IRB Tip Sheet: Inclusion of Children in Clinical Research with Component Analysis*

Regulatory Definition of Children

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under applicable law of the jurisdiction in which the research will be conducted.

Research Involving Children

- Must follow additional protections beyond those for adults. These are described in 45 CFR part 46, Subpart D: Additional Protections for Children Involved as Subjects in Research.
- The protocol must justify the rationale for inclusion of children.
- The IRB must consider potential benefits, risks, and discomforts of the research to children.
- If procedures are unclear, the IRB may ask for more detail.
- If the study includes different groups (such as healthy and sick children), the protocol must describe which procedures apply to each group.
- The risk of one procedure cannot be balanced by the benefit of an unrelated procedure.
- All categories of research with children require assent of the children and permission of their parents or guardians unless waived by the IRB.
- Wards of the State or other institutes have additional protections. (See §46.409.)

Permission – Assent – Waivers

Parental / Guardian Permission

Permission means a parent or guardian agrees to the child's participation.

- **One parent signature:** Allowed for research under §46.404 or §46.405, though the IRB may require that two parents sign.
- **Two parents' signatures:** Required for research under §46.406 or §46.407 though there are exceptions (See §46.408(b).)
- If the research involves **any** procedures that are greater than minimal risk without prospect of direct benefit, the IRB must require both parents sign.

Assent of the Child

Assent is a child's affirmative agreement to participate in research. Silence or lack of objection is not assent.

- The protocol should propose the age at which children will provide assent based on the type and complexity of the research. Children too young to assent should still have the study explained to them using age-appropriate language.
- The complete plan for obtaining written/verbal assent needs to be included in the protocol.

Waivers Specific to Children

- The IRB requires child assent unless it can be appropriately waived, or if the child is not capable of providing assent.
- Requests for IRB waiver of assent for some or all of the participants should be described in the protocol
- Circumstances where assent can be waived:
  - If the capability of some or all of the children is so limited that they cannot understand.
  - If the intervention or procedure involved in the research has the prospect of direct benefit to the children's health or well-being and is available only in the context of the research.
  - If the research meets the same conditions as for waiver or alteration of consent in research with adults.

HHS (45 CFR 46.408(c)), but not FDA regulations, allow the IRB to waive parental permission if it is not a reasonable requirement to protect the child. (For example, research with neglected or abused children). However, a substitute mechanism for protecting the children must be identified.

*For additional information see Guidance: Information on Special Protections for Children as Research Subjects (OHRP)

Levels of Risk in 45 CFR part 46, Subpart D: Additional Protections for Children Involved as Subjects in Research

§46.404 Research not involving greater than minimal risk	• **Minimal Risk (MR)** means the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during routine physical or psychological examinations or tests. • **Examples of MR Activities***:* Physical exam, small volume blood draw, non-invasive specimen collection (urine, saliva, hair, etc.), non-contrast MRI without sedation, a single skin biopsy of < 3mm. • Regulations only permit healthy children to participate when research involves no greater than minimal risk.
§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	• The IRB must find that: ○ 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
§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition	• The IRB must find that: ○ The risk represents a minor increase over minimal risk ▪ **Minor increase over MR** is a procedure for which risks or discomforts are temporary and not severe. Examples include MRI with contrast, a CT scan, a biopsy of a superficial lymph node. ○ The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition
§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 above, but it presents 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 Secretary of HHS for review under conditions identified in section **§46.407.** • The HHS Secretary (or OHRP if delegated by the Secretary) consults with a panel of relevant experts (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines that certain conditions identified in section **§46.407(b)** are met. For details of this process, see OHRP Guidance: Children as Research Subjects and the HHS "407" Process.

Pediatric Component Analysis **

- "A research protocol, including a protocol studying a pediatric condition, may, and usually does, include multiple research-related interventions or procedures, some that offer prospect of direct benefit and some that do not. Any intervention or procedure conducted solely for research purposes and not needed for clinical management or routine clinical care should be evaluated separately to determine whether it offers prospect of direct benefit to the enrolled child (known as a "component analysis" of risk). If a specific intervention or procedure does not offer prospect of direct benefit, the risk of the intervention or procedure should be limited to a minor increase over minimal risk, and meet the other conditions outlined under 21 CFR 50.53 unless the protocol is referred for review, as per 21 CFR 50.54."
- "Failure to carefully evaluate the different components of a clinical investigation may result in an intervention or procedure that does not offer prospect of direct benefit exceeding the allowable ceiling of a minor increase over minimal risk."
- "Prospect of direct benefit should result from the research intervention or procedure being studied (e.g., the investigational drug or medical device) and not from ancillary interventions or procedures, such as physical exams done as part of the trial."

