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Issues of ethics in pediatric clinical research

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Abstract

Introduction: New methods of diagnosis, treatment and medications have proved to improve the quality of community's life. This is directly related to the implementation of clinical investigations, however in children diverse ethical issues are posed.
Purpose: The description of the basic ethical principles for pediatric clinical research.
Material and Methods: A literature review took place in the electronic database "PubMed", "Google Scholar" and "WHO" during the period of 2000 to 2015. Finally, thirty seven articles were included, while ten articles written in languages different from English and Greek and twenty articles with no full access were excluded.
Results: The Code of Nuremberg and later the Helsinki Declaration contributed to establishing ethical principles in clinical research in humans, ensuring individual's benefit and the establishment of informed consent form. In pediatric population, the process of participation in a clinical trial carris out only after obtaining the consent of the parents or the legal guardian, while the consent of the child himself is recommended, as well, depending of his age.Finally, they have the right to withdraw the pediatric clinical trial at any time without consequences.
Conclusions: Children constitute a vulnerable and sensitive population which entails the necessity of establishing certain ethical criteria in order to consider a clinical research as ethical. It is also important to point out that children have their own personality and their point of view is needed to be taken into consideration.

Keywords: clinical research, children, ethics, deontology

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1 Introduction

''Scientific process'' is characterized the controlled observation made through an experiment [1] The conditions under which an experiment is performed, are created and controlled by the researcher in order to minimize or even reduce the external factors that could affect the outcome. Regarding the health sector, the discovery of new medicines, new diagnostic and therapeutic techniques, are prerequisite for the society's quality of life improvement. Clinical research plays a crucial role for the contribution of these achievements [2, 3].

In a clinical investigation subjects are humans themselves contributing to the development of science, with the precondition of being protected by specific standards that safeguard properly the human rights. Some of the most known examples of progress, in which humans had a key role through their participation in clinical research, are cardiovascular surgeries, transplants, vaccines development and specialized gene therapies [3, 4, 5].

The Code of Nuremberg (1949) was the first step for establishing ethical principles for research on humans and was set as a result of the criminal "research" made by the German Nazis during the Second World War. The experiments made during that period were characterized not only as unethical but also as human rights abuse [3]. The Nuremberg Code was followed and completed by the Declaration of Helsinki, which was first formulated by the World Medical Association (World Medical Association) in 1964. Helsinki Declaration has the basis of population's health promotion. The prerequisite for the participation in clinical research is the completion of the informed consent form by the participant volunteer or the legally authorized representative [6, 7, 8, 9, 10]. Regarding the children population, clinical research is totally needed for the development of safe pediatric formulations-medications and therapeutic interventions (*Guidelines for Good Clinical Practice*) [11].

2 Material and methods

The literature review was based on the search of data from electronic databases: PubMed, Google Scholar and WHO. The articles used in this review included research studies and reviews, referring information about ethics and guidelines for the conduction of clinical research made in children population. The criteria for the exclusion of articles were languages different from English and Greek and articles for which there was no access to the full text. The selection of articles was limited in time from 2000 to 2015, using as key words: clinical research, children population, and ethics. Totally, 50 (fifty) articles were found, 10 (ten) of them were rejected due to title and 3 (three) articles were excluded because they were

not available as full texts. Finally, 37 (thirty seven) articles were studied for this review.

3 Results

3.1 Clinical research and children

Clinical research in children is accompanied by a range of specialized clinical and ethical issues. The vulnerability of this population should be taken very seriously into consideration in order not only to avoid the possible risks resulting from research but also to ensure the safety and the well-being of children. In some countries, children are not jurisdictional to provide legally binding consent to participate in a clinical trial. The International Clinical Trials Registration Platform (ICTRP) of World Health Organization (WHO) is committed to promote better access to guidelines, regulations and protocols of clinical trials in children [10, 12, 13].

It is a fact that many of medicines administered to children have not been specifically developed for them. In other words, specialized pediatric clinical trials have not been conducted to determine the safety and efficacy that these formulations immunize to adults. In many trials, are used reduced doses and often the only criteria is the weight of the child. This process can be extremely dangerous since children cannot be considered as "small adults" as their reaction to medication can be totally different depending from their age and development. Even if this way of drug use is very widespread, it is defined as "not provided for children". Serious consequences, side effects and inefficiency, often come from wrong dosage regimens. It is estimated that in European Union (EU), at least 50% of medicines used in children have never been studied in this population, but only in adults, and possibly in different indications. The need for more studies in children is now a matter of consensus on a global basis [14, 15].

Children constitute a unique population with developmental and physiological differences from adults. Clinical studies in children are necessary for this age group to develop specific, empirical - certified treatments and interventions both to define and improve the best available medical treatment [7]. Before a child's participation in a clinical research is decided to happen, it is important for both parents and the child itself to have well understood the risks and benefits that may be aroused as a result of this involvement. For a minor child, a signed consent will be asked by the legal guardian in order the requisite legal cover to exist, while it is necessary to give itself their consent after the indications, possible side effects and the benefit to be derived will be explained properly for their age. Finally, parents and children have the opportunity to submit any question before, during or after the end of clinical research [16, 17].

