

ARTÍCULO

**Clinical Research involving Children: consideration
relating to assent**

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Index

Introduction

Assent and ethical and legal guidelines in clinical research

Discussion

Abstract

Physicians and others conducting medical and dental research involving children as participants face quite challenging questions and responsibilities, especially in developing countries. Age, maturity, cognitive development, previous experience, social and cultural contexts, are all factors involved in a minor's competence to assent. However, the literature has suggested some age thresholds for children to meet assent requirements and skills that they should have to participate meaningfully in decision-making situations regarding their health. This paper discusses the international regulatory documents regarding children consent in Clinical Research.

Key words: informed consent; bioethical issues/legislation & jurisprudence; assent; children.

Introduction

Informed consent for vulnerable populations is a sensitive subject, especially when involving minors. Parental authorization is always required for clinical interventions to be performed in children and adolescents, even when not related to a clinical trial. However, most of the international ethical guidelines for research with human beings suggests that minors must be involved within the limits of their capacity, on their health related decisions. The idea is not to bureaucratize the process or to create a minor's consent. Consent, that is the legal condition whereby someone can express agreement or permission for a specific act based upon a clear appreciation and understanding of the facts, is not obtainable from children in this sense, but an affirmative agreement is. This agreement is often called assent, the expressed judgment of minors to refuse or to accept medical care as a patient or as a research subject.

From infancy to adulthood, it is evident that there is a gradual development of emotional, cognitive and social skills that progressively increase a child's ability to make self-defining autonomous choices. That is not to say that children develop equally in every aspect of their lives or that there is a definite pattern of development that applies to all of them. Those facing serious life threatening conditions or chronic diseases are often more skilled in their health related conditions than healthy overprotected children and also more likely to be involved in an assent context. Today, several jurisdictions legitimize the minor's participation in shared decision-making, implying that even though assenting or dissenting to a choice of treatment or participation in a clinical trial does not count as an authoritative wish, it should be weighed on the decision. Though, assent or dissent do not legally bind physicians to accede to the patient's or subject's specific requests, they require ethical reflection and commitment to a righteous conduct having the child's best interest in mind. That is not to say that good care requires informed patient/subject participation, or that it is fundamental for the professional to take a paternalistic conduct when deciding what is best for the patient, particularly in pediatrics where clinical choices in some instances involve conflicting conducts considering opposing values such as quantity and quality of life.

The purpose of this paper was to explore the principles for obtaining assent from minors, based on the relevant literature and international and local regulations and guidelines, to help physicians and clinical investigators in the process of involving children in clinical trials.

Assent and ethical and legal guidelines in clinical research

Since the Helsinki Declaration in 1964⁽¹⁾, ethical guidelines in clinical research all over the world have been progressively acknowledging the child's right, as research subjects and patients, to

1 WORLD MEDICAL ASSOCIATION (WMA). Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki. *Br Med J* 1964; 2(5402): 177.

participate in decision-making processes related to their health. The concern with respect to their choice not to participate in a clinical procedure strengthened, in what has been described as expressed dissent. Under these circumstances, understanding is important, but the protection of the child is paramount. In fact, the Helsinki Declaration and its later amendments^(2, 3) have addressed deficiencies in the Nuremberg Code⁽⁴⁾, particularly in respect to research with the legally incompetent. From a more international perspective, the Council for International Organizations of Medical Sciences (CIOMS) in 1993⁽⁵⁾, and then in 2002⁽⁶⁾ and 2008⁽⁷⁾, issued specific guidelines on ethical conduct in biomedical research with human beings.

In 1976, the American Academy of Pediatrics (AAP)⁽⁸⁾ published their considerations on informed consent, which was a new concept at that time. The document, while ethical in principle, was normative in form: it emphasized the legal implications of informed consent on the daily practice. Practical yet important issues were addressed. Regarding an age for seeking assent, the document avoided chronological standardization as well as strict correlations with maturity or intelligence. Nonetheless, there were references to certain age landmarks. Generally, consent was to be obtained from children over the age of 7, but, for surgical cases and treatment, the recommended age was 13 or older, "a reasonable safeguard for physicians in all elective cases". As for responsibility on signing the consent forms, the minor's legal representatives, namely one of their parents or a person *in loco parentis* (acting as parent), was considered sufficient to provide consent, unless a dispute existed between parents. In such cases consent from both parents was necessary. For divorced parents, the parent with legal custody was the one to sign the document. A year later, the National Commission for the Protection of Human Subjects and Biomedical and Behavioral Research published a report on research involving children⁽⁹⁾. The extensive and well-written report acknowledged the importance of the informed consent as a compromise of the patient's whole family to the comprehension of the procedures to be undertaken on the minor, and argued that, although based on empirical data, there

2 WORLD MEDICAL ASSOCIATION (WMA). *Declaration of Helsinki*. 1975, 1983, 1989, 1996, 2000. www.wma.net/en/30publications/10_policies/index.html (accessed 18 Jan 2013).

