involving educational tests or observation of public behavior where the investigators **do not** participate in the activity being observed.



INFORMED CONSENT

WHEN DO BOTH PARENTS NEED TO PROVIDE PERMISSION FOR THEIR CHILD TO PARTICIPATE IN A RESEARCH STUDY?

- Permission should be obtained from both parents before a child is enrolled in research.
- HOWEVER, the IRB may find that the permission of one parent is sufficient for research to be conducted under 46.404 (Category 1) and 46.405 (Category 2). For the two remaining categories (46.406 and 46.407), permission MUST be obtained from both parents...

WHEN DO BOTH PARENTS NEED TO PROVIDE PERMISSION FOR THEIR CHILD TO PARTICIPATE IN A RESEARCH STUDY?

...unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

CAN PARENTAL OR GUARDIAN PERMISSION FOR RESEARCH INVOLVING CHILDREN BE WAIVED?

- Yes – The regulations do allow the IRB to waive the requirements for obtaining parental or guardian permission.

WHAT IS CHILD ASSENT?

- Assent is the child's affirmative agreement to participate in research. Therefore, the assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in the research would involve.
- The child must show their willingness to participate in the research. Not saying "no" does not mean "yes."

DISSENTING BEHAVIORS

- Dissenting behaviors may include, but are not limited to, excessive crying, hiding behind the parent, refusing to interact, attempting to leave, trying to physically strike out or being destructive.

WHEN DOES THE CHILD NEED TO PROVIDE ASSENT?

- The IRB will make the determination when assent is required and includes their decision in the meeting minutes and in the final approval letter sent to the Investigator.
- The IRB should require child assent unless it can be appropriately waived, or if the child is not capable of providing assent.

WHEN SHOULD A SCRIPT BE USED INSTEAD OF AN ASSENT FORM?

- Ages less than 7 years: An **oral script** in very simple language appropriate for children less than 7 years of age
- Ages 7 to 12 years: An **assent** form written simply and at a comprehension level appropriate for a child 7 years of age
- Ages 13 to 17 years: An **assent** form which may be in the same language as the adult consent document

WHAT HAPPENS WHEN A PARENT SAYS “YES” AND THE CHILD SAYS “NO?”

- If the child dissents from participating in research, even if his or her parents or guardian have granted permission, the child’s decision prevails.
- HOWEVER, the regulations state the IRB may waive the assent requirements if the intervention or procedure involved in the research holds out the prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of research.

WHAT IF A FEMALE CHILD DISCLOSES THEY ARE PREGNANT?

- IRB Template Language:
 - If you are a girl and are able to become pregnant, you will have a (*insert appropriate measurement: blood or urine*) test to make sure that you are not pregnant before you receive treatment in this study. If your parents or guardian asks, we must tell them the results of your pregnancy test or that you are using birth control.

HOW DOES THIS CHANGE THE CONSENT PROCESS IF PREGNANT MINORS ARE ENROLLED?

- The parent(s) of the pregnant child will need to provide permission for their child to participate in the research. However, if the baby will be a study participant, the baby's mother will need to provide permission for her child to participate.

DO CHILDREN EVER NEED TO BE RE-CONSENTED?

- Long-term Studies
- If a child reaches the legal age of consent while enrolled in a study, the subject's participation is no longer regulated by the requirements of 45r CFR 46.408 regarding parental or guardian permission and subject assent.
- Therefore, unless the IRB has waived the requirements for obtaining informed consent, the investigator **MUST** obtain the legally effective informed consent in accordance with 45 CFR 46.116, from the now-adult subject to continue ANY interactions or interventions.

EMANCIPATED MINORS

- The inclusion of mature **minors** or **emancipated minors** in research activities in the absence of the permission of a parent or legal guardian is considered narrowly by a Judge.
- Further, each situation is judged on a case-by-case basis, and Hospital Administration and the Office of General Counsel are consulted before initiating any research activity including screening. Documentation of those decisions must be included in the research file.



Investigator Basics

PI RESPONSIBILITIES

- In a nutshell, the PI is responsible for:
 - Human Subject Protection
 - Training
 - Conflict of Interest
 - IRB Approval
 - IND/IDE
 - Study Conduct
 - Informed Consent
 - Amendments
 - Continuing Review
 - Data Safety Monitoring
 - Adverse Events
 - Complaints
 - Record Retention
 - GINA

In other words...EVERYTHING!

TRAINING

- PI must complete initial and annual VU IRB human research protections training.
- It is also the responsibility of the PI to assure that other Investigators and key study personnel who are responsible for the design and conduct of the research are adequately trained in human research protections and completion of continuing education requirements.

TRAINING

- The PI is also responsible for ensuring that all individuals conducting the research are adequately qualified and licensed to perform the research related procedures.

CONFLICT OF INTEREST

- All conflicts of interest (PI and KSP) must be disclosed to the IRB and the Medical Center Conflict of Interest Committee (MCCOIC).
- Disclosures must be provided with the initial IRB application, at each continuing review and within 10 days of becoming aware of any previously undisclosed financial interest (via a Request for Amendment).

