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Consent forms: the participation of children in research

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Abstract

The Resolution 466/2012 of the National Council of Health establishes the term of assent as compulsory for research carried out with children. However, the resolution presents the definition of assent without specifying the terms necessary for the document. This gap makes current and pertinent the approach of this topic by this study, which aims to discuss the participation of children in research. The results present a theoretical framework from which we can reflect on the ethics of Research with children, considering their vulnerability, which can lead to irreparable situations. We conclude that the theme must remain in the academic and professional debates since, on top of being a dynamic reality, this population segment has many specificities.

Keywords: Ethics. Ethics committees, research. Child.

Resumo

Termo de assentimento: participação de crianças em pesquisas

A Resolução do Conselho Nacional de Saúde 466/2012 estabelece a obrigatoriedade de termo de assentimento para pesquisas realizadas com crianças. No entanto, a resolução apresenta a definição de assentimento livre e esclarecido sem especificar os elementos necessários para o documento. Essa lacuna torna atual e pertinente a abordagem desse tema proposta pelo presente estudo, que tem como objetivo discutir a participação de crianças em pesquisas. Os resultados apresentam um arcabouço teórico a partir do qual se pode refletir sobre a ética em pesquisas com crianças, tendo em vista sua vulnerabilidade, que pode levar a situações irreparáveis. Conclui-se que o tema deve permanecer nos debates acadêmicos e profissionais, pois, além de a realidade ser dinâmica, muitas são as especificidades desse segmento populacional.

Palavras-chave: Ética. Comitês de ética em pesquisa. Criança.

Resumen

Término de asentimiento: participación de los niños en investigación

La Resolución del Consejo Nacional de Salud 466/2012 brasileño dispone que el término de asentimiento es obligatorio en las investigaciones que involucran a niños. La resolución trae la definición de asentimiento informado, pero no detalla los elementos que deben contener el documento. Con base en esta laguna actual y relevante, este estudio pretende discutir la participación de los niños en investigación. Se presenta un marco teórico desde el cual se reflexiona sobre la ética en la investigación que involucra a niños dada su vulnerabilidad, lo que puede llevar a situaciones irreparables. Se concluye que el tema tiene que seguir en los debates académicos y profesionales, porque, además de que la realidad es dinámica, existen muchas especificidades para esta población.

Palabras clave: Ética. Comités de ética en investigación. Niño.

Research

The authors declare no conflict of interest.

Children began to take place in the laws and codes of the world only in the 20th century. The discovery of children as a subject of rights led several institutions and segments of society to fight for laws in defense of this population, considering its fragility and dependence [1]. Hence, we have made some progress in respecting children as moral agents, citizens with rights and duties. Thus, we highlight the creation, in 1946, of the United Nations Children's Fund (UNICEF), considered one of the main institutions in the fight for the defense and guarantee of the rights of children and adolescents.

Brazil enacted, on July 13, 1990, the Statute of the Child and Adolescent (ECA) via Law 8,069 [2]. For the purposes of this law, children are people up to 12 years of age and adolescents, those between 12 and 18 years of age. The statute, the most important document to protect this population, establishes, among other determinations, that children have the right to freedom of opinion and expression and that their autonomy must be respected [3]. However, Brazil considers children legally incapable of making decisions since they do not meet the minimum conditions to make autonomous and rational choices, requiring other people to decide for them. According to article 3 of Law 10,406/2002, which establishes the Civil Code, *minors under 16 (sixteen) years of age are absolutely unable to personally perform the acts of civil life* [4].

Thus, children are leveled to one and same condition, requiring that other people decide for them. These people are usually the children's parents who, in principle, have an interest in their children's well-being. This right is a sociocultural issue which is inherent to the condition of paternity and motherhood and, therefore, parents' decisions must be respected. When parents are absent, or unable to decide for some reason, there may be intervention by the Judiciary to appoint a legal guardian [1].

The Federal Constitution and the ECA cover the rights of children in general and, although some articles are more specific to the area of health, there was a need to protect the right of children within the hospital. For this reason, another specific document was promulgated on the subject in Brazil: Resolution 41/1995, of the National Council for the Rights of Children and Adolescents, which approved in its entirety a text from the Brazilian Society of Pediatrics entitled *Direitos da Criança e do Adolescente Hospitalizados* (Hospitalized Children's and Adolescents' Rights) [5].