3 WORLD MEDICAL ASSOCIATION (WMA). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. 2008. www.wma.net/en/30publications/10policies/b3/17c.pdf (accessed 18 Jan 2013).

4 WAR CRIMES TRIBUNAL. *The Nuremberg Code*. 1947. www.research.buffalo.edu/rsp/irb/forms/Nuremberg_Code.pdf (accessed 18 Jan 2013).

5 COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS; 1993.

6 CIOMS. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS; 2002.

7 CIOMS. *International Ethical Guidelines for Epidemiological Studies*. Geneva: CIOMS; 2008.

8 BROWN R.H. Task Force on Pediatric Research, Informed Consent and Medical Ethics. *Informed Consent and Medical Ethics*. *Pediatrics* 1976; 57: 414-416.

9 THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH. *Research involving children: report and recommendations*. Washington DC: Department of Health, Education and Welfare; 1977.

were studies that indicated that at particular ages children demonstrated the maturity to be involved in making ethical judgments. The age of seven was considered a time by which the child could express some reflexive judgment. For procedural reasons, this age was then considered suitable for consulting the child about their willingness or not to participate in research. Beneficence (the doing of good) was the main principle to be addressed in the research protocol and, in terms of non-maleficence (the avoidance of harm) the document considered that the child was protected by several mechanisms: the protocol review by the Institutional Review Board (IRB), the need of formal parental permission, the child's own consent and their "veto with regard to involvement in a research project"⁽⁹⁾.

The ethical principles of research involving human subjects was further developed on the Belmont Report⁽¹⁰⁾, a milestone in the bioethics field, which provided a straightforward expression of what was necessary for obtaining informed consent: information, comprehension and voluntariness. Children, recognized as individuals with limited comprehension on account of their immaturity, were briefly discussed; they had to be considered on their own terms and, out of respect, they had to be given opportunity "to choose to the extent they were able, whether or not to participate in research". The limit of dissent was to be set by the availability of the proposed therapy elsewhere. Again, protection from harm would be ensured by seeking permission from third parties interested in the matter.

Later, the first publication of the CIOMS/WHO undertaking was published⁽¹¹⁾. From this to the latest edition, in 2008⁽⁷⁾, the concept of assent has evolved considerably. The initial 80's proposition that consent was to be obtained within the limits of the child's capacity, advanced to obtaining the child's assent, provided information was given to the extent the child's maturity and intelligence allowed. The guidelines mention that local legislation in respect of the legal "age of consent" had to be respected, even though normative parameters might not correspond to the child's maturity and ability to knowingly agree to serve as research subjects. Thus, this informed agreement, occasionally referred to as assent, would be insufficient to permit the child's participation, unless supplemented with a legal consent (from parents or legal representatives). The right to refuse to participate, which had already been mentioned in the 1982 document⁽¹¹⁾, was also further developed. Younger children, too immature to be able to express assent, would at least be able to register their "deliberate objection", an expression of their disapproval or refusal to participate in a proposed procedure. Even so, it was cautioned that this non-written, expressed dissent had to be distinguished from an infant's normal conduct when facing different stimuli, like crying or withdrawal. Limits for honoring an expressed dissent remained conceptually the same: the child's well being. When a child needs an intervention that is not available outside the context of the research, or when the intervention has demonstrated promising therapeutic benefits or when there are no acceptable alternative treatments,

10 THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH. *The Belmont Report*. Ethical Principles and Guidelines for the protection of human subjects of research. 1979. www.hhs.gov/ohrp/humansubjects/guidance/belmont.html (accessed 18 Jan 2013).

11 CIOMS. *Proposed international ethical guidelines for biomedical research involving human beings*. Geneva: CIOMS; 1982.

consent of the parent(s) or legal guardian might override the child's objection. In these situations of conflict, it was advised that investigators should seek specific approval or clearance from the scientific and ethical review committees for initiating or continuing the treatment being researched.

