
Special Considerations for Pediatric Trials

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DESCRIPTION

Clinical research with minors poses several significantly different issues than research conducted on adults. Therefore, researchers must address a number of special considerations when conducting any pediatric clinical trial.

TOPICS

- DEFINITIONS
- EVALUATING THE RISKS AND BENEFITS OF THE STUDY
- PARENTAL PERMISSION AND ASSENT OF THE MINOR

Special Considerations for Pediatric Trials

Definitions

MINOR

A minor is an individual who, under local law, has not yet reached the age of majority. The age of majority is the age at which the individual is considered an adult. Under most local laws, an individual cannot bind himself/herself legally by contract until that individual has reached the age of majority.

MATURE MINOR

The term "mature minor" is a term often used to refer to individuals who, under local law, are entitled to consent to certain health care treatment or procedures (such as for drug or substance abuse or sexually transmitted diseases) even though they are still minors. A number of local governments have general consent statutes that permit minors to consent to medical or surgical treatment at a specified age. In some states and provinces, a minor who is subjectively assessed as capable of giving the same degree of informed consent as an adult may be treated without a parent's involvement.

EMANCIPATED MINOR

An "emancipated minor" is an individual who is recognized to have the full legal rights of an adult under local law even though the individual is under the age of majority. Minors can become emancipated through certain actions, such as marriage, enlistment in the military or living independently. Emancipation also sometimes requires a court order.

CHILDREN

Under the federal human research protection regulations, the term "children" is defined to mean "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations" under local law. In other words, the term "children" is a subset of the term "minors."

Minimizing the risks of the study

Risks in a study involving minors must be minimized as much as possible. In designing the study plan, take into consideration these suggestions:

- The risks associated with interventions must be evaluated from the perspective of a child. Therefore, where possible, provide services that will reduce a child's discomfort, such as using topical anesthetic for blood draws and providing a child-friendly atmosphere.
- Make an effort to reduce the total number of interventions by combining research interventions with other research and/or clinical interventions. For instance, use an indwelling catheter if several blood draws are needed. You could also conduct the research interventions such as blood draws at the same time clinically indicated blood draws are scheduled.

Evaluating the risks and benefits of the study

Generally, only certain levels of risk are acceptable in a pediatric study and are dependent on the amount or type of benefits derived from the study. Research involving minors should only be conducted once an IRB has determined that the risks to the minor are reasonable in relation to the benefits, if any, and the importance of the knowledge that is expected to be garnered from the study. A sliding scale of the "risks versus benefits" is usually used to determine whether a study involving minors may be ethically conducted.

For research involving children, an IRB makes a determination regarding the level of risk and the prospect of benefit in accordance with applicable federal regulations (Subpart D of 21 CFR Part 50 or Subpart D of 45 CFR Part 46) if the requirements of 21 CFR §56.111/45 CFR §46.111 are also met. The three categories are as follows:

- Research "presenting no more than minimal risk to children";
- Research or intervention presenting more than minimal risk to children that offers the "prospect of direct benefit" or may "contribute to the subject's well-being"; or
- Research involving an intervention or procedure that presents "only a minor increase over minimal risk," yet does not offer any "prospect of direct benefit" or "contribute to the well-being" of the child, but is "likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance."

An IRB may refer to the appropriate regulatory agency research involving children that is not approvable in one of the three categories above, provided that "the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of serious problems affecting the health and welfare of children."

On February 26, 2013, the FDA published a final rule amending the Subpart D regarding children in research, effective March 28, 2013. This final rule clarifies that the FDA does not consider the administration of a placebo to offer a prospect of direct benefit. Due to this new rule and FDA interpretation, a component analysis of the possible risks and benefits of each arm of a placebo-controlled study is conducted, as opposed to a single evaluation of the risks and benefits of the entire study.



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The protocol design

Protocols should be designed to reduce discomfort and risk to minors as much as possible. For instance:

- Include a sample size justification that shows risks are minimized and reasonable with regards to the benefits of the knowledge or outcomes that will be gained.
- Try lessening the overall amount of blood needed for the entire study by using sensitive assays, pediatric-enabled laboratories, and population pharmacokinetic approaches.
- Where possible, limit research to pharmacokinetic and safety data studies and combine this data with pharmacodynamics data.
- Design the protocol to protect against adverse outcomes that generally only affect minors, such as impairments of cognitive growth or skeletal development.

Parental permission and assent of the minor

If an IRB approves research involving children, it must also follow the parent/guardian permission and child assent requirements of 21 CFR §50.55 for FDA-regulated studies and 45 CFR §46.408 for HHS-regulated studies.

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PARENTAL PERMISSION

Where parental permission is to be obtained, an IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405 or clinical investigations under 21 CFR 50.51 or 21 CFR 50.52. Where research is covered by 45 CFR 46.406 and 45 CFR 46.407, and clinical investigations are covered by 21 CFR 50.53 and 21 CFR 50.54 and permission is to be obtained from parents, both parents must give their permission 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. Please note, that pursuant to 45 CFR 46.408(c), the Board may waive or alter parental/guardian permission requirements for children when certain conditions are met. FDA regulations, however, do not give authority to the Board to waive or alter parental/guardian permission requirements; therefore, these requirements will not be waived for research that is FDA regulated.



ASSENT OF THE MINOR

In determining whether a minor is capable of providing assent, an IRB must take into account the age, maturity, and psychological state of the minor. This judgment may be made for all children that will be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

The assent of the minor is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

1. That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or
2. That the intervention or procedure involved in the clinical investigation 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 clinical investigation/ research.

Even if the IRB determines that a child is capable of assenting, the IRB may still waive the assent requirement if:

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Note that due to the vulnerability of minors in research, assent plans and forms

should be as understandable and concise as possible. If there is a range of minors participating in a study (for example, ages 7 - 17), the assent form may reference the core consent form so older subjects may read further if they choose. The following statement would suffice: "You can also talk to your parents about this study and ask to read the information the doctor gives them."

You can also use assent forms aimed at different ages (such as an assent form for ages 7-11 and a separate assent for ages 12-17). The language of the assent form should be appropriate for the youngest of subjects that will read the form.

Risks in pediatric clinical trials must be minimized as much as possible. The special considerations outlined in this whitepaper are some of the critical issues, and your IRB can provide insight into other key considerations.

It's important that the IRB used to review pediatric trials is one that regularly reviews human subjects research with minors and must be able to provide the appropriate expertise to effectively and ethically review such studies.

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About Kinetiq

Kinetiq is the clinical research and technology consulting division of Quorum Review IRB. We offer a powerful consultant network and decades of experience in streamlining operations and maximizing efficiency.

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Protocol Development and IRB Tailored Documents

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On-Demand Research Consulting

Kinetiq helps you navigate an ever-changing national and international regulatory landscape, including:

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- Medical Devices
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- Good Clinical practice

Why consult with us?

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