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Mother, may I? Obtaining consent in pediatric clinical trials

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Children are notorious for asking questions, aren't they? "Mom, can I do this?" "Dad, can I go here?" Parents are tasked with the responsibility and obligation to lead and protect their children; they are expected to do what is in their child's best interest.

But parents are not always the only ones who hold this responsibility. Sadly, and all too often, children become sick and require knowledge and intervention from medical experts. Once healthcare professionals are involved in the child's care, they now also share in this solemn responsibility.

And the stakes are especially high when a child with fragile health is involved and difficult medical decisions must be made.

The great news for children with delicate medical conditions is that pediatric research has made great strides in recent history. In fact, participation in a clinical trial can be some patients' best treatment option.[1] However, despite growing acceptance and popularity noticed by the author, pediatric clinical trials continue to have very distinctive challenges and characteristics, in part due to their unique subject population.

In this article, we will discuss informed consent and assent and the associated implications for the institutional review board (IRB), the parent(s) or legal guardian(s), the child, and the investigator.

Child assent, informed consent, and parental permission

Both the U.S. Food and Drug Administration (FDA) and the U.S. Department of Health & Human Services (HHS) have set forth additional safeguards for child participants in clinical research. These safeguards are codified in regulations located in the Code of Federal Regulations (C.F.R.) and extend beyond what is applicable for clinical research and the adult population.[2],[3] The FDA's rules (21 C.F.R. § 50.55) are similar but not identical to the regulations of the HHS that cover research conducted or funded by HHS (45 C.F.R. § 46). 45 C.F.R. § 46 subpart D provides protections for children involved in HHS-conducted or HHS-supported research. If an FDA-regulated clinical investigation is not conducted or supported by the HHS, 45 C.F.R. § 46 subpart D does not impose requirements on the investigation. However, the FDA has historically relied on the HHS regulations to provide appropriate guidance for pediatric studies.[4]

Child assent

In order to enroll a pediatric patient in a clinical trial, the child must assent, and permission must be granted by the parent(s) or legal guardian(s), as opposed to obtaining traditional "consent" from the patient (as appropriate, per 45 C.F.R. § 46.408 and 21 C.F.R. § 50.55). Assent is defined as a child's affirmative agreement to participate in a clinical investigation.[5] Mere failure to object should not, absent affirmative agreement, be construed as assent. Obtaining informed consent or assent does not merely consist of an individual signing and

dating an arbitrary piece of paper; rather, it is a process that begins with the initial interaction between the investigator and potential subject through completion of the clinical trial.

Assent has long been a controversial topic among those in the research community, with much of the debate arising where the regulations are silent. The regulations do not clearly define what information about the clinical investigation should be provided in the assent, or at what age clinicians should begin seeking assent from subjects.

Informed consent

Our medical practitioners are keenly aware that, apart from a few exceptions, the practitioner must obtain informed consent before treating the patient.[6] One stark contrast between getting consent from an adult and a pediatric patient is that a child is legally unable (i.e., has no legal standing) to provide informed consent on their own behalf, so investigators (and the child) are dependent on the child's parent(s) or legal guardian(s) to assume this duty.[7]

In 1991, the Common Rule established that the following components be addressed during the informed consent process, although a new element has since been added:[8],[9]

1. Explanation of the research;
2. Foreseeable risks;
3. Potential benefits;
4. Alternative treatment;
5. Confidentiality of records, compensation, and research-related injury;
6. Description of available medical care and compensation should an injury occur;
7. Contact information; and
8. Statement of voluntary participation.

These requirements of an informed consent still apply today; however, additional safeguards for children have also been established. These safeguards, as they are described in subpart D of 45 C.F.R. § 46 , address:

- Additional duties of the IRB;
- Clinical investigations not involving greater than minimal risk;
- Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects;
- Clinical investigations 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;
- Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children;
- Requirements for permission by parents or guardians and for assent by children; and

- Children who are wards of the state or any other agency or institution.

Although the components of information that are required to be provided to the prospective child participant have not been clearly described in the regulations, it would be reasonable to also include information about the child's condition, about what will happen and what to expect, and asking the child whether they would like to participate.

It is also imperative to ensure that the assent process be age and developmentally appropriate. A child's understanding and their preference for being included in decisions about their care are essential components of assent. Shared decision-making between the child, parent, and practitioner is a strong foundation on which to base assent. This process should be empowering and respectful, regardless of the child's age.[10]

Additional duties of the IRB

Although the absence of guidance in the C.F.R. does allow each IRB flexibility to implement assent requirements for their institution, it also affords the pediatric research community opportunities for inconsistencies across organizations during the assent process. Ensuring that additional safeguards and practices surrounding pediatric research are followed will certainly involve increased effort and more responsibility from the IRB; however, these safeguards are essential to ensuring meaningful and respectful research involving children.

While the IRB is expected to comply with general clinical research regulations, when enrolling a child for the participation in a clinical trial, 45 C.F.R. § 46.408 notes that the IRB must also determine that adequate provisions are made for soliciting the assent of the children and the permission of their parent(s) or guardian(s). These provisions include taking into consideration the child's age, maturity, and psychological state to ensure the child has the ability to assent. This determination may be performed for all children enrolled in a particular clinical trial, or on a case-by-case basis, as the IRB deems appropriate.[11]

In addition to ensuring that IRB membership requirements are met, 45 C.F.R. § 46.107 emphasizes that if an IRB regularly reviews research that involves a vulnerable class of subjects, such as children, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

An IRB may also determine that assent is not necessary or may waive the assent requirement in certain situations. For example, the assent of children is not a necessary prerequisite for proceeding with a clinical investigation if the IRB determines 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 child and is available only in the context of the clinical investigation.[12]

Likewise, the IRB can waive the assent requirement for children who are capable of assenting if the IRB finds and documents that the clinical investigation involves no more than minimal risk to the subjects; the waiver will not adversely affect the rights and welfare of the subjects; the clinical investigation could not practicably be carried out without the waiver; and, when appropriate, the subjects will be provided with additional pertinent information after participation. [13] Parental permission requirements remain in these circumstances.