Informed consent in vulnerable groups: participation of children and adolescents in research protocols

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Abstract

Informed consent is an active process of communication that includes decision making and shared responsibilities between physician and patient. It is a key point in clinical practice and aims to protect the patient from other potential interests. The assent of the child, once the responsible persons have consented, and the rights of the child to ask questions and to discuss are two issues of great significance in scientific research in children.

Key words: vulnerable groups, informed consent, informed consent in children, autonomy.

Introduction

Informed consent is a topic of great interest and debate, not only within the medical profession but also in the general population. The increase in medical-legal cases and the introduction of international guidelines have formalized the manner in which consent is obtained and, in particular, how the potential risks are reported.¹ ²

Recruiting of children for research, especially those children who have chronic diseases, places them in a vulnerable group because they have great interest in the possible benefits of the technological advances, even though significant risks may exist. This implies that safety is a supreme consideration in the design of clinical trials because we are in danger of exploiting this vulnerability. Promotion of competition involves responsibility to increase public consciousness and to stimulate debate on controversial themes.³

Given the possibility of unknown risks, it may be unethical to propose clinical studies in children, especially if there are other less controversial alternative therapies even with a normal life expectancy significantly reduced because these clinical trials may impose a considerable burden for the child and his family. Research should be viewed in the context of limiting progressive illness for which no cure exists. Kodish says that “for many years children have been therapeutic orphans, denying them the benefits of clinical research”.⁴

The inclusion of children in research protocols has forced some collegiate bodies such as the GTAC (The Gene Therapy Advisory Committee) and the RCPCH (Royal College of Pediatric Child Health)⁵ ¹⁰ to publish guidelines recommending
that children can be included only under the following circumstances:

1) The investigation is necessary to promote the health of the study population
2) The investigation cannot be done using adults or cannot answer the same questions
3) Children have unique additional needs and can be the benefactors of an ethical investigation
4) There is a possibility of therapeutic benefit
5) The potential risks can be defined or predicted
6) There is no other therapeutic alternative
7) It may not be desirable, or not possible, to limit the investigation, which may have non-quantifiable benefits

Who has the right to choose?

Adults responsible for children are considered competent to assimilate, understand, retain, and weigh the information and use it to make the decision of whether to participate in a research study. Parents have the authority and responsibility, i.e., legal and ethical rights to make decisions on the child’s behalf and it is understood that they act in the best interests of the child, which involves weighing a range of physical and psychological risks and benefits.

The consent of the child, once those who are responsible for that child have given their consent, and the rights of the child to ask questions and participate in a discussion are two issues of great relevance in scientific research in the pediatric population.

The concept of competence is inextricably intertwined with information. The child is entitled to be informed in a manner that the child can understand, regardless of his/her ability to make decisions. Children <10 years of age may not be able to consent to participate in research projects. Competence to make decisions is based on the child’s ability to fully understand the nature and purpose of the involved protocol and the impact that it may have on the family. The psychosocial dynamics of families of patients with chronic disease are complex and may involve misunderstandings about knowledge and understanding of children including mutual deception (both parties evade difficult issues). This may limit the child’s participation in decision making.

All medical research and treatments involving children must weigh between what produces more benefit than risk, as well as to encourage children to participate in the decision (autonomy) as much as they are able or want to. Many children lack these skills, but this should not be assumed in the context of a chronic disease when the child’s experience could confer unexpected competencies unrelated to age.

In the presence of a disease that limits the child’s life expectancy, desperation of parents may cause them to accept significant risks for the child, with little hope of benefit, involving themselves in research protocols they do not fully understand. These difficulties are overcome if informed consent is considered a dynamic process in which the researcher’s duty is to increase the competence of the parent and child through education, negotiation and dialogue.