**Quoted citations on this page are from FDA's 2022 Draft Guidance, *Ethical Considerations for Clinical Investigations of Medical Products Involving Children Guidance for Industry, Sponsors, and IRBs.*

In other words…

- Each population must be considered separately.
- Each study intervention or procedure must be considered separately for risk level AND prospect of direct benefit.
- Direct benefit is a positive outcome that may be experienced due to the study intervention.
- Interventions or procedures with no individual prospect of direct benefit cannot be justified by perceived benefits from other parts of the study.

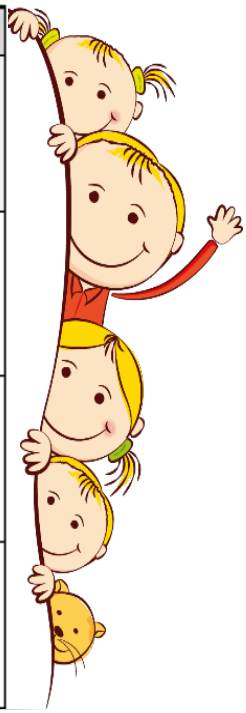
Perform a Pediatric Component Analysis.

Break the Protocol Down Step by Step:

1. Identify subject groups being enrolled. For example, affected children vs. healthy children.
2. List **every** research intervention or procedure for **each** group.
3. For **each** intervention or procedure, decide if there is the prospect of direct benefit. Then decide if the benefit is at least as great as available alternatives. If the specific group has a chance of getting placebo, there is no prospect of direct benefit.
4. For **each** intervention or procedure, decide risk level (MR , minor increase over MR, greater than MR).
5. Determine approval category for **each** intervention or procedure for each group.
6. Decide if a one or two parent signatures are required for **each** intervention or procedure.
7. **Overall determination** is based on the **highest individual** procedure/intervention for that group.

Example

Specific Pediatric Population Being Evaluated (Fill out a New worksheet for Each population): Affected Kids						
Name of Individual Protocol Procedure or Intervention	**Is there the prospect of direct benefit?**	**What is the direct benefit?**	**Risk Level of intervention?**	**Approval Category?**	**How many parent signatures are required?**	**Procedures with the highest regulatory requirements**
Study Drug	☒Yes ☐No	Treatment with no other viable options ☐None	☐Minimal risk ☐Minor increase over minimal risk ☒GTMR	☐404 ☒405 ☐406 ☐407 ☐None	☒One Parent ☐Two Parents	☐
Questionnaire	☐Yes ☒No	 ☒None	☒Minimal risk ☐Minor increase over minimal risk ☐GTMR	☒404 ☐405 ☐406 ☐407 ☐None	☒One Parent ☐Two Parents	☐
Superficial Lymph Node Biopsy	☐Yes ☒No	 ☒None	☐Minimal risk ☒Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☒406 ☐407 ☐None	☐One Parent ☒Two Parents	☒



Please see the next page for a worksheet to be used for component analysis when research involves children.

Pediatric Component Analysis Worksheet: Fill out a NEW worksheet for each population.

Specific Pediatric Population Being Evaluated: ____ (e.g., Affected Children, Healthy Children, Toddlers, Infants, Disease Populations, etc.)						
Name of Individual Protocol Procedure or Intervention	**Is there the prospect of direct benefit?**	**What is the direct benefit?**	**Risk Level of intervention?**	**Approval Category?**	**How many parent signatures are required?**	**Procedures with the highest regulatory requirements**
	☐Yes ☐No	☐None	☐Minimal risk ☐Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☐406 ☐407 ☐None	☐One Parent ☐Two Parents	☐
	☐Yes ☐No	☐None	☐Minimal risk ☐Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☐406 ☐407 ☐None	☐One Parent ☐Two Parents	☐
	☐Yes ☐No	☐None	☐Minimal risk ☐Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☐406 ☐407 ☐None	☐One Parent ☐Two Parents	☐
	☐Yes ☐No	☐None	☐Minimal risk ☐Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☐406 ☐407 ☐None	☐One Parent ☐Two Parents	☐
	☐Yes ☐No	☐None	☐Minimal risk ☐Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☐406 ☐407 ☐None	☐One Parent ☐Two Parents	☐
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	☐Yes ☐No	☐None	☐Minimal risk ☐Minor increase over minimal risk ☐GTMR	☐404 ☐405 ☐406 ☐407 ☐None	☐One Parent ☐Two Parents	☐

Highest Level of Approval Category for Population: ____________________
Greatest Number of Parent Signatures for Population: ____________________