The Essentials of the Informed Consent and Assent Process in Paediatric Clinical Trials

Everybody involved in paediatric drug development is aware of the complexity and sensitivity of the consent process in clinical trials involving the paediatric population. The specifics are due to the vulnerability of this population and the fact that somebody else (subject's parents or legal representative) has legal rights to make decisions on a child´s behalf. Additionally, in paediatric clinical trials, there is a requirement to have an assent form, a separate document addressing minors who are offered participation in a clinical trial. Since within the paediatric population, there are several age groups with varying levels of maturity and understanding capacity, the assent forms should be age-group-specific.

The informed consent form (ICF) and assent form (AF) documents play an essential role in paediatric clinical trials. The successful enrolment, compliance and retention of paediatric patients, as well as the overall success of a study, rely on the quality of these documents as well as the quality of the consent and assent process.

Informed Consent in Paediatric Clinical Trials

Informed consent in paediatric clinical trials is the voluntary agreement of (an) individual(s) with parental responsibility, or a legal representative, who has the legal capacity to give consent on behalf of the paediatric subject, and who also exercises free power of choice, without undue inducement or any other form of constraint or coercion.

Parental responsibility is defined as the rights and responsibilities that parents have according to the law for their children, including the right to consent to medical treatment for them, usually up to the age of 18. Mothers and married fathers have parental responsibility. In the majority of countries, unmarried fathers of children have the same responsibilities as long as the father is named on the child's birth certificate; however, in some countries it is not clearly specified within clinical trial legislation. Similarly, unmarried fathers who are not named on the child's birth certificate do not automatically have parental responsibility. Parents do not lose parental responsibility if they divorce, but it is important to know how the custody is assigned. Adoptive parents have parental responsibility, as do those appointed as a child's testamentary guardian, special guardian or those given a residence order. There are also country-specific differences when it comes to both parents needing to sign the ICF.

The definition of *legal representative* is a matter for national legislation and may include natural or legal persons, an authority and/or a body provided for in national law. Similar to clinical trials involving an adult population, the legal representative must not be "a person connected with the conduct of the trial."

The parent or person with parental responsibility is always the first step in the hierarchy of informed consent for a minor. If the child does not have parents, a personal

legal representative can sign the ICF and in the last instance, a professional legal representative.

Assent in Paediatric Clinical Trials

Assent is a term used to express willingness to participate in research by persons who are, by definition, too young to give informed consent, but who are old enough to understand the proposed research in general, its expected risks and possible benefits and the activities expected of them as subjects.

While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent to or dissent from participation and should be asked whether or not they wish to participate in the research.

The evaluation of whether or not a child can give assent should not solely be based on chronological age, but also on other factors such as developmental stage, intellectual capacities, life or disease experience, etc. The assent information sheets and assent forms should be age-appropriate and include information on the purpose of the trial as well as potential benefits and harms, in terms that are deemed honest, but not frightening. Ideally, such material should be shorter than that designed for adults. The legal requirements for an assent signature are country- and frequently EC- / IRB-specific. The assent form for a paediatric patient participating in a clinical trial is necessary, though in most countries there is no legal requirement stating the form has to be signed by the child, or at least not until up to a certain designated age. The clinical trial and the assent form must have prior approval from national competent authorities / ethics committees.

Although not legally required, it is advisable that the assent form contain a parent's signature as well, where parents will confirm by their signature that the study was discussed with a child, that the child has received answers to possible questions he / she had and that the child has agreed to participate in a clinical trial. Investigators should clearly document the date and time of the assent process in the child's medical records and briefly describe the whole process including any possible questions asked by the child.

In the majority of cases, the assent forms are used for children of school age (about 5-8 years old) as it is assumed that they are able to read and write by that age. It is common to have one assent form for children between the ages of 5 and 11, although some IRBs / ECs require having two separate documents for younger children (5-8 years) and older children (9-11 years) because of the different understanding capacity and educational levels between these two groups. Adolescents (12-18 years of age) usually have only one assent form covering the whole age group. In specific circumstances, the assent form can be developed for children younger than 5 years of age. This should be predominantly pictorial, with very simple sentences to be shown/read to the child by his/her parent/guardian. Protocols could be supported by videos or audio-tapes, cartoons or drawings.

Apart from the legal and local IRB requirements for the ICF / AF, it is essential to stress the importance of the proper consent and assent process at the site level. Investigators should be well trained and prepared on how to approach parents and their children, as well as potential study subjects.

The family should have sufficient time to consider the information, as well as time and opportunity to ask questions and have those questions answered. During this process, investigators/ coordinators are allowed to use the IRB- / EC-approved informational brochures for parents and children and other aid tools in the consent and assent process. Recognising the perspective of families is critical to supporting site efforts to recruit and retain children in trials.

To many, the term informed consent / assent is mistakenly viewed as the same as getting a research participant's signature on the consent / assent form. However, obtaining a research participant's verbal or written informed consent is only part of the process. Especially in paediatric clinical trials, it is important to have regular conversations with the whole family to provide necessary information and answer any possible questions asked by parents / legal representatives or from the child throughout the entire duration of the study.

One of the most important hallmarks of paediatric clinical trials is that the participating subject is really the whole family. That is why the consent / assent process is much more complex and challenging. The process of consent and assent in paediatric clinical trials is an interactive and iterative process among investigators, parent(s) and the child that needs to satisfy regulatory policies and ethical principles for consent. Parents and patients need details about the clinical trial requirements and time commitment, while children need materials that accurately reflect what will be asked of them in a language they will understand.

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