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Review article

ЕТИЧКИ АСПЕКТИ НА КЛИНИЧКИ ИСТРАЖУВАЊА НА ДЕЦА

ETHICAL ASPECTS IN CLINICAL TRIALS IN CHILDREN

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Abstract

Conducting clinical trials in children has particular importance as they strive to provide optimal care and therapy for this specific group of patients, but their implementation is still complex. This is often due to the lack of agreed-upon research objectives, unresolved questions about informed consent, and the general perception that children are a vulnerable group of subjects. For providing the best clinical care for pediatric subjects, it is important to conduct careful, effective research that has a scientific basis to answer important clinical questions. The main challenge of pediatric research is the risk and therefore the question arises whether the purpose of the research justifies the risks associated with the study? The four ethical principles should serve as a framework in the process of conducting clinical trials in children: benefacere, justice, respect for personality and confidentiality. One principle is no more or less important than the others, so all four must be taken into account when conducting a research. The ethical principle of "respect for personality" is the basis for the process of informed consent. It is a legal document by which the patient voluntarily agrees to participate in a research. The informed consent must be signed by child's legal guardian(s) and this step cannot be delegated to other family members or friends unless there is a legal basis. However, with proper planning and monitoring the study process, a research can be conducted in children even though they are considered as a vulnerable population.

Keywords: clinical research, informed consent, children, participation

Апстракт

Спроведувањето на клинички истражувања кај деца-та е особено важно бидејќи истите имаат за цел обезбедување на оптимална нега и терапија кај оваа специфична група на пациенти, но спроведувањето е сепак сложен процес. Тоа често се должи на недостатокот на договорени крајни цели на истражувањето, неразјаснетите прашања околу информираната согласност како и генералната перцепција дека децата се вулнерабилна група на субјекти. За обезбедување најдобра клиничка нега на педијатриските субјекти, важно е да се спроведе внимателно, ефикасно истражување кое има научна основа за да се одговори на важни клинички прашања. Основниот предизвик на педијатриските истражувања е ризикот и затоа се наметнува прашањето дали целта на истражувањето ги оправдува ризиците поврзани со студијата? За вклучување на децата во клинички истражувања како рамка треба да служат четирите етички принципи: benefacere, правда, почитување на личноста и доверливост. Еден принцип не е повеќе или помалку важен од другите, според тоа сите четири мора да се земат во предвид при спроведување на истражувањето. Етичкиот принцип „почитување на личноста" е основа за спроведување на процесот на информирана согласност. Информираната согласност е законски документ со кој пациентот доброволно се согласува да учествува во истражувачка студија. Информираната согласност мора да биде потпишана од законскиот старател(и) на детето и овој чекор не може да се делегира на други членови на семејството или пријатели, освен ако тоа нема законска основа. Но сепак со соодветно планирање и надзор над студијата, истражувањето може да се спроведе кај децата иако се сметаат за вулнерабилна популација.

Клучни зборови: клиничко истражување, информирана согласност, деца, учество

Introduction

Conducting clinical trials in children is crucial for providing optimal care and therapy in this specific group of patients. Although the need for pediatric research is

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great, their implementation is still complex. This is a result of a number of factors including the lack of agreed-upon research objectives, informed consent issues and the general perception that pediatric patients are a vulnerable group of subjects. This vulnerability is based on several factors: [1] insufficient decision-making capacity, [2] children's lives are under the protection of adults, [3] children's rights and interests are often underestimated by the society. Research is necessary and should be aimed to improve well-being and treatment, prevention and diagnosis (as defined by the WHO) in subjects, including children [1]. There are many differrences in physiology, pathology, pharmacokinetics and pharmacodynamics between children and adults. For example, in pharmacokinetics there are differences in metabolic pathways and organ function. In pharmacodynamics there are differences in the functions of the receptor, effectors systems, and homeostatic mechanisms. Side effects affect growth and development, and the dose of medication depends on body weight or surface. Furthermore, childhood has several stages and studies are performed in certain age groups such as prematurity, term infants, infants, young children, older children and adolescents [2].

For providing the best clinical care in pediatric subjects, it is important to conduct careful and effective research that has a scientific basis that should answer important clinical questions. The main challenge for pediatric research is the risk. What is the risk of conducting / or not conducting the research and who has the right to decide for the child's risk? What should the child say that he/she agrees to participate in the research? What does the legal guardian have to say in order for the child to agree to participate in the research? What is the ultimate goal of the research? Finally, does the purpose of the research justify the risks associated with the study [1]?

History of research in children

In the past there were cases in which the interest of the legal guardian of the child was contrary to the best interest of the child. The Willow Brook State School for Children with Disabilities is one such example, where legal guardians allowed their children to be involved in a suspicious study for hepatitis just to ensure that the children would be enrolled in the same school. Although legal guardians knew it was risky to allow their child to participate in such a study, they feared that refusing to participate in the study would have repercussions on enrolling in the same school where enrollment was difficult. This example shows how much children's rights can be compromised by caregivers and health communities.