During the last century there was a movement to create a consensus on the need to ensure basic care of children, both from a social as well as a medical point of view. There are different types of fundamentals to legitimize the participation of minors (especially among those >12 years of age) in the process of informed consent. The International Convention on the Rights of the Child establishes that the child is a human being who has rights and obligations, which is why the child must be taken into consideration in his/her own right, never as a means or object, respecting his/her being as a subject. The leading role of the child is growing, resulting in a full recognition of minors and promoting their personal autonomy.11
In the following scenario, we can assess this fact through the analysis of an ethical dilemma in clinical practice. We present the case of a 10-year-old patient with multiple trauma following an automobile accident. It is necessary to amputate his right leg to avoid the patient’s death. The mother is in a coma following the accident. The father refuses to accept the amputation. The child accepts the surgery and wants to continue with his life. What should the medical staff do? From the ethical standpoint, the physician has an obligation to preserve the patient’s life and to administer the treatment of choice. From the aretological point of view, the physician in terms of his mission and vocation is in the service of life. From the utilitarian viewpoint, the highest benefit at the lowest cost is the amputation to save the life of the patient. Therefore, from an integral ethical standpoint, it is best to save the life of the patient.

Due to the foregoing, the physician cannot accept the father’s refusal for surgery and, in his ethical discernment, decides to request the intervention of the state prosecutor to acquire responsibility for the child so that treatment can be performed. The end result is that the child’s leg was amputated, and he was fitted with a prosthesis and administered comprehensive treatment. The father finally accepted the fact that he was wrong and thanked the medical personnel for acting on behalf of his child.

What is informed consent?

Informed consent is an active process of communication including decision making and shared responsibility between physician and patient. It is a key point in clinical practice, which aims to protect the patient from other potential interests. It is much more than just a legal requirement or an administrative process: it is “prima facie” a human right.

The purposes of informed consent are as follows:

- To report risks and complications
- To respect the right of patient autonomy
- To educate the patient about treatment options
- To provide benefits to the patient
- To improve the physician-patient relationship
- To improve treatment adherence
- To reduce patient anxiety
- To protect the doctor from medical-legal claims

What must be explained to the patient during the informed consent process?

Each patient is unique in his/her own right and the information needs to vary in relation to the amount that he/she may be able to understand and retain. Many patients do not recall all the information provided during the process of informed consent.

The following must be explained to all patients:

- What does the study imply?
- What are the objectives of the study?
- What are the realistic benefits of the study?
- What are the possible risks and potential or predictable complications?

What factors should be taken into account in the amount of information to be provided to the patient during the informed consent process?

- Age of the patient
- Level of education
- Complexity of the study
- Curiosity of the patient
At what incidence should the risks be reported to the patient?

All major risks should be revealed, particularly if the incidence is 1/1000.\textsuperscript{14,16} Minor risks should be detailed, and in case of risk being >1/20 we must confirm that the patient is aware of these risks.\textsuperscript{17}

Actors involved in the process of informed consent

The focus of the ethical problems of medicine is the physician-patient relationship, understood as fidelity and medical subordination to the absolute values of the human being, in the sense of a constant assessment and reassessment of this relationship.\textsuperscript{18} It is a confidence with a conscience. Medical treatment and medical management are synergistic. The patient cannot request just any type of action from the physician or usurp the powers of the physician. The conscience and competence of the physician is maintained, as well as the obligation they have to act in an ethical manner.

The patient is always the principal agent of managing his/her own health and has the duty to safeguard life and to promote health. The patient who has accepted his/her state of health and limitations and who recognizes his/her incompetence in the disease that is threatening him/her and undermines his/her autonomy in order to recover or prevent damage to himself takes the initiative to go to another person who, as a result of their training and experience in the practice of their profession, is able to help.

The physician is the professional requested and freely chosen and accepted by the patient (or in any event called by the family or offered by society) due to his/her professional preparation and experience to help prevent, cure or rehabilitate the disease experienced by the patient.

The physician is regarded as a qualified service provider (professional) who works with a primary person in order to achieve a particular purpose. The mission of the physician is to ensure the health of mankind. This mission is fulfilled when the physician develops his/her full knowledge and conscience. Peabody expressed that “the secret of patient care is interest in him”.\textsuperscript{19} The legal representative is a major figure in pediatrics because this person adopts the active function of decision making.