3.2 Children's participation

Children's participation in a clinical study take place only after the approval of parents, guardian or legal representative while the consent of children's themselves are also required, if it is permitted by their age. Specifically they will be invited to give their agreement even from the age of six or seven years [17]. In case of refusal to participate, the etiology is recorded in consent form and it is signed by the parents and the investigator [9, 17, 18, 19].
To be considered that a clinical research carried out in very young children is governed by ethical principles, in addition to the Nuremberg Code and the Declaration of Helsinki it is required the relevant guidelines to be followed, as well [6, 20, 21].

According to Guidelines of British Medical Association (BMA), consent must be given only when it concerns intervention which aims to improve child's health. The consent or assent of the child itself is necessary and in case of showing active reluctance, respect to their opinion must be attributed. Enforcing its participation in research has to be avoided. The consent of the child is not sufficient to permit participation in research unless it is accompanied by an adult's informed consent, provided that there are no other interests except child's life. Personal newsletters and consent forms, shaped appropriately for each age group, will be used to provide information. The informed consent's form should among other things explain the purpose of the study, the benefits but also the possible damages while the evaluation of psychological and spiritual maturity of the child should not be forgotten, too [16, 22, 23].

The consent is an ongoing process that is being sought throughout the course of clinical research. The objections raised by a child needs to be taken into account and its desire to be respected, without being obliged to apologize for this, provided that it is not considered to be detrimental to its health. Their right to withdraw a clinical trial must always be remembered and reminded at any time, without any consequences [17]. As already mentioned, the child is given the opportunity to codecide for clinical research that concerns them, from the age of six (6) years. The form and the level of participation in the process, generally, vary according to the age group where the child belongs to [1].

3.3 Neonates, infants and preschool children (very young population)

In these age groups, there is no possibility of implementation of the consent procedure and it is not expected the research understanding. In exceptional cases where the preschool child holds even a little ability of understanding, the age-appropriate information although it is not possible the consent to be obtained, is still necessary to be given [24, 25, 26].

3.4 School-age children (≥ 6 years)

In this age group there is the child's potential ability to consent. Studies on cognition show that children older than the age of six (6) have developed important skills which enable them to participate in the consensus process. It is thought that by the age of three (3) to four (4) years children can understand some expression of altruism, from the age of nine (9) years are able to understand the benefits and risks arising from the survey, although their ability to understand contradictory or incomplete information is still limited. Especially chronically ill minors, seems that often develop increased decision-making capacity while most children and some parents may not understand the process of randomization [24, 25].

This information is necessary to be taken into account when preparing the information document addressed to underage participants [27]. In any case, according to the guidelines of International Conference of Harmonization (ICH E6), it is of major importance to inform the child and to obtain their assent, preferably in writing when the child is in "school age", namely they are able to read and write [1, 24].

3.5 Young people and teenagers

The ability to conduct research in this group is still difficult and many threats adolescents' health still remains. They continue to belong to the pediatric age group, although they have developed the ability of making decisions in various aspects of their lives. Seeking consensus, the ability of a teenager for independent decision-making and the need for continuing the special protection provided by the parents, guardian or legal representative must be put in balance. Most instructions and literature recognize the fact that teenagers, at least under certain conditions can take independent decisions, namely to provide their own informed consent which must be respected. Already in some states, discretion and confidentiality may become binding for healthcare professionals when dealing with adolescents. Consequently, disclosure of information regarding the options and the opinion of adolescents for clinical research as well as the empowerment status and age ability to consent medical treatment to parents, should be evaluated with great seriousness and sensitivity [24].

3.6 The informed assent of the child

Even if the parental permission plays the most important role for the child's protection, the child's assent is of major importance, as well. For this reason, it is vital that every possible information and rules related to this assent are disclosed to the child. However, it is not necessary the child's mood to be borne by all those decision-making standards that concern the adult's informed consent. Children of

any age that participate in clinical trials or research have the right to express their opinion and to be taken seriously into consideration before the final decision relatively to their participation. When the assent is referred to a minor or even a teenager, it is really important all these elements arising from their expressed opinion to be taken into account and lead to the most beneficial decision for them [25, 27, 28].

3.7 Divergence of views between the child and the legal representative

Children, as it is already mentioned, are invited to give their consent, on condition that they are at least six (6) years and always taking into account the specific maturity. Apart from the possibility of expressing assent, there is the possibility of disagreement. This means that they refuse to participate in a research project. In most cases this means that children are invited to take a part of the decision, after the key elements will be explained to them [9]. It is essential that, in order the differences between the views of the child and the legal representative to be understood and respected, every possible effort to take place. The respective National Legal Provisions related to this situation must be followed [24, 29, 30]. If the parent or legal representative in general and the child cannot agree, the dispute can be resolved with the help of a specialized expert group [18].

The participation of the child without its written consent due to extraordinary circumstances constitutes a special case. This recommends, as in adult cases, an attempt to be made so that the consent and assent to be obtained in accordance with national legislation, as soon as possible [24].