Ethical guidelines then on began to use the phrase "when comprehension conditions allows" repeatedly when the child's consent was to be solicited, always in addition to parental consent. The 1993 International Ethical Guidelines for Research Involving Human Beings⁽⁵⁾ ratified this position, as well as recommended deference to the child's expressed dissent, as noted above. In 1995, the AAP issued a policy statement on informed consent, parental permission and assent in pediatric practice⁽¹²⁾. This document presented a more formal and evolved concept of informed consent than previous statement⁽⁸⁾. The policy stated that at 14 years and older, a child should already have adult skills for making informed health care decisions. Bartholome⁽¹³⁾ raised a few interesting concerns regarding this understanding of dissent. He stressed that children should always be part of the medical decision-making process, when judged to be old enough to participate meaningfully in the process. Even when an intervention had to be undertaken against the child's will, reasoning over the dissent was sensible and considerate.

In 2001, the term assent appeared in topic E11, Clinical Investigation of Medical Products in the Paediatric Population, of the International Conference of Harmonization, ICH, of the European Medicines Agency (EMA)⁽¹⁴⁾. According to this guideline, children's legal guardians are responsible to provide informed consent in accordance with regional laws and regulations and participants have to be informed to the fullest extent possible about the study in language and terms they are able to understand. No regulatory specific age for assent was anticipated, but when appropriate, the IRBs or IECs would specify ranges accordingly, taking into consideration legal requirements. Interestingly, intellectually mature minors were deemed capable of signing the assent form or giving written informed consent. Deference to dissent was emphasized within the usual limitations of respecting the child's well being when facing serious or life-threatening diseases, in the opinion of the investigator and parents or legal guardians. Later, ICH Topic E 6, Guideline for Good Clinical Practice⁽¹⁵⁾, adopted a more formalistic approach when suggesting that capable children should sign and personally date the written informed consent. Despite reinforcing the investigator's responsibility to inform minors accordingly to their capacity to understand trial risks and benefits, the 2001/20/EC Directive of the

12 AMERICAN ACADEMY OF PEDIATRICS (AAP). Committee on Bioethics. Informed consent, parental permission, and assent in pediatric practice. *Pediatrics* 1995; 95: 314-317.

13 BARTHOLOME W. *Ethical issues in pediatric research*. In: Vanderpool HY (ed.) *The Ethics of Research Involving Human Subjects*. Frederick: University Publishing Group; 1996. p.360-1.

14 EMA. International Conference of Harmonization. *Clinical Investigation of Medicinal Products in the Pediatric Population*. E11. 2001. www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002926.pdf (accessed 18 Jan 2013).

15 EMA. ICH. *Guideline for Good Clinical Practice*. E6 (R1). 2002. www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002874.pdf (accessed 18 Jan 2013).

European Parliament and the Council of the European Union⁽¹⁶⁾ broadened the concept of this responsibility by recommending that the information process should be provided by “staff with experience with minors”, therefore acknowledging that the information process could be properly delegated to others by the investigator.

It is interesting that at the time, the 2000 Declaration of Helsinki⁽²⁾ focused on the main investigator or the physician’s qualifications to handle the process, having this concept changed only in 2008⁽³⁾, when the figure “another appropriate qualified individual” was recognized as a suitable proxy to handle the information process, still under the responsibility of the main investigator. Then again, the 2002, World Health Organization Handbook for Good Clinical Research Practice (GCP)⁽¹⁷⁾, under ‘Informed Consent’, was very comprehensive on the investigator’s role to acknowledge the prospective subject’s ability to understand the information necessary to give consent. Individual maturity, intelligence, education, and belief system were to be considered. Children had to be considered on their own terms, and be given the opportunity to choose, to the extent they are able, whether or not to participate in research.

More recently, the American Code of Federal Regulations⁽¹⁸⁾ brought a more thoughtful perspective on the subject, which dissociated assent from the informed consent principles. Under “Additional Protections for Children Involved as subjects in Research”, assent was defined as a child’s affirmative agreement to participate in research. It also added the precept that mere failure to object should not be construed as assent. Besides the essential responsibility of protocol review, determining when prospective young subjects are capable of providing assent, considering age, maturity, and psychological state was assigned to the IRB’s duties. Among this attributed responsibilities, it is important to recognize that under certain circumstances, the IRB can even waive the assent requirements, such as in studies to evaluate public benefit or service programs, in situations where the research cannot practicably be carried out without the waiver, in conditions where the child’s well being and health would potentially benefit from the intervention or procedure available only in the context of the research, or in situations where the child’s ability to assent is too limited to be consulted. UNESCO’s Declaration on Bioethics and Human Rights⁽¹⁹⁾ is concise regarding the consent process, and stresses the standard concerns. The Good Clinical Practice: Document of the Americas⁽²⁰⁾, issued by the Pan American Health Organization (PAHO), was equally succinct on the matter but, at the same time, it empowered the child by recommending that children, when able, should sign and

16 THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION. Directive 2001/20/EC. *Official Journal of the European Communities* 2001 May 5; L121/34-44.