We highlight the following points in this document: the right to adequate knowledge of their illness—according to their cognitive phase, therapeutic care, diagnosis, prognosis; the right to receive psychological support when necessary; the right not to be subject to clinical trials or diagnostic and therapeutic evidence without their informed consent—when they have the judgment to do so—and from parents or guardians; the right to confidentiality of clinical data; and full respect for their rights by hospitals [6].

The principles of beneficence, non-maleficence, justice, and equity are implicit in these documents, making it clear the importance of including children, according to their degree of development, in the decisions which concern them. This is true for children included in scientific research and for providing them with assistance.

Despite advances in the protection of children's rights (hospitalized or not), gaps remain between theory and practice and these rights are still violated around the world. Thus, must know the rights of children and make a joint effort to guarantee them, enabling children to participate in this process, helping them in their development as moral agents and subject of rights.

In this context, CNS Resolution 466/2012 [7] and CNS Resolution 510/2016 [8] contemplate the obligation of informed consent forms for research conducted with children. These resolutions are clear as to what should compose this term but interpretation of these regulations is left to local research ethics committees (RECs), which are also responsible for defining the age at which assent should be obtained. Considering this context, this study aims to discuss the use of informed consent form in research protocols.

Method

A narrative review of the national and international scientific literature was carried out in three electronic databases: Scopus, LILACS, and SciELO. Complete review articles, editorials, and

theoretical studies written in Portuguese, Spanish or English were included.

In addition to using the descriptors "ethics research *and* child" in the search on these databases, the word "children" was used but no change was observed in the results—to reach this conclusion, the titles of all articles were checked. No restriction on date of publication was set as this was a variable of interest, that is, knowing when issues related to ethics in research with children began to be discussed. Finally, it should also be noted that many articles on LILACS also appeared in the SciELO database.

Thus, adding the selected articles in the three chosen databases, a sample of 39 articles was obtained after our entire selection process (shown in Figure 1 and Chart 1).

Figure 1. Flowchart of the search on the three chosen scientific databases

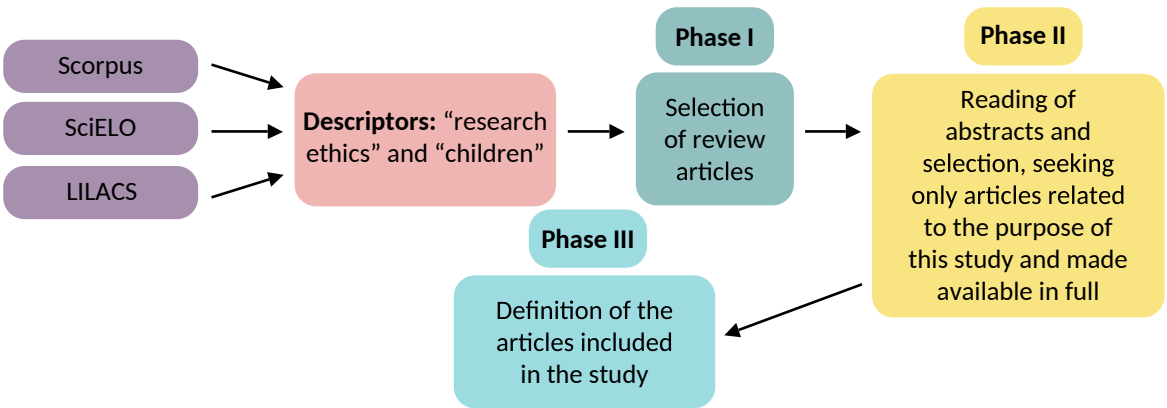

Chart 1. Number of articles found in the three scientific databases

Database	Phase I	Phase II	Phase III
Scopus	117	53	33
SciELO	50	4	3
LILACS	57	7	3

Analysis of the articles followed the thematic strategy proposed by Bardin[9]. After the articles were read, registration units were identified, considering the phrases or expressions which represented what authors thought on ethical issues. Then, these units were grouped into themes. In total, four themes were found: research with children, consent, parental consent, and risk-benefit analysis.