Basic duty of each researcher is to fully respect the fact that the participation in any clinical trial is completely voluntary. The child, like the adult, may request to discontinue their participation and their parents to withdraw their child from a clinical trial at any time if for example, there are even suspicions that the treatment does not work for the benefit of them, or that serious side effects may occur to their child [18, 31].

4 Discussion

Participants in a clinical research are particularly vulnerable, as they usually suffer from a serious disease for which there is no available specific, completely effective treatment [8, 20, 32]. Children are perhaps the most vulnerable group of patients. The hospital, which is the usual venue for clinical investigations, is an unfamiliar environment that causes intense negative feelings, especially feelings

of insecurity and fear. Often, children themselves realize that they are sick and they may believe that the situation will incur if they do not participate in clinical research. At the same time, parents consider that their child should participate, as well, in order to be considered as "good patient" and be provided with optimal care by health professionals [20, 32, 33].

Children's rights follow the basic principles of adults' rights with significant changes, though. Especially, in accordance with Article five (5) of the "Convention on Human Rights and Biomedicine", it is necessary the developing capacities of children to be respected, while also with Article twelve (12) their right to be heard with attention and to have their opinion assessed becomes indisputable. In addition, Article sixteen (16) ensures the privacy of the children and the confidentiality of medical procedures performed on them and generally concern them [32, 33, 34].

According to the British Medical Association (BMA) a clinical investigation is needed not only not to be against the interest of the child, but must also be for its benefit because otherwise it is considered that the child is used as a means of processing the survey [20].
On ethical guidelines of Royal College of Paediatrics and Child Health (RCPCH) / British Paediatric Association (BPA) to conduct a clinical research in children, it is stated that "an investigation that is not directly intended for the benefit of the child is not necessarily unethical or illegal". The examples given are the observation and measurement of normal development as well as the evaluation of different diagnostic methods. In the same guidelines it was stated initially that "it would be unethical for children to undergo procedures lurking greater than minimal risk when there is uncertain or no benefit to themselves. Consequently, it is unethical to place bleeds when the goal is not to benefit the child individually, but to combat future diseases" [20, 32, 35]. The initial wording was considered as too restrictive and it was revised so that "serious examination of ethical parameters are required for research in which children are exposed to more than minimal risk, with only small, uncertain or no benefit to themselves". With this revision, it is not ensured that the child will not be an agent for the benefit of "future children". It seems that the provision five (5) of the Declaration of Helsinki, which categorically prohibit the realization of a clinical research that does not aim to welfare of the participant, is breached. There is therefore a conflict between the revised guidelines of Royal College of Paediatrics and Child Health (RCPCH) / British Paediatric Association (BPA) and the Declaration of Helsinki [21].

On ethical guidelines of Royal College of Paediatrics and Child Health (RCPCH) / British Paediatric Association (BPA) three risk categories are distinguished: minimum, low and high. In the minimum risk, for example, the performance of a

study using blood from a blood sample is involved. The low risk includes procedures that cause slight pain or low sensitivity such as injections or blood sampling. The high risk includes particularly painful procedures which are not justified for research purposes only, such as liver biopsy [32].

According to the instructions of the Council for International Organizations of Medical Sciences (CIOMS), when there is ethical and scientific justification to conduct a clinical research involving persons incapable of giving consent in full awareness as children, and the benefit of this process is uncertain, the risk should be minimized. Namely, risk higher than that expected of a routine examination must not be aroused. An exception to this condition is the imperative need to conduct a specific study, provided that the approval from specific ethics committee is firstly obtained. Therefore, this guideline appears to support and leave no scope for the conditional conducting research in children even when they "do not directly benefit but low risk of failure lurks". This guideline could potentially lead to infringement of provision five (5) of the Declaration of Helsinki [6, 36].

The case of a non-treatable condition, where it is not clear what exactly benefits the children and if they finally have the option of participating or they are simply used as agents for the benefit of future patients, is also puzzling [6].
The condition for entering and participating in a clinical research, which is a written, signed informed consent of the participant on a special form, confirms the knowledge of all relevant information regarding the investigation, and the voluntary participation in it. Consent is not some form of agreement-contract and allows free withdrawal at any time [18, 22].

5 Conclusions

Those seven (7) characteristics that according to Ezekiel et al define and characterize a clinical research as ethically acceptable are chosen to be briefly mentioned as conclusions of the review. These are the following: (1) Research should aim to improve health or existing
knowledge. (2) The research should be methodologically rigorous and based on scientific validity. (3) There is a requirement for merit-based selection of individuals who participate in research. Certain scientific criteria must be met owing to the fact that participation cannot be considered as any kind of punishment or privilege. (4) There is a benefit-risk ratio (benefit / risk). The risks must be minimized and the potential benefits both for individuals and for science must be strengthened in order to compensate these minimized risks. (5) A review

of the purpose, progress and initial results of the investigation by an independent special committee is required in order interruption or continuation of research to be decided. (6) Volunteers - participants should be informed about the survey and provide a signed consent. (7) Respect for the participants, protection of their privacy and possibility to withdraw from research without consequences are necessary. Finally, these data which are being interpreted according to the highly sensitive ethical requirements for the pediatric population, can provide a framework for acceptable clinical research in tomorrow's adults [7, 37].

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