TYPES OF IRB DETERMINATIONS

- Non-Research
 - Research = systematic investigation designed to develop or contribute to generalizable knowledge.
 - Case studies
 - Quality assurance projects
- Non-Human Subjects
 - Human subject = a living individual about whom an Investigator obtains data either through intervention or interaction with the individual or identifiable private information.
 - De-identified specimens from a repository
 - BioVU

TYPES OF IRB DETERMINATIONS

- Exempt – 6 categories
 - Educational tests, surveys, interviews, observations of public behavior
 - Collection or study of existing data
- Expedited – 9 categories; minimal risk
 - Research on individual or group characteristics
 - Collection of data from voice, video, or image recordings
 - Blood draws – 550ml/8wks; ≤ 2 draws/wk or 50cc (3cc/kg)
- Standard – greater than minimal risk
 - Pharmaceutical/drug studies
 - Device studies
 - Intervention studies

STUDY CONDUCT

- Investigators responsibilities during the conduct of an approved research study include:
 - Obtaining and documenting informed consent of subjects or subjects' legally authorized representative PRIOR TO the subjects' participation in the research unless the IRB has approved a waiver of consent.

STUDY CONDUCT

- Obtaining prior approval from the IRB for **any** modifications of the previously approved research, except those necessary to eliminate apparent immediate hazards to the subject(s).
- Ensuring progress reports and requests for continuing review and approval are submitted to the IRB in accordance with IRB P&P's, and the institution's Federal Wide Assurance.

STUDY CONDUCT

- Providing to the IRB prompt reports of any unanticipated problems involving risks to subjects or others.
- Providing to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB.

INFORMED CONSENT PROCESS

- **Continuous process**
 - The Investigator assures the informed consent process in research is an ongoing exchange of information between the research team and the study participants throughout the course of a research study. Informed consent is a continuous process of communication and acknowledgement over time, not just a signed document.
- **Free from coercion and undue influence**
 - An Investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
- **Documentation**
 - Provide document for review
 - Questions
 - Verbalizes Understanding

AMENDMENTS

- Any changes to the IRB approved research must be submitted, reviewed, and approved by the IRB PRIOR to implementation.
- The only time the investigator may make a modification to research activities without prior IRB approval is to avoid an immediate hazard to the participant. The PI must report the event to the IRB within 10 working days.
- The Request for Amendment form is no longer listed as a form on the IRB website. To create an amendment, log into DISCOVER-E and click the "Create Submission" button located on the upper right corner.

COMPLAINTS

- The most common methods complaints are received by the IRB are:
 - Phone call from participant or family member
 - IRB Website
 - IRB Committee Members
 - Research Staff
 - Anonymous sources

COMPLAINTS

- Examples of complaints:
 - Have not received compensation
 - Have been billed for a research procedure
 - Upset with some aspect of the study
 - Wants results when the ICD stated they would not be shared
 - Information regarding study participation has not been sent as promised
 - Parking

EXAMPLES OF COMPLAINTS

- The most frequent complaint received by the IRB is from participants who have been charged for research-related procedures or have not received their compensation.

RESOLUTION

- Work with either the study coordinator or billing department to get the charges removed from the participant's account and billed to the appropriate D&H account or to obtain their compensation.

EXAMPLES OF COMPLAINTS

- A potential participant contacted the IRB to find out if the study she had received an informed consent document and questionnaire for had been approved by the IRB.

RESOLUTION

- The study was “approved pending modification” and the PI had not responded to the Committee Action Letter (CAL).

The incident was reported to the IRB as a protocol deviation and the PI sent a letter of apology to the participants he contacted prior to having IRB approval. In addition, the RSA met with the PI to ensure his understanding of the approval process. The potential participant was contacted and informed to disregard the mailing since final IRB approval was pending. *She stated she had noticed the consent form did not have an IRB approval and expiration date included on form, which prompted her to call.*

EXAMPLE OF A REPORTABLE INCIDENT

- A PI contacted the IRB to report his jump drive had fallen out of a hole in his pocket and down through the crack of the elevator landing in the bottom of the elevator shaft.

RESOLUTION

- The event was reported as an adverse event to the IRB. OHRP was notified of the incident due to the potential breach of confidentiality. The VU Privacy Officer was also notified; however, the incident was not reportable at either the Federal or State level. Participants whose data was on the drive were notified.

STEP BY STEP

- Address any urgent medical concerns.
- Obtain as much information as possible about the event.
- Inform the person filing the complaint that someone from the Vanderbilt Human Research Protection Program will be contacting them.
- Determine if other departments need to be contacted.
- Contact Jan Zolkower at 343-8395 or via email at jan.zolkower@vanderbilt.edu.

REFERENCES

- <http://answers.hhs.gov/ohrp/categories/1570>
- IRB Policy and Procedure IX.A and IX.A.1
- IRB Vulnerable Population Form #1117 (Children)
- IRB Policy IV.A
- IRB Informed Consent Document - Instructions

Questions?

Contact information for future questions:

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