

# Challenges and practicalities of obtaining parental consent and child assent in paediatric trials

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## Abstract

*The paediatric patient population represents a vulnerable subgroup of potential clinical trial participants requiring special measures to protect their rights, their dignity and their welfare. Although they are not treated as autonomous decision-makers, paediatric patients have the same basic rights as adults. This means that sponsors, investigators and parents must respect their growing decision-making capacities and involve them in discussions about their health and participation in a clinical trial. Most importantly, the dissent of a child capable of understanding the information presented to them should be honoured.*

*The Clinical Trials Directive 2001/20/EC defines the requirement of assent from the participating child, although to date there is no uniformity in Europe about the procedures and content of informed child assent which takes into account the capacities of different age groups.*

*Local laws and regulations should be followed, but often only the legal age of adulthood is clearly defined. The investigator must define whether a child has the capacity to give informed assent, and the relevant Ethics Committee needs to approve assent forms in different paediatric age groups.*

*This article provides an overview of the paediatric consent process and discusses practical considerations and potential obstacles in different age groups.*

## Introduction

The use of unlicensed and off-label medicines in children is widespread and has been of increasing concern over the years, with around fifty per cent of medicines currently used in children never having been studied in this population.<sup>1</sup> The general lack of information and appropriate pharmaceutical formulations may expose children to unwanted side-effects or under-dosing without the expected efficacy. These concerns have resulted in a demand for more paediatric studies to support use of medicines in children on a European and global basis.

The European Paediatric Regulation No 1901/2006 was implemented in January 2007 to facilitate clinical research in children. As of February 2010, the Paediatric Committee (PDCO) at the European Medicines Agency (EMA) has validated 683 Paediatric Investigation Plan (PIP)/waiver submissions. Of these, more than 500 paediatric clinical studies have been required, with efficacy and safety studies representing the majority.<sup>2</sup>

Paediatric clinical studies pose unique challenges to the pharmaceutical industry with regard to trial design, owing to the physiological and psychological diversity of paediatric age groups. Often, different approaches are necessary in respect of study design, study assessments (especially those concerning potential harm and invasiveness) and the use of age-appropriate paediatric formulations.

One of the most significant hurdles to successful recruitment into paediatric studies is obtaining informed consent from the parents/legal guardians and, where applicable, assent from the participating children. This can result in the extension of study timelines and excessive costs. In the set-up and conduct of paediatric studies, the assessment of risk and impact on the study is paramount. A careful evaluation of the obstacles to patient recruitment is essential, as it will allow recruitment strategies to be developed with robust contingency planning.

## Paediatric informed consent process

Generally, four elements are required for a fully valid consent: competency, information/disclosure, understanding and voluntariness.<sup>3</sup> According to the Good Clinical Practice guideline (ICH-GCP E6), informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial (voluntariness), after having been duly informed of all aspects of the trial, its nature, significance, implications and risks that are relevant to the decision-making process (information/disclosure) in a way that the patient can comprehend and understand the relevant information (understanding). Informed consent must be documented in a written, signed and dated informed consent form.<sup>4</sup> The patient must have the capacity and competency to make the decision. Competency is a legal term used to indicate that a person has the ability and is mentally capable to make and be held accountable for his/her decisions (competency).

The above general rules for informed consent were established for clinical trials performed in adults who are able to give informed consent personally. However, there are specific trial settings where adaptation of the above is required, such as trials involving mentally incapacitated persons or emergency settings as well as in paediatric clinical trials. The consent process here is more complex as it involves both parents and child:

- **Competency:** As a rule, a paediatric subject is legally unable to give informed consent, and can only 'assent'. The child's assent is required, depending on age, but not sufficient allowing participation in a clinical trial. Therefore paediatric study participants are dependent on their parents to consent to their participation in clinical studies.<sup>5,6</sup>
- **Information/understanding:** Depending on the age, a child does not yet have the decision-making capacity to fully comprehend all information on study details, its nature, implications, related risks and benefits. Thus, the parents are required to make an informed decision on their child's study participation and must represent the child's will.

**Table 1: Summary of important elements to be considered when obtaining parental consent**

**General:**

- Complete and balanced information
- Understandable information
- Thorough risk and benefit assessment
- Measures taken to preserve child's safety
- Rights of parents and child
- Consider child's presumed will
- Voluntariness of participation
- Enough time for parents to consider the options available and discuss with family
- Investigator and site staff available to answer questions
- Keep parents informed throughout the study
- Parent information package (see below)

**Parent information package:**

- The need and purpose for clinical studies
- Rationale for experimental treatment
- Background information on the disease
- Detailed information on the study drug
- Condition under study.

Therefore special consideration needs to be given to the consent process in paediatric clinical trials, also considering that different approaches are required depending on the age of the paediatric patient.

According to the note for guidance ICH Topic E11, paediatric age groups are separated into the following categories mainly based on physiological and developmental similarities and pharmacological parameters:<sup>6</sup>

- Preterm newborn infants (<36th gestational week)
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years (dependent on the geographical region)).