Results and discussion

The studies found were classified by year of publication and country of origin. Overall, four registry units were identified: 1) research involving children; 2) consent forms; 3) parental consent; and 4) risks and benefits in research involving children.

Regarding country of publication, most articles were published in the United States and Western European countries, showing a predominance of discussions and standards imposed by these regions in bioethics and, more specifically, in research ethics.

Of the 39 articles, only three are from Brazil. This finding shows the late entry of the country in the discussion and the importance of a review like this to identify the points of debate to establish ethical guidelines in research with children.

Research involving children

Children, newborns, infants, and adolescents are considered vulnerable participants in research. Some reasons for this vulnerability are lack of legal capacity to provide informed consent, of self-determination or autonomy, and of understanding of the risks and benefits of participation since cognitive skills at this stage are still partially undeveloped. Thus, children—and,

in general, all research participants—are considered susceptible to coercion or undue influence regarding their decision to participate in a study [10,11].

For Davidson and O'Brien [12], if a survey can be conducted with adults or children who are equally likely to generate the same knowledge, guidelines dictate that it be conducted with adults. However, Harris [13] states that there must be a balance: if such a prohibition compromises an investigation, research should neither assume that children would refuse to participate nor that they are excluded from the exercise of citizenship that all people share.

Pediatric investigations are essential to improve children's health outcomes. According to Burns [14], Spriggs and Caldwell [15], and Brierley and Larcher [16], it is unethical to deny this population the benefits of new interventions or new drugs. Those who think they are protecting the interests of children by preventing them from participating in investigations are deceiving themselves. In the absence of specific clinical trials, doctors, families, and health authorities are forced to extrapolate the results of studies with adults. This generates a series of problems as children are not small adults and can show different responses (including harmful ones) to an intervention depending on their degree of development.

Thus, research should avoid extrapolating data obtained in studies with adults as children show differences in pharmacokinetics and pharmacodynamics, which makes it difficult to predict the ideal dose of a drug before the first pediatric trial. This prediction is fundamental since overdose increases the risks of adverse events and low doses may result in drug resistance in the presence of a viral load. Without pediatric trials, until the dose-discovery process is completed, many children fail to benefit from the drug. Moreover, there are pediatric diseases whose treatments can only be evaluated specifically for this group [17,18].

It is estimated that 80% of the drugs considered suitable for use in children have inadequate information on pediatric dosage [17]. The literature offers many reasons for its lack of studies, such as little financial incentive for pharmaceutical companies to develop pediatric research, high cost of studies compared to the size of the potential market, and complex ethical issues involving research with children [19].

Researchers must respect children's cognitive ability to understand the investigation in which they will take part, considering them as citizens and autonomous people to respect the bioethical principles of equity and justice. Preventing investigations in children, denying them the benefits of the fruits of research, violates this principle of justice [20].

Thus, Kopelman and Murphy [21] emphasize that the core of the moral and social problem of research with children is the concern to protect them as research participants and, at the same time, promote the advancement of knowledge for this group. For Harris [13], every person is morally important and must be respected and protected by society. Thus, the principle of equality, the first principle of ethics in research, is postulated.

Finally, paraphrasing Cabral [22], we can say that the ethical issues involving research with children are situated in two dimensions: that of morality and that of the legality of scientific acts. On the one hand, there are the laws, norms, and declarations regulating researchers' relationship with their participants; on the other, the awareness of adult-researchers in understanding that fulfilling these requirements is caring for the children participating in research—a moral commitment, an exercise of citizenship which is built into human relations.

Consent Form

"Consent" is a term widely used by the scientific community, established in international regulations and research guidelines. It is defined as the affirmative agreement to participate in an investigation [23]. One understands that, although children are incapable of giving their legal consent to participate in studies, they can and should provide their consent, expressing their will and individuality. This condition of respect must be guaranteed, in addition to parents or guardians' informed consent [24,25].

Factors which should be considered when assessing children's ability to consent include age, maturity, and psychological status. A developmentalist approach sees the ability to consent as a continuum and suggests that children's understanding of the content and process of assent varies according to their level of development [26].

Consent must be obtained from children who have the intellectual and emotional capacity to understand the concepts involved but can be waived if they are deemed unable to assent, or if the intervention or procedure may directly benefit their health or well-being and is available only in the context of research [27].

