

Ethical Concerns in Research Involving Children: “*Understanding in order to Evolve*”

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Abstract: The involvement of children in clinical research is inevitable if major breakthroughs are to be achieved and healthcare improved. However, children are a most vulnerable population and require special protections since they are less able to express their needs or defend their interests. To encourage pediatric research, studies to be conducted responsibly, an extensive ethical debate has unfolded over the past decade. This article analyzes specific ethical concerns surrounding pediatric research. The primary ethical principles as well as some persistent ethical dilemmas are discussed in order to evaluate how these issues are commonly addressed. The main objectives include developing a discussion on how these paradigmatic approaches work within the specific setting of pediatric research and how to use those approaches for this population for the safety and success of pediatric research.

Keywords: Pediatric research, children, research, ethics.

BACKGROUND

Research involving human beings has established adequate regulations over recent decades based on a significant volume of well-understood principles. From a historical perspective, it is currently possible to appraise the entire evolutionary process of ethical research in adult patients and adeptly and appropriately apply it to the pediatric population. Unfortunately, children may still be treated as a miniature adult and some investigators insist on maintaining the outdated and unfair idea that the pediatric patient will always be incapable of assent or even consent in the mature minor. Recognizing children as beings endowed with agency and able to understand the world around them, even considering their subjective identity, is essential [1-3].

Prior decades have borne witness to remarkable advances in pediatric care, many of which are based on clinical observations or results extrapolated from studies in adults. However, the physiological differences between adults and pediatric patients often do not allow findings from research conducted in adults to be generalized to the pediatric population [4]. As children are clearly not small adults, are affected by a different variety of diseases and metabolize medica-

tions differently which results in responses to treatment that are unpredictably different from those found in adults, studies undeniably need to be conducted in children in order to achieve major breakthroughs and to substantially improve pediatric healthcare and quality of life [4, 5].

While research in pediatric patients is unquestionably essential, children require special protection since they are less able to express their needs or defend their own interests. Therefore, children should not be subjects of research if the experiments can be performed on adult patients, i.e. subjects capable of giving their informed consent [6]. Consequently, clinical research involving pediatric patients must respect the dignity, the well-being and the rights of children, all of whom are vulnerable and unable to give informed consent [6].

Based on respect for pediatric patients and their uniqueness, and recognizing that it is important to “understand in order to evolve”, the purpose of this paper is to outline and explore some of the most important aspects of research involving children which provides researchers an improved approach to the safety and the success of pediatric research.

RESEARCH INVOLVING CHILDREN

A fundamental pillar of any research study involving children is the ethical principle of “scientific necessity”.

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This principle recognizes that children should only be the subjects of research if the experiment cannot be performed in adults or if the results obtained from that population cannot be extrapolated to pediatric patients. However, if the research has been shown to be necessary, it should involve the least vulnerable among them [5, 7] and the interest of the child must always prevail over the interests of both, science and society [6].

Children are considered vulnerable subjects who should be protected from research risks [2, 5, 6, 8]. Indeed, vulnerable populations include all those lacking the capacity to understand information presented to them and are unable to give their informed consent [2]. The vulnerability of pediatric patients results from a number of factors, including their lack of maturity to make decisions and their dependence on caretakers, which can devalue their rights and interests [5, 9]. Recognition of this vulnerability is imperative when developing regulations and guidelines for research in pediatrics. Given the duality of the matter, in which both protectionist and participatory positions on pediatric research are involved, efforts should focus on supporting the practice of high quality research and on upholding ethical principles [6, 10].

As in the case of research conducted with adult patients, the core ethical principles in research involving children are respect, justice and benefit [6]. Each one of these principles merits critical discussion and debate since understanding the meaning and application of these principles is crucial in ensuring the integrity of the research on these vulnerable subjects.