Informed consent as a dynamic process throughout the physician-patient relationship

The process of informed consent begins at the time the physician-patient relationship is established and continues throughout the follow-up period.\textsuperscript{20} The physician maintains three roles: counselor, educator and that of providing health care or medical assistance. It is an educational activity between physician and patient and requires defined times for review and discussion of the document of informed consent, time for questions and answers, and time to discuss the issue with family and friends (Fig. 1).

Figure 1. Informed consent as a process.
The ethical foundations of informed consent are derived from Kant’s ethics in which the central thesis is to Treat people as an end and not as a means. The key points are as follows:

1) Autonomy and dignity

2) Respect

3) Rights

Informed consent is defined as follows:

1) It is an essential tool of the physician-patient relationship to promote confidence, harmony and to balance the interpersonal relationship.

2) It is a key point in clinical practice and scientific research aimed at protecting the patient from other potential interests.

3) It is one of the fundamental ethical rules that shapes medical responsibility, derived from the coordinated application of the principles of dignity, respect for autonomy and confidence of the people, in the same way as the rules of truthfulness and confidentiality.

4) To be valid, it must meet the criteria of voluntariness, sufficient information and competence.

5) It is used as a means to request permission from persons exposed to medical acts while at the same time to respect individual dignity.

6) It relies on values associated with individual freedom.

7) It recognizes that the patient is the best one to judge and decide about oneself and, even if not, it is preferred that one can choose freely according to the criteria of others.

8) It is part of an excellent practice for the physician-patient relationship.

9) It is always in the best interest of the patient.

Fig. 2 demonstrates all that the informed consent process implies. Communication plays an important role. The physician-patient relationship is an encounter between two persons. Each comes with cultural baggage. The physician has roles, experience, training, knowledge and skills, whereas the patient has beliefs, values, ideas, expectations, and biases.

The meeting between patient and physician through a health facility is due to the establishment of effective communication that searches for the patient’s well-being above scientific, professional and technological expectations. The physician-researcher who participates in a clinical trial has a double function: being responsible for the welfare of the patient and being the investigator whose primary function is to ensure that the clinical trial is developed properly. The physician-researcher is responsible for the physical, mental and social well-being of the participant and must make effective the principle of non-maleficence, keeping in mind that protection of the participant has higher importance than the search for new knowledge, the scientific benefit to be gained from research or personal or professional interest of the investigation.

Informed consent should:

1) Be written in simple language and, where possible, not use technical language (it may be necessary to create a video that explains the complete process before a decision is made).
2) Avoid phrases that compromise or manipulate the patients in order that they participate in the study.

3) Clearly explain the purpose of the study.

4) Define the time period in which the subjects will participate in the study.

5) Describe the procedures to which the patients will be subjected.

6) Explain the procedures, medications or devices used in the treatment, as well as to point out possible benefits, risks or complications that may occur.

7) Explain any costs associated with the studies and, if cost-free, explain all steps of the investigation.

8) Clearly explain if they will or will not receive compensation for participating, the amount of any compensation and the manner in which payment will be received.

9) Above all explain the possible alternatives to the procedures, medications and devices available and the possible short- and long-term risks and benefits.

10) Clearly explain follow-up (number of visits, time between visits, studies in each visit).

11) Detail the manner in which potential adverse events will be monitored.

12) Explain the possible alternatives of treatment, in case of a complication during or after the study.

13) Specify in the section on “compensation for injuries” that the investigator will be responsible for providing care to the participating subject in the event of injury as a result of treatment or intervention under study and the sponsoring company will cover the cost of such care.

14) Indicate the possibility of withdrawing from the study at any time without prejudice to the participating subject.
15) Specify the possibility of access to treatment once the study is concluded.
16) Clarify what will happen with the samples once the study has concluded.
17) Detail the manner and the time in which the results of the study will be known.
18) Clearly explain that the results of the study may be published, guaranteeing confidentiality and anonymity of the subject.
19) Answer any questions or doubts regarding the study and name of the persons who may resolve questions along with the hours those persons are available.
20) Indicate the telephone number(s) and name(s) for the study subjects to communicate with the investigators and the committee in case of any questions or if additional information is desired.