It is inappropriate to strictly define the minimum age of assent, as children's maturity to understand and accept risks for altruistic reasons varies according to their development and the complexity of the research project. However, some institutions recommend that assent be considered from the age of seven. This cut-off point, however, is based more on tradition and cultural values than on any evidence [28]. It should be considered that this is, on average, the age at which children are literate.

For Smith-Tyler [23] and Buchner and Hart [25], the age at which a minor is considered to have the ability to understand varies from individual to individual and eludes generalization. Corroborating Davidson and Babl [27] and Zeigler [10], the authors report that the ability to act from moral motivations such as altruism probably develops between 11 and 14 years of age, when understanding is already significantly greater compared to children under 11 years of age. For Harris and Holm [26], this greater understanding from age 11 may be related to the stages of Piaget's[29] developmental theory.

When consent is considered, there are four categories of pediatric participants: 1) infants, who are unable to enter into any discussion about the research and depend exclusively on parental consent; 2) children who understand some or all of their participation but remain vulnerable to coercion or may be so in other respects (in these cases, consent is required in some situations but parental consent is always required); 3) young people of developing maturity, able to understand the most relevant information but whose relative immaturity still makes them vulnerable (in these cases, consent is necessary, but insufficient to authorize the investigation, with the need for parental or guardian consent); and 4) young people who are mature minors and can understand research and consent to their participation with good reasons for the consent of a parent or guardian not being required [12,27].

The challenge is to evaluate children's cognitive development and propose appropriate elements of assent for different stages. Investigators often approach assent in the same way as informed consent, assessing children's understanding of such consent as a measure of adequacy of assent. However, if consent criteria are used, most (if not all) younger children will be considered incapable of assenting and, consequently, denied of the right to decide whether or not to participate in a study [22].

Johnston [19] refers to William Bartholome, advocate of children's rights as patients and research participants, who defined four fundamental elements of assent: 1) adequate understanding of the condition; 2) disclosure of the nature of the proposed intervention and what it will involve; 3) analysis of the understanding of the information provided and the influences that impact the child's assessment of the situation; and 4) request for manifestation of the child's will to accept the interventions. These elements reflect the fundamental provisions of informed consent, as referred to in the *Belmont Report* (information, understanding, and voluntariness), modified to reflect children's capacity development.

For Rossi, Reynolds, and Nelson [6], obtaining consent aims to show respect for the development of children's autonomy, whose ability to assent must be seen as a continuum which changes with the increase in cognitive capacity. Spriggs and Caldwell [15] add that the value of assent is the principle of respect for people and the well-being and interests of children. Children participating in research enjoy the benefit of receiving information and getting involved in discussions, as children in treatment should also have the benefit of knowing what will happen to them, even when they do not have decision-making authority.

Cardoso and Calabró [28] point out that even a properly planned interview fails to ensure the understanding of patients and their parents and if they request that the information is repeated is also not a guarantee of understanding. It is recommended to corroborate understanding, asking, for example, for patients to explain the information in their own words. Ideally, there should be some time before they make their decisions so they can discuss, for example, with friends or family.

Thus, Carsi Bocanegra [30] emphasizes the importance of investigators dedicating, in any investigation involving children, the necessary time not only to guardians but especially to minors, explaining the actions according to the level of development. According to the American Academy of Pediatrics [31], children should never be deceived. Therefore, if they have no choice in relation to the care or interventions which will be provided, they should be informed, rather than asked.

In 2000, at the International Symposium on Bioethics and the Rights of the Child, a document was prepared which highlights the protection of the rights of children who participate in scientific research. The text, known as the *Monaco Declaration*, emphasizes that attention to children's health must include due consideration for clarification, consent, and, as the case may be, refusal of consent, according to individuals' increasing degree of autonomy. The declaration also states that the protection of rights should be strengthened in the case of children with disabilities and that scientific progress and its applications, especially regarding prevention and treatment, should benefit these children without ever excluding or marginalizing them [32].

Regarding the norms of good clinical practice, when it comes to children as research participants, their condition of vulnerability should be considered, since this is a group whose self-determination regarding informed consent is reduced. Still, children's refusal to participate in research must be respected unless, according to the research protocol, the therapy the child will receive has no medically acceptable alternative [21].