The *Respect* principle means valuing the children and recognizing their dignity. Despite being one of the most important principles, it has seldom been taken into consideration in research involving children [6, 11, 12]. Obtaining informed consent from the guardians and assent from the children when applicable is the most correct manner in which to show respect. This entails negotiation with the children participating in the research process and their parents/guardians. Furthermore, it involves respecting individual and collective rights during explanations and negotiations, ensuring that all the information is given, including the right not to participate [4, 12, 13].

The ethical principle of *Justice* arises in the relationship between the research, the children and their guardians. It requires dialogue and conversation, and is based on the capacity to provide the attention

needed to the differences. *Justice* ensures that children will be treated fairly and equitably. According to Aristotle, distributive justice consists of "treating equals equally and unequals unequally" [14].

The *Benefit* principle is of extreme importance in safeguarding children in research. This principle is made up of two different components: non-maleficence and beneficence. The first means *to do no harm*, i.e. it requires the investigators to avoid harming or injuring children [8, 15], whereas, beneficence refers to actions taken to promote well-being [10].

Indeed, before initiating a research study involving pediatric patients, it must first be shown either that the intervention involves little risk or that there is a sufficient direct benefit (well-being). Therefore, to enroll a child in a research study, an appropriate balance has to be established between the risk and the potential direct benefit. The risk must be small and the child should not be placed at any disadvantage, exposed to any excessive risk or fail to receive necessary healthcare [7, 16].

In practice, it is difficult to assess the risk to pediatric subjects, since this measure is extremely subjective and may change over time; however, it is essential to determine the level of risk and the associated potential benefits in order to guarantee the child's ethical rights. The following risk levels must be taken into consideration prior to approving any research study involving children [6, 16]:

- Minimal/low risk - probability of harm or discomfort not greater than that ordinarily encountered in daily life.
- Minor increase over minimal risk
- Greater than minor increase over minimal risk

A *benefit* can be defined as any improvement in treatment, diagnosis or prevention that will result in benefit to the child (direct benefit) or to children as a group [6]. However, there is a general consensus that a child's exposure to any kind of risk in research must be minimal or low in the absence of any direct therapeutic benefit to that child. In the case of a direct benefit, the US Food and Drug Administration (FDA) regulations allow pediatric research involving an intervention or procedure with more than a minor increase over minimal risk if the outcome of that research could contribute towards increasing the wellbeing of that research subject [5, 16].

The above mentioned considerations highlight how difficult it is to determine the threshold at which there is sufficient direct benefit to justify the risk of the experimental intervention. This, in turn, depends on the severity of the disease and the adequacy of the alternative forms of treatment available [9].

Recently, increased attention has been paid to specific ethical concerns such as informed consent and assent, payment and placebo groups [6]. Therefore, a brief discussion on each one of these topics is provided below.

INFORMED CONSENT AND ASSENT FOR CHILDREN

Informed consent represents a fundamental step in ensuring that research conducted with human beings is performed ethically and appropriately. As children are considered a vulnerable group because of their limited capacity to make decisions, their parents or legal guardians are asked to provide their informed consent. The child's legal representative is his/her parent or legal guardian, as defined by the relevant legislation of the country; the individual who is able to consent on the child's behalf [5, 13]. Consent, if given, must be written, dated and signed, and all the information about the experiment, such as its implications, benefits and risks, must be appropriately documented. If the person is unable to write, oral consent in the presence of at least one witness is permitted in certain exceptional cases [13, 17].

Regarding the informed consent process, regulatory guidelines require that consent must be sought prior to enrolling a child to a study. More specifically, consent should be given in advance, with sufficient time and the necessary information to allow the study and its procedures to be analyzed carefully by the parents/guardians [3, 17]. The only situation in which the consent form could be waived is in emergency settings in which there is a direct benefit to the subjects or low risk studies involving retrospective chart reviews when it is impossible to contact the participants. Other specific situations such as those involving abused or neglected children must be analyzed carefully by the relevant review board in order to protect the children participating in the study [8].