Historical background of informed consent
In Britain, in 1215, the right to touch someone without his or her consent was limited, including the king. In 1765, Blackstone wrote on the laws of England: “The physical or emotional assault, with violence or anger, is a violation towards the person, and the law cannot separate the act of violence; therefore, all forms of violence towards another person without their consent are prohibited”. According to European laws and ethical tradition the following are distinguished:

1) When something is taken (theft) or when it is given (as a gift)
2) Violation or love
3) Surgical procedure or aggression and mutilation

The Constitution of the United States of America protects the right of citizens to privacy. The Code of Federal Regulations of U.S. Common Rule requires the following:

1) Prior approval from the ethics committee
2) Informed consent and written documentation
3) Equitable recruitment of research participants
4) Special protection for vulnerable groups
5) Continuous review of the approved investigation

The National Bioethics Advisory Committee (NBAC) requires that:

1) All research in developing countries relates to local health needs.
2) Researchers and sponsors should involve representatives of the community and potential participants.
3) Use of placebos must be justified and control group members must be provided with an established and effective treatment, irrespective of local availability.
4) Informed consent should be culturally appropriate.

During 19th century medicine, with a Hippocratic basis, the patient generally had the right to refuse treatment. Throughout the history of medicine, cases have emerged that have highlighted the need for regulation in medical intervention and the physician-patient relationship.

The case of Maria Schloendorff, 1914: autonomy-justice:

1) The patient agreed to undergo exploratory surgery for diagnosis of a fibroid tumor that resulted in being malignant.
2) The patient specifically asked the surgeon not to remove it.
3) The surgeon, after seeing that it was malignant, removed it.

4) The patient sued.

5) Maria won the judgment.

The judge’s ruling stated that “Any adult person of sound mind has the right to self-determination and decide over his own body and if a surgeon performs a procedure without the patient’s consent then an assault has been done and the physician is required to pay damages” (The Cordoza decision).

The case of Mr. Canterbury (1972): risk benefit–adverse effects:

1) The patient was paralyzed after spinal surgery.

2) The physicians were aware that paralysis was a possible risk of surgery, but this fact was not communicated to the patient.

3) The patient won the judgment.

Nuremberg trial: respect for the individual autonomy:

Research was performed on Jews in WWII concentration camps where the study subjects did not know what the research was and were forced to participate in the study. It seriously questions the medical/scientific community and enhances the importance of respect for the individual autonomy of informed consent.

In 1947, the Nuremberg Code was proclaimed, which explicitly references the voluntary consent of the subject. Voluntary consent of the subject is absolutely essential. This means that the person involved should have the legal capacity to give consent, should be in a condition to allow the free exercise of the power to choose without the intervention of any element of duress, fraud, deception, coercion or compulsion, should have knowledge and sufficient understanding of the elements involved in the investigation, which will enable a lucid decision with knowledge of cause. In 1964 the Declaration of Helsinki was formulated and in 1966 Stewart established the requirement for informed consent.

The Belmont report

The Belmont report establishes the fundamental ethical principles of human research. The principles of respect for persons, beneficence and justice are accepted as the three fundamental principles for the ethical conduct of research involving humans.

The Tuskegee Study (1932-1972): lack of research protocol, total lack of informed consent, racial segregation, denial of specific treatment:

1) To determine the natural history of syphilis in the black population

2) Although treatment was available, it was not provided

Given these facts, civil society was organized and emerged:

1) First Charter of Patient Rights (1970) developed by the American Commission on Accreditation of Hospitals

2) Patient’s Rights Charter adopted by the American Hospital Association (1973)

3) Charter of Rights and Duties of Patients in France (1974)

4) Charter of the Hospital Patient, the Hospital Committee of the European Economic Community (1974)
how the informed consent process is conducted and whether it meets international guidelines. It is important to improve awareness and training among clinicians about the attitudes during the informed consent process and to design studies to learn more about how this process is carried out, particularly in vulnerable groups of subjects.

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