The second example in the history of ethical offense is the radiation experiment on pediatric subjects conducted at the Walter E. Fernald in Waltham, Massachusetts. In this experiment, wards with boys in the institution were exposed to traces of radioactive calcium and iron, in order to detect problems with mineral absorption. The parents of the children involved in the study received incomplete information about it when they gave their consent. Parents were never told that children were exposed to any radiation, while children were told that they simply joined a science club. The experiments raised important questions about what "informed consent" really is and whether institutionalized children should eventually be included in clinical trials, given that they are by nature a vulnerable group [3].

Ethical principles

Four ethical principles should serve as a framework for involving children in clinical trials: benefacere, justice, respect for personality and confidentiality. One principle is more or less important than the other, so all four must be taken into account when conducting a research. In some circumstances, all principles may be in conflict with each other, and the researcher must choose the appropriate direction that best suits for the scientific question.

Benefacere

Benefacere is an ethical principle based on kindness and well-being. It is a moral obligation and refers to the benefit of the other, to help him in his interest and to prevent or eliminate possible harm (primum non nocere). In a pediatric research, it is important that the research does not exploit the vulnerability of minors who cannot give genuinely informed consent to participate in the study. Therefore, the researcher must know that the research is scientifically based and that "unnecessary" damage is not done to the research subject. The key aspect of harm is actually the risk. There is a serious debate about the role of benefit for the subject when he/she will not benefit directly from the research. It is widely accepted that in the adult population, a researcher may risk a small level of harm to the subject, if the subject voluntarily agrees to a treatment that will make a benefit for the humanity. The child's ability to understand the risk on human health in a wider sense and the child's willingness to accept such a risk are the issues of considerable debate.

Justice

The principle of justice is an ideal distribution of risk and benefit throughout the population in conducting a research. The choice of subjects should be fair and the vulnerable ones should not be exploited for the benefit of the general population. The inclusion and exclusion of subjects in research protocols should be based on a valid scientific question but not on the basis of discriminatory factors or ease of enrollment. One aspect of

biomedical research is to determine whether the intervention improves, does not improve or has no effect on the pathophysiological condition. The principle of justice indicates that individuals in a population should have equal access to potential benefits and potential risks. Factors that may disrupt the equitable distribution of participation include demographic differences (for example, minority and social differences, mother's language...), mental status, and coercion by researchers based on financial incentives. The last aspect of particular importance for the pediatric population is concern that researchers may force children with financial incentives to obtain consent (for example, a gift card for a toy store or a fast food restaurant). The value of such financial incentives is often reviewed by Committees in order to confirm that it is acceptable with the community standards and it is not a source of potential misconceptions.

Respect for personality

The third ethical principle of "respect for personality" emphasizes an important issue in pediatric research: paternalism *versus* autonomy. Autonomy is considered when the person has the capacity for rational decision making. However, paternalism implies that the individual is incapable for decision making and another person must make the decision in the best interest of the individual. A key principle in the research of the subject is the ability to make a decision on whether to participate despite the perceived risk. The autonomous decision of the adult is clear, but at what point can an autonomous decision be made by a child? Do children have the ability to make autonomous decisions, or should a paternalistic decision be made in the best interests of the child? Societies define the ability to make autonomous decisions according to various factors such as age, sexual development and education. It is generally accepted that a child can make an autonomous decision at the age of 18 [4].

Confidentiality

The right to confidentiality of the research results, testing and screening of children is accomplished by their parents or legal guardians. The results are given to the child's parents [5].

Informed consent

The informed consent process is based on the ethical principle of "respect for personality". The informed consent standards include: [1] providing research information and opportunity to decide whether to participate in it, [2] presenting the information in a comprehensible manner, and [3] voluntary participation of the potential subject and the opportunity to withdraw freely at any time without any repercussions. Applying these standards to pediatric patients is a challenge. For example, what is the most appropriate way to make sure that a 10-year-old understands the information presented by the researcher? Therefore, it is an imperative for researchers to meet the standards of the informed consent with the child's caregiver in the best possible way. The informed consent is a legal document and therefore the age required for consent is coming with the adulthood. Institutional Review Boards (IRBs) are responsible for assessing risk levels in collaboration with the lead researcher. This assessment is made after reviewing the research protocol. The primary responsibility of the IRB is to protect the rights of the research subject by assessing the risk and obtaining informed consent and proper review and enforcement. The informed consent is a legal document in which the patient voluntarily agrees to participate in a research study. The informed consent must be signed by the child's legal guardian(s), depending on the risk of the investtigation. This step cannot be delegated to other family members or friends unless it is legally based. The informed consent must be written in a way that meets IRB standards that "information must be provided in a form that is understandable". Adults who are the child's legal guardians must sign the informed consent. The concept of Informed Consent for Children is similar to obtaining Informed Consent for Adult Research Subjects.