Parental consent

Intrinsic to the concept of consent is the understanding that it concerns the person who consents. Therefore, the consent of those responsible is called "consent by proxy" since it reflects the convictions, values, and wills of guardians and not of the child. Since ethics in research refers to the commitment to safeguard the integrity of the people involved, limiting the child to the right to information, or even allowing their participation only in specific situations, is insufficient as it violates respect for their interests [33].

The practice of concentrating the decision on the adult is based on a paternalistic premise which considers the child to be incapable and, therefore, helpless. However, based on the premise that children are subjects of rights and, therefore, have the right to their voices, it is essential that researchers guarantee conditions for them to participate in the decision to collaborate or not with research. The process of consent/assent requires a more active involvement from children so they express their desire, unrestricted to guardians' expression. Parents' informed consent, although indispensable, is insufficient [34].

However, there is the problem of the legal impossibility of obtaining informed consent from children, considering that it is based on the person's ability to receive information and assign meaning to it, recognizing its relevance and recalling facts. Once they are established with reference to their capabilities and the adult universe, these competencies reinforce the representation that children are unable to consent.

Due to their limited ability to decide on their own and their unequal relationship with adults who involve them in research or make decisions on their behalf, children are a vulnerable population. They do not always have the cognitive ability to understand risks and may feel unable to say "no" to parents and researchers. Therefore, children need someone to speak and make decisions for them, requiring an additional layer of protection in the form of the consent of a guardian, in addition to the protection offered by the analysis of research ethics committees [15].

Thomas [35] points out that there are several factors capable of inappropriately influencing parents, who may feel compelled to participate in research when people who provide direct care for their children are also responsible for recruiting participants. Parents of patients in neonatal intensive care units are particularly vulnerable in this case due to the stress related to their children's disease. Therefore, it is essential that well-constructed and careful studies are conducted to expand knowledge and improve care. In these studies, recruitment and procedures should be sensitive to the suffering experienced by parents.

Thus, before starting research involving children, investigators must assure guardians that the investigation in question cannot be satisfactorily

conducted with adults; that the objective of research is to obtain knowledge relevant to children's health needs; that all risks (physical, psychological, emotional, etc.), even if minimal, have been disclosed; that the favorable opinion of each child must be obtained to the extent of their abilities; and that children's eventual refusal to participate or continue in research will be respected.

Risks and benefits in research involving children

"Risk" refers not only to physical harm produced by experimental research devices, procedures or medications but also to damage which may occur due to loss of confidence, psychological distress or social embarrassment. There is minimal risk when the physical or psychological harm or discomfort predicted in the survey (in terms of probability and magnitude) is not greater than that normally encountered in routine examinations or tests. Children in different societies and with distinct health conditions face very different risks in their daily lives [36].

This definition of minimum risk is known as the objective standard for daily life risks, whereas the relative pattern considers as minimal risks those which are not higher than research participants' daily life risks [37]. This relative pattern has been widely rejected by the argument that it has the potential to allow riskier investigations with children who face situations of greater daily life risks, such as wars and hospitalization in intensive care units [38].

Adopting the objective standard avoids this potential for exploitation. In general, research ethics committees use the relative pattern when the risks of research are not greater than the risks children face in daily life, when their daily life risks are considered acceptable by society, and when the risks of research replace children's daily life risks [14,25].

The objective pattern may block investigations aimed at improving the lives of children living in situations of greater vulnerability. When research is intended to investigate procedures and products to improve the lives of these children, research may need to study them in circumstances worse than those of daily life, exposing participants to greater risks which go beyond the minimum. The dilemma, however, is whether it is possible to avoid the exploitation of unfortunate children without excluding important research aimed at improving their circumstances [36].

According to Wendler [37], to protect children from exploitation, investigators and research ethics committees must adopt a standard position of not including them in research which fails to offer the best methods and shows greater risks than those already present in their daily lives. Exceptions to this standard are allowed only when research meets four additional ethical requirements: relevance, scientific need, sufficient benefits, and non-maleficence. Viada González, Ballagas Flores, and López [17] advocate an intermediate position, proposing that the types of research offered be analyzed and that any intervention with predictable risk, whether physical or psychological, be denied to the health of the child. Corroborating this perspective, Peerzada and Wendler [38] state that research with risks should be done in children only when studies in adults are unable to answer scientific questions.

As noted by Johnston [19], the National Human Research Protections Advisory Committee has suggested an alternative definition of minimum risk. According to this definition, minimal risks are those which are socially permissible, that is, to which parents themselves allow their children to be exposed outside of research. Clearly, the definition of minimum risk must be constantly reassessed so that researchers and research ethics committees can consistently and ethically interpret regulations.

Going beyond the minimum risk category, regulations allow the approval of pediatric investigations which show a "small increase" on the minimum risk, with no prospect of direct benefit, only when research can produce generalizable knowledge about a disease. For this purpose, it is necessary, in addition to obtaining the approval of research ethics committees, to consult with a group of experts capable of deciding whether the study is so important as to justify a small increase in the minimum risk without direct benefit to the participating children [39,40].

Risks greater than the minimum are acceptable if the direct benefits justify the risks and the risk-benefit ratio is at least as favorable as that

of available alternatives. In such cases, research ethics committee should ensure that the risk is justified by the anticipated benefit to participants and document this situation. Moreover, adequate provision must be made to request children's consent, when possible [41].

Most guidelines for research with children distinguish between therapeutic and non-therapeutic research. Although direct benefits are not their main objective, therapeutic research is defined as one which can directly benefit participants, whereas non-therapeutic research produces knowledge of general importance, without any direct benefit to participants [42].

Direct benefit is defined as a tangible positive outcome—such as curing diseases, relieving pain, or increasing mobility—which individuals can experience. Typically, investigations which maintain the prospect of direct benefit evaluate interventions aimed at preventing, diagnosing or treating diseases or injuries, offering access to standard treatments or experimental therapies. Thus, the person who will benefit directly from the research has (or is about to develop) the disease or injury for which the study offers an intervention [43,44].

Engelhardt [45] claims that, when research generates direct benefit to children and is the only alternative for the necessary treatment, the coercion of children is acceptable as long as it is supported by guardians' consent. But even in such circumstances, there must be an investment in voluntary participation and the preservation of the dignity of the child. On the other hand, when there is no such benefit, the only ethical way to involve children in research is to ensure their consent.

The Bioethics Committee of the American Academy of Pediatrics argues that studies with children should have all of their potential risks examined, including risks which typically pose no concern in adult research. These risks include discomfort, inconvenience, pain, fright, separation from parents or the family environment, effects on organ growth or development, and size or volume of biological samples [31].

Finally, further studies are needed on risk limits and the relation between research policy with children and other legally established policies for this group. There are limits, for example, to exposing children to risks to obtain information [46]. The duty to protect children is more important than the duty to advance knowledge. Guidelines vary between countries but the principles remain the same: risk stratification, balance between risk and benefit and between risk and importance, and, in general, less acceptance of risks in research with children, compared to adults.

Final considerations

Regulations aimed at children were developed and implemented over time, enabling the evaluation and appreciation of many of this group's specificities. Vulnerability and inability to provide full consent have led to the establishment of ethical guidelines and regulatory bodies which insist on the need for special attention to children.

Some regulatory research documents seek to include and respect children in the process of assenting to research according to their emotional and cognitive maturity. Considering the level of maturity is paramount to ensure understanding and facilitate children's decision-making. As a result of this inclusion, the current premise is that children, despite not having the legal capacity to assent, must provide consent to participate in research, unless they lack the ability to do so or their clinical condition prevents them from communicating their choice.

It is worth noting that assent is a continuous process which seeks, by disseminating information and procedures in an adequate language, to make children manifest their preferences. Such preferences, it is worth mentioning, can change over time, which must be respected.

It is believed that this literature review, without claiming to exhaust the discussion, builds a theoretical framework for reflection on social responsibility in the scenario of ethics in research with children—one in which vulnerability often generates undesirable situations.

Much has already been achieved regarding respect for ethics in research with children but this is a topic which needs to remain in academic and professional debates because, in addition to the dynamism of reality, this population shows many specificities. Therefore, research on this study subject should be encouraged, especially when considering that this review failed to find references on how researchers should proceed in case of conflicts between children's opinion and parents' consen, and that Brazil lacks regulation on this topic, unlike other countries.

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