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REVIEW

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Research in children. A report of the Ethics Working Group of the CESP

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Abstract Research is essential for the improvement of care in patients, including children and incapacitated persons of whom children form a special group. Inclusion of an individual in research requires informed consent. As informed consent is impossible in children, they might be excluded from studies. Research in children, however, is needed to improve health care in this group. In this paper we discuss the pros and cons regarding research in children. *Conclusion:* research in children is acceptable if it is necessary to promote the health of the population represented and cannot be performed on legally competent persons instead.

Keywords Children · Consensus · Research

Introduction

Medical research is essential for the improvement of care in patients. The results of medical research may not in all cases lead to immediate improvements in care. The aim, however, should always be that it will ultimately benefit patients. According to the Helsinki Declaration, including the most recent amendments of October 2000, research in humans is ethically acceptable under certain conditions. The Declaration gives special guidelines for persons who cannot express their will, as for instance infants and children. Article 24 of the Declaration indicates that "for a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally component persons". Despite these clear guidelines, concerns as to the acceptability of research in children continues. This paper tries to outline the ethical aspects regarding research in children and to give practical guidelines.

Medical research involving children is an important means of promoting child health and well-being. Such research includes investigation into normal childhood development and the aetiology of disease as well as careful scrutiny of the means of promoting health care and diagnosing, assessing and treating disease in children. It is also important to validate in children the beneficial results of research conducted in adults. Medical research involving children therefore can be regarded as essential for the improvement of care in children.

Autonomy and respect for human dignity

Respect for the autonomy of the individual is one of the fundamental precepts of medical ethics (Table1). The principle originally came to the fore in reaction to the paternalism which always has been a prominent feature of the medical profession. Autonomy involves the right of every individual to make decisions regarding their body and their health, on the basis of their own values and opinions. The establishment of this principle meant that it was no longer purely up to the medical profession to decide what is in the patient's best interest. Rather, the final decision lay with the patient. In health care, the principle of autonomy is incorporated into the rules on information and consent. However, incapacitated persons are not able to decide what is in their best interest, or anyone else's. They cannot ask for the things which are in their interest or refuse the things which are

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Table 1 Principles in medical ethics

Principles in medical ethics
Autonomy and respect for human dignity
Beneficence
Non-maleficence
(Distributive) justice
Community spirit and solidarity

not. Such persons depend on the care of others and are consequently very vulnerable.

Where incapacitated persons are concerned, therefore, other related values assume greater importance than the principle of respect for individual autonomy. These are respect for the individual's physical integrity and personal feelings: in short, respect for human dignity. Therefore, additional safeguards are needed to protect the dignity of persons who lack the capacity to consent to treatment or to disruption of their daily lives. Such safeguards should be designed to ensure that any infringement of the dignity of an incapacitated person is kept to the absolute minimum and remains in proportion to the importance of the research. Thus, attention focuses on two main areas. The first is the relation between the degree to which dignity is infringed and the nature and purpose of the research. In this regard it is necessary to consider whether the research could be of direct benefit to the subject, and whether in due course it could benefit persons such as the subject. The second point of focus is the nature of the person whose participation is being sought. Is he or she easily unsettled? What powers of comprehension does he or she possess? Has he or she ever been capable of self-determination?

Respect for the autonomy of the child and incapacitated individual could be solved by not including them in research. However, this is to the detriment of children and incapacitated individuals, as is explained later. Another option to solve the dilemma is the following. First, the consent of a representative must be obtained. This representative, usually the parent, will know what the individual would have wanted. Secondly, children should be told what is going to happen in a way they might understand. All efforts in this respect have to be taken. Finally, infants and children should not be involved in medical research if they show clear and unusual objections against the studies.

Beneficence and non-maleficence

The principles of beneficence and non-maleficence lie at the very heart of health care. Medical science and the caring professions are dedicated to reducing, ending and preventing human suffering and to promote human welfare. The two principles reflect the importance generally attached to good health and general well-being.

The principle of beneficience is more broadly applicable. Action undertaken in the immediate interest of an individual patient is clearly an application of the principle, but just so is action which is of indirect benefit to patients such as the acquisition of knowledge regarding, or skill in the art of healing and nursing. The second principle, "do not harm" is narrower and gives much stricter guidance regarding the treatment of individual patients.

On the face of it, the implications of these principles for medical research seem contradictory. Certain aspects of medical research appear to be at odds with a commitment to beneficence and non-maleficence. First, some studies might not be of direct benefit to those who participate in it. It may be argued, therefore, that non-therapeutic research is contrary to the interest of the participants, certainly when it involves persons who are not able to consent. On the other hand, the welfare of persons is closely linked to the advancement of medical science. Therefore, studies in which the burden and risk associated with such research are low or insignificant, do not have to be against the interest of infants involved in studies.

Distributive justice

The following basic principle of medical ethics is founded upon the notion that "equals in similar circumstance should receive equal treatment". In social terms this means that benefits and burdens must be distributed as fairly as possible throughout society, taking individual's circumstances into account. Any difference in circumstances should be reflected in the way people are treated. If this general principle is applied to medical research involving incapacitated persons, the following considerations come into play. Incapacitated persons like infants and children have just as much dignity as other persons. In that respect infants and children are the equals of non-incapacitated persons. However, by virtue of their incapacity, the incapacitated also differ from other persons. In accordance with the principle of distributive justice, the incapacitated should be treated in a way which compensates for this difference. There are at least two ways in which compensation could be made. The first is to give the incapacitated more care and attention, the second could be to excuse them from having to contribute in the functioning of society, for instance not to involve them in medical research. If one accepts that greater care and attention can be given to the incapacitated, then medical research which is focused on areas relevant to such persons that cannot be done in other individuals, will be acceptable according to distributive justice, also when this research is not directly in the interest of the child itself. In a number of circumstances, improvements in treatment and care cannot be made without research in infants and children themselves.

Community spirit and solidarity

No man is an island. Human beings are social by nature. Society and social structures are essential to the (continued) existence of the individual. Society functions through the involvement of the individuals of which it is comprised and depend upon their willingness to play a part. Contributing to the functioning of society involves subordinating one's own interest to the general interest. By improving the way society functions, such community spirit ultimately promotes the welfare of the individual as well.

The care of persons in need of help involves a greater degree of altruism. Solidarity with persons who are unwell or disabled and who for whatever reason are dependent upon the care of others, is considered to be a virtue. However, to which extent is it reasonable to expect persons to contribute to the greater good if they lack capacity to do so of their own volition? and to which extent can such a person be assumed to have a sense of solidarity with others?

The society in which a child perceives itself to live is initially very small, but as he or she grows up, so his/her horizons are broadened. Very gradually, children learn and are encouraged to become more involved in and to accept responsibility for a wider