Challenges in performing pediatric research

Carrying out research in pediatric populations is extremely difficult because it brings a special package of challenges.

Guardianship

Guardianship is a term used to describe someone who has been elected or appointed to make legal decisions for another person who cannot make those decisions on his or her own. Guardianship's issues can become legally complex, and can occur with or without termination of parental rights. If parental rights remain in the presence of alternative guardianship, it may not be clear to the researcher who can legally make decisions regarding the child's participation in pediatric research (who may agree, whether both parents and guardians should consent, etc.). For this reason, researchers often avoid involving pediatric patients when guardianship is unclear. Adopted children, orphans and disabled children are usually excluded from participation in a research.

The role of compensation

The role of compensation in medical research is always controversial, regardless of the age of the subjects included in the research. Opponents of participant's com-

pensation argue that compensation reduces the willingness of informed consent. Proponents of compensation, on the other hand, consider it unethical to participate in the research when the subject is not paid. Fees for pediatric research are allowed in the United States, yet many countries, including those in Europe, do not provide compensation for pediatric research subjects. Compensation for medical research subjects quickly became standard practice in the United States, and thus the problems of compensating participants in pediatric research were gradually resolved. The payment to parents must be sufficient to cover the costs for transport, medical care or food. However, the compensation of the parents or guardians must not exceed the amount that would influence the decision whether to include the child in the clinical study.

Commercial sponsorship

Insufficient involvement of pharmaceutical companies in pediatric research is a result of several obstacles. The costs associated with conducting research in children are significantly higher than the costs associated with conducting similar research in adults. In addition, fewer patients are available to participate in pediatric research, making recruiting subjects a challenge. Finally, the final product market determines whether the pharmaceutical company is willing to participate in pediatric research, as profits often dictate product development. Unsuccessful research and unexpected safety issues that may occur in younger patients can quickly increase the costs associated with conducting trial in children. The complexity of ethical issues surrounding pediatric research is often enough for pharmaceutical companies not to participate. The lack of researchers to participate in and conduct pediatric research makes it difficult for pharmaceutical companies to involve sufficient research subjects with sufficient power to obtain statistical and clinical relevance. Many strategies are used in an attempt to overcome these barriers for commercial participation in pediatric research.

Research competencies

The shortage of trained clinical researchers focused on pediatric studies still remains. Very often, pediatricians choose not to participate in clinical trials, since they believe it may jeopardize the link between them and young patients. Doctors have fear regarding the impression they will leave on parents or guardians if they offer the opportunity to involve their child in a research. On the other hand, doctors simply believe that they do not have the training and skills to participate in clinical trials. Developed countries offer a variety of training programs for physicians to conduct pediatric clinical trials. These programs consist of scholarships, training grants, continuing education, and certification programs. However, there is a shortage of physicians and clinical staff trained to conduct pediatric research. Doctors with training in conducting pediatric research often migrate to certain children's hospitals in the hope of becoming more involved in pediatric studies [6].

Good clinical practice (GCP)

The principles of Good Clinical Practice (GCP) provide a balance: subjects to be adequately protected in research studies; studies to be scientifically based, well designed and properly analyzed; and study procedures to be properly undertaken and documented. If GCP principles are not followed, participating children may be at risk, the data may be unreliable or unusable, and the study would be rejected by the Ethics Committee. A good clinical practice follows the general principles of medical ethics: respect for life, human dignity and personal autonomy, benefacere, primum non nocere and justice. From these ethical principles, general guidelines for good clinical practice in pediatric research can be drawn [7]. Trials should be focused on knowledge, treatment, relief or prevention of a disease in children. Biomedical studies must be dedicated to reduce suffering and improving disease prognosis. The expected benefit must outweigh the recognizable risks. Serious predictable risks must be avoided. Only well-designed research is ethically appropriate. Research protocols must be evaluated by Ethics Committees (Institutional Review Boards) and reviewed by pediatric experts. Ethics Committees are an effective tool for protecting subjects from inappropriate research. The Ethics Committees that review pediatric research should have members who have experience in pediatric practice. Pediatric studies should be performed by medical and scientific staff who are familiar with GCP and are capable of a confidential relationship and communication with the child and parents. Studies should be conducted in institutions that provide a child-friendly atmosphere [8-9].

Conclusion

Pediatric clinical trials provide valuable information for physicians, giving them the guidance and knowledge in providing optimal care for their patients. With proper planning and reviewing of the study, trial can be conducted in children even though they are considered as a vulnerable population. Children are not "small adults". Compared to adults, there are differences in pharmacokinetics and dynamics, as well as side effects that are common in children. Certain consequences of medical interventions can be seen in children and can occur long after exposure. Because of the special care they deserve, children should not be the subject of clinical trials when research can be done on less vulnerable subjects such as adults. If research in children is ne-

cessary, then less vulnerable children should be included, i.e. older children [10].

Conflict of interest statement. None declared.

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