17 WHO. *Handbook for Good Clinical Research Practice (GCP): Guidance for implementation*. Geneva: WHO; 2002. whqlibdoc.who.int/publications/2005/924159392X_eng.pdf (accessed 18 Jan 2013).

18 DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS). *Code of Federal Regulations. Title 45 - Public Welfare, part 46, Protection of Human Subjects*. 2005. www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html (accessed 18 Jan 2013).

19 UNESCO. *Declaração Universal sobre Bioética e Direitos Humanos*. Lisboa: UNESCO; 2005.

20 PAN-AMERICAN HEALTH ORGANIZATION (PAHO). *Boas Práticas Clínicas: Documento das Américas*. Washington: PAHO; 2006.

personally date the informed consent. Information about the study has to be provided insofar as the minor is able to understand.

Ethical Considerations in Biomedical HIV Prevention Trials⁽²¹⁾ was published by UNAIDS (Joint United Nations Programme on HIV/AIDS) to mark the third decade of the HIV pandemic. Cautiously, it indicated that, regarding assent, local legislation had to be recognized and the permission of minors had to be sought according to their evolving capacity. Refusal to enroll in trials had to be respected. Importantly, it introduced the notion that the adolescent assent process should be carried out separately from the parental consent process, the latter obtained not necessarily from both parents. Information, key in any consent or assent process, was also considered in terms of the elements of the trial that would be disclosed to parents and legal guardians. It acknowledged that in certain settings where minors might have guardians who were not legally recognized by a court as such, they should not be automatically excluded from participation in a biomedical HIV preventive intervention trial. In such cases, provided local legislation was respected, the adolescent's participation in a trial might be considered, as long as protective ethical oversight mechanisms can be established. In addition, mechanisms for an independent evaluation of the capacity of such adolescents to assent should be instituted so that they could express valid informed consent (and not assent). This is particularly important in countries where the civil family structure might differ from the social one.

The 2008 CIOMS International Ethical Guidelines for Epidemiological Studies⁽⁷⁾ build upon all the previously published guidelines. Assent has to be sought after the child has been informed to the extent their maturity and intelligence allow, and deliberate objection has to be acknowledged as an expression of disapproval or refusal of a procedure, even if parents have given permission. When choosing an age range of children to participate in a trial, older groups, that are more capable of giving assent, should be selected before younger children or infants, unless there are valid scientific reasons for involving younger children first. The limits of dissent are as previously presented on other CIOMS guidelines. To override a very young or immature child's dissent, parental consent is sufficient. For older and more capable children, the investigator has to seek the specific approval or clearance of the scientific and ethical review committees. Permission for participation in a trial has to be obtained from a parent or guardian in accordance with local legislation. The document indicates that even though children over 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, their consent (assent) should normally be complemented by the permission of a parent or guardian, even when local legislation does not require such permission. Parental permission may be waived in certain cases by the ERC, such as for studies of domestic violence or child abuse.

Finally, the WHO Research Ethics Review Committee⁽²²⁾ posted an electronic document on procedures for obtaining informed consent that addresses the assent process. Under "Obtaining

21 UNAIDS (Joint United Nations Programme on HIV/AIDS). Ethical considerations in biomedical HIV prevention trials. Geneva: UNAIDS; 2007.

22 WORLD HEALTH ORGANIZATION RESEARCH ETHICS REVIEW COMMITTEE (WHO ERC). *The process of*

Consent and Assent in Research involving Children”, they acknowledged that the document follows the Convention on the Rights of the Child⁽²³⁾, and therefore considers children to be every human being below the age of eighteen years, unless under the law applicable to the child, majority is attained earlier. It then emphasized the importance of the subject on the process, and not procedural concerns, by suggesting that children able to understand the proposed research should have the opportunity to be informed about the research, to have their concerns addressed and to express their agreement or lack of agreement to participate. The age at which informed assent had to be taken was recognized as variable. However, researchers were advised to consider asking for the assent of children over the age of seven. After age twelve, assent should be taken from all children. Contrary to the non-bureaucratic recommendations of the AAP, an informed assent form was suggested, written in age appropriate language, to be presented to the child so that he or she could register their agreement to participate. This assent form would be in addition to parental consent. “Assent which is denied” was a caution to be taken very seriously. The assent form made available on-line is very instructive⁽²⁴⁾.