On the one hand, the informed consent form is mandatory and the assent form should be obtained whenever possible. On the other hand, assent can be waived under certain circumstances such as: if the

children are judged incapable of giving permission or if the study offers substantial direct benefit to the child [4, 13, 18]. The reports regarding the assent form do not specify what elements have to be included, but for the majority of experts they do not need to be as rigorous as with the consent form [13]. However, some aspects are essential, such as providing a proper understanding of the nature of the condition and disclosing everything about the intervention and who will be involved [13, 14].

In fact, there are no specific rules regarding the content of the assent form, including whether it indeed needs to be signed. Some regulatory boards understand that the assent form should include all the elements contained in the consent form, differing only with respect to the need to evaluate children's comprehension of the elements as a measure of the adequacy of assent [19]. These elements include all the procedures, risks and benefits, freedom to withdraw, voluntariness and confidentiality. Nevertheless, some studies have determined that younger children have a poor understanding of those contents [20].

In general, children from birth to 3 years of age are unable to comprehend research studies or to give assent; rather, children of this age have an emerging tendency to agree. At 3-4 years of age, children are able to comprehend a certain degree of altruism, and by the age of nine, children may be able to understand benefits and risks, although they are less able to understand conflicting or abstract information. Cognition studies support that children below 9 years of age are incapable of truly understanding research. At any age, the most important aspect is to provide the child with the greatest amount of information possible in accordance with their degree of understanding and to obtain assent, preferably in writing, if the child is able to read and write (preschool and school age) [6].

Adolescents constitute a complex population subset in pediatric research. They are part of the pediatric population but are capable of making decisions just as adult patients are. Since adolescents are able to make decisions, regulatory boards recommend obtaining informed consent from the parent/guardian and assent from the child. Special attention should be paid if an adolescent of 16 to 18 years of age is defined as legally capable according to the country's legislation or in the case of an emancipated minor. In such cases, it is mandatory that the adolescent sign the informed consent form as would any adult patient, with the consent of the parent/guardian not being required [6].

PAYMENTS TO PARTICIPATE IN RESEARCH STUDIES

There is still no well-established regulation on compensation for participating in clinical trials given the obvious conflict that any kind of incentive may affect decision-making [21]. It is important to distinguish between reimbursements and payments aimed at encouraging potential participants to enroll in the study. The former consists of compensating participants for their travel expenses, parking costs or for the inconvenience of taking part in the research study, whereas payments for enrollment consist of giving money to individuals who agree to participate. Most review boards consider reimbursement for time and inconvenience to be appropriate and believe that such reimbursements do not appear to violate any ethical principles, and are indeed essential in enabling children to participate in the research study. On the other hand, payments to encourage enrollment should be avoided, since they could potentially affect the parents' decision in favor of participation against the vulnerable child's wishes and best interests [22].

PLACEBO GROUP

The use of a control group, more specifically a placebo group, in studies involving children is more limited than studies involving an adult population. The use of placebos in children has to be evaluated carefully and the "principle of equipoise" should be applied. This combines the "principle of uncertainty" (there is no scientific evidence that any one of the treatments is better than any of the others) and the concept that no one enrolled in a trial should receive an inferior treatment [23].

Therefore, the situations in which placebo may be considered for use in a control group occurs when the experimental intervention is the first therapy that could potentially modify the course of a disease process or when the efficacy of the current therapy available is questionable or the frequency of undesirable side effects is high [24].

CONCLUSION

Research in pediatric patients is unquestionably important and essential if major breakthroughs are to be achieved and healthcare improved in our most vulnerable patient population; due to this inherent vulnerability of children, investigators must be aware of the ethical requirements and follow such principles

aimed at guaranteeing children's safety when participating in research studies. Because of these complex ethical issues associated with research studies involving children, researchers need to recognize which children are capable of being involved in decision-making and must critically engage the ethical principles which are essential to safe and successful investigations. Well-designed studies ensure that no ethical requirements are violated. Therefore, it is important to approach both guardians and children regarding enrollment without exerting any pressure on them, while providing all the necessary information, explaining all the pertinent benefits and risks, and, most importantly, ensuring that the child may withdraw from the research study without compromising the child's healthcare.

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