This categorisation of age groups provides a basis for developing the study design in paediatric patients and discussion of different approaches in the consent process.

### Obtaining informed consent from parents/legal guardians

Recruitment of paediatric patients into clinical studies is challenging for several reasons. These include parental anxiety relating to the diagnosed condition and prognosis, and to submitting their child to 'experimental

procedures'. The fear of invasiveness and pain for their child, and taking responsibility to consent their child to a study, can greatly concern parents and result in their not giving consent. This is particularly important for studies in newborns and infants where the child cannot express any willingness to participate.

The structure and content of the parent information sheet and the parent informed consent form follows the same international rules as for an adult patient information sheet and informed consent form. In general, both parents need to give consent and sign the informed consent form, although there are regions where the consent of only one parent is considered adequate.<sup>7</sup> Informed consent should be obtained from parents in accordance with local laws and regulations. Table 1 provides a summary of important elements to be considered when obtaining parental consent.

Trust and a close relationship between site staff, the parents and the child are of crucial importance and have been shown to be one of the major factors for parents agreeing to a clinical study in addition to balancing risks and benefits to their child. Besides that, altruistic factors, like helping to develop medical knowledge and learning more about the child's disease, play an important role in parental decision making.<sup>8,14</sup>

### Obtaining assent from paediatric subjects

In paediatric study settings a triad exists between the investigator, parents and child, which requires special attention in the informed consent process.<sup>9</sup> The child should be included in the decision-making process to the extent possible depending on their age and maturity. According to the Declaration of Human Rights, a child is to be considered as a person with all basic human rights from the day of birth. Asking the child for assent recognises the dignity, integrity and autonomy of self-determination and respects the expression of the child's willingness to participate. Assent means having the child express agreement to undergo a medical procedure in a clinical trial.

The informed consent process should be conducted appropriately to discover the will of the child and respect the decision-making capability of the child. It is necessary for site study personnel to have experience in the caring for and treatment of children in the respective age group, and that they are familiar with age-specific issues. The parents must assist in determining the will of the child which also needs to be considered in the parental consent.

Generally, depending on the age range of clinical study participants, separate information sheets and assent forms should be created to provide information in age-appropriate language and wording and should be focused on the purpose of the trial, the procedures required, the benefits and risks, the voluntarily participation in the trial and most importantly the child's agreement to participate. The child's involvement in the decision process and ability to give assent increases with their age; in the US, the age of assent is endorsed to be seven years, whereas in the EU, with no clear guidance, nine years is considered reasonable.<sup>10,11,12</sup>

Of course there is variation among children of the same chronological age in the level of understanding, mental maturation and ability to make decisions. The underlying condition and disease pattern also plays a role. The information provided to the child should be adequate to his/her individual level of understanding but also consider the child's individual psychological and intellectual maturity and social environment. Children are not autonomous individuals and therefore decision-making is also dependent on the social structure of the family. Some children of the same age may be fully involved in the consenting process and be able to give informed assent, whereas others will feel more comfortable deferring the decision to their parents.

The investigator must decide whether an individual child has the ability to understand the information and provide assent. The minimum age of assent should be decided in advance of study start with the Ethics Committees, considering the study setting and underlying disease.<sup>13</sup>

Paediatric participants of appropriate intellectual maturity should personally sign and date a written assent form. In all cases, the paediatric participants should be made aware of their rights to decline to participate or to withdraw from the study at any time.

There might be clinical study settings, however, where the child's dissent may be overridden when participation is likely to benefit the child (eg, life threatening diseases or if no alternative therapies exist or these are only available in the context of research).<sup>10</sup>

### Newborn and infants/toddlers

Paediatric patients aged 0-2 years cannot express their willingness to participate and so consent of the parents is sufficient. However, special notice needs to be given to signs of undue distress in patients who are unable to articulate.

**Table 2: Differences in assent process among paediatric age groups**

Age Group	Assent contents	Expression of child's willingness to participate
Preterm, infants and toddlers 0-2 years	Informed consent of parents sufficient	Monitor signs of undue distress
2-5 years	Informed consent of parents sufficient; but: verbal simple explanation of specific study procedures, where appropriate, possibly supported by pictures or videos	Monitor signs of undue distress and child's unwillingness to undergo specific procedures
6-8 years	Pictures of study procedures, short comics or videos to help child to understand what they can expect	Monitor signs of undue distress and ask child about its feelings and willingness to undergo a specific procedure
9-11 years	<ul style="list-style-type: none"> <li>● Basic information supported/illustrated by pictures</li> <li>● Short and simple assent form</li> <li>● Age appropriate language</li> <li>● Should be directed to the child</li> <li>● Consider signature for written agreement from child</li> </ul>	Ask child about its feelings and get verbal agreement of child to undergo a study procedure. Consider if older children should sign on the assent form when agreeing to the clinical study procedures. Minimum age for signed assent form is dependant on EC requirements, disease condition and child's individuality
12-17 years	<ul style="list-style-type: none"> <li>● Could mimic informed consent form of parents</li> <li>● Age appropriate language for younger adolescents</li> <li>● Should be directed to the adolescent</li> <li>● Date and signature field for adolescent's written agreement</li> </ul>	Obtain verbal and written agreement (signature on assent form) of adolescent for study participation

In newborns and infants, clinical study considerations include the vulnerability of the patient population and the development status of critical organs such as the skin, liver, kidneys, gastrointestinal tract, immune system, central nervous system, heart and lungs. Parents of babies, specifically those born prematurely, may be reluctant to allow their child to participate in a clinical trial with an experimental product as they are often in a tremendously emotional situation which makes it difficult for them to absorb information on a disease they may have little understanding of. Especially in this age group, the parent/investigator/research nurse relationship is crucial. Importantly, investigators need to provide sufficient time with the parents to discuss their concerns and questions at the beginning and throughout the study, so the parents are comfortable with their decision throughout the study. Previous investigations have shown that parents were significantly more unlikely to accept research in an emergency setting, as it is in neonatology.<sup>14</sup>

Bearing this in mind, considerations need to be given on the content of the parent information sheet. The information should be provided in a concise but thorough manner. Possibly, the study drug in question may not have been given previously to children of this

age and therefore no detailed information on risks and side effects is available. Thus, the risks and benefits of this study setting needs to be discussed in detail with the parents.

### Children (2-11 years)

This patient group may understand basic information on the nature and purpose of specific study procedures and the possible distress connected with them, and they may express willingness to undergo specific procedures within a clinical trial.

As this age group includes several cognitive and mental development stages, different approaches are required in obtaining assent.

Children from 18 months up to around seven years interpret reality in an egocentric fashion and from their own experience and cannot consider another point of view.<sup>15</sup> Therefore, it is difficult to assess the child's willingness to participate. The investigator and parents must carefully consider participation of the child in the clinical trial. Although a written assent cannot be obtained in this age group, there are ways to provide the child with basic study information; for example, the study could be presented in terms of a picture story or a comic or even a video. Ethics Committees usually do not request assent in this age group

(2-6 years) and parent consent is sufficient, although signs of unwillingness from the child or objections to specific procedures need to be respected and handled appropriately by the investigator by continuously evaluating further study participation of the child.

As children of school age can usually read and write, a written assent form should be provided. Children just starting school still have difficulty reading, so the text can be illustrated with pictures. From the age of around nine, children may be able to understand the aim, benefits and risks of research but are less able to understand conflicting or abstract information.<sup>11</sup> For this reason, written assent forms are often requested by Ethics Committees for children in this age group. However, opinions differ on whether the assent form requires signature at this age, as some consider obtaining assent of such young people as inappropriate, due to the minimal level of understanding and comprehension. The Austrian Ethics Committees Forum, for example, recommends the age of assent as 14 years.<sup>16</sup>

It was shown that children with chronic diseases are well-informed about their disease and may already understand study settings, benefits and risks earlier than their peers.<sup>10,16</sup>

**Adolescents (12-17 years)**

Adolescents have the capacity for independent decision-making and already make decisions in many other areas of their lives.

Adolescents go through huge hormonal and emotional development between the ages of 12 to 17 and have issues with accepting authority, sexual development and possible exposure to drugs of abuse. Abstract thinking is achieved at around the age of twelve and is well-developed by the age of 14. Reasoning becomes more logical.<sup>17</sup> Thus they are capable of discussing hypothetical situations and problems by considering personal experiences and other external factors. It has been shown that adolescents have almost the same level of understanding of informed consent information as adults, but their decisions may be based on present feelings/emotions and often not include or consider future implications, especially in younger adolescents.<sup>18</sup>

Adolescents always need to be included to the greatest extent possible in the informed consent process by providing written assent. In this age group the content of the assent form might have the same structure and may cover the same aspects as the one for the parents. The assent form should be separate from the parents' information sheet and consent form and should be directed to the child, personally asking the child of agreement to participate.<sup>10</sup>

**Conclusion**

The consenting process within paediatric clinical trials is more complex than in adult trials. Paediatric patients are legally incapable of providing valid consent on their participation in a paediatric clinical trial and require parental written informed consent. The consent of the parents should express both their own wishes and the will of their child.<sup>7</sup> Table 2 summarises different approaches of obtaining assent in the different age groups.

An assent process that protects the child's dignity and welfare is crucial, and should be adapted to the developmental, social and psychological variabilities among paediatric patients. Investigators, study sponsors and Ethic Committees must take these variabilities into account.

Meanwhile, future efforts should be directed to provide a clearer picture of the ability of children to understand research and provide detailed guidance on the informed consent and assent processes in different developmental ages, while also considering cultural and familiar influences.

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