Discussion

The number of pediatric and adolescent trials has increased all over the world, which has increased the bioethical and regulatory concern on how to properly involve minors in the consent process. There is also the anguish of dealing with their dissents and being able to meet sample sizes in a timely matter considering all normative criteria. In addition to the obvious paternalistic assessment of the situation, and the logistic and economic concerns, the real question centers on “are we prepared to evaluate children’s capacity to assent and to involve them in their health related decisions accordingly to their evolving capacities?” How is it possible to have a six year old understand and agree to participate in the calibration procedure of an epidemiological trial where he or she will have to be assessed by more than one examiner? Or how should they be included in assenting to injections and vaccinations while healthy?

Primo non nocere. First do no harm, is the fundamental principle of the patient-physician relation. To do good and not to do harm, was first stated by Hippocrates and transcend any regulatory guideline, at any level (physical, mental or social). In fact, most of the revised guidelines require the investigator to ensure that the child’s or adolescent’s autonomy is preserved, so long as this is not to the detriment of their well being. Ethical sensitivity⁽²⁵⁾, in this sense, is critical for the pediatric

obtaining Informed Consent. 2009. http://www.who.int/rpc/research_ethics/Process_seeking_IF_printing.pdf (accessed 18 Jan 2013).

23 UNITED NATIONS. *Convention on the rights of the child.* 1989. www2.ohchr.org/english/ (accessed 18 Jan 2013).

24 OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP). *A pediatric research “assent” decision matrix.* 2003. archive.hhs.gov/ohrp/children/407-01pnl/riskcat.pdf (accessed 18 Jan 2013).

25 WEAVER K., MORSE J., MITCHAM C. Ethical sensitivity in professional practice: concept analysis. *J Adv Nur*

researcher. Schwartz⁽²⁶⁾ brilliantly analyzed the principles of beneficence and non-maleficence, and concluded that in situations where the outcome is unknown, “first do no harm” might mean that an active attempt to do good must triumph over a passive attempt not to cause harm.

But investigators have to fundament their conduct on procedural justice, which is often reductionist in nature. It would be impossible, even for the most judicious regulatory police, to cover every possible circumstance that might occur during research with human beings, particularly with minors. Worst even, would be to consider capacity based solely on bureaucratic regulatory processes.

In general, international regulatory guidelines recommend that children and adolescents be involved in their health related decisions to the limits of their evolving capacity. There is no definite practice to access a child’s capacity to assent to participate in clinical procedures nor orientation on how to acknowledge this competency however there are some chronological and procedural parameters suggested.

First, it has been suggested that affirmative agreement would be a better term to convey the meaning of the minor participation in a clinical trial, distancing the concept of assent to that of a minor’s consent. Therefore, the idea of respect to the evolving autonomy broadens to respect to another human being, regardless the autonomic stage. The advocated chronological parameters are interesting references, particularly important when considering a multicenter international protocol. They are not intended to bureaucratize the assent process but as in any procedural regulatory process, provision of legal documentation is expected and necessary. If no particular procedure to assess capacity is recommended or is required by the local regulatory guidelines, the investigator or the IRBs might consider using suggested age milestones as parameters to implement in protocols. The recommendations of the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC⁽²⁷⁾ are a sound starting point as well as the matrix provided by the Office for Human Research Protections⁽²⁴⁾.

One of the most important tasks left to the IRBs is to protect vulnerable populations by thoughtfully assessment of the research protocol, which, in regard to involving children in the information and consent process, is an ethereal responsibility if considered only through procedural processes. Demanding a child to sign or print their finger on the consent process according to chronological or literacy parameters does not guarantee that information was age appropriately provided or that comprehension took place.

2008; 62: 307-618.

26 SCHWARTZ G. Hippocrates revisited. *Einstein J Biom Med* 2004; 21: 33-34.

27 EUROPEAN COMMISSION. *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*: Recommendations of the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. Final 2008. ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf (accessed 18 Jan 2013).

Institutional Review Boards are maturing, as are national and international regulatory systems. They are gaining social and academic respect, not by ruling, but by legitimate ethical conduct. However, there are some areas, like pediatric research, where decisions are more strongly influenced by rules than by ethical judgments, mostly because there is strong paternalistic tradition and a lack of knowledge about how to include children in their health-related decisions. Research on this area must be prioritized in all countries, especially in the local contexts of developing countries, where they share many features of family structures and relations, but where these are somewhat different from European and American families, which is where most of the assent data has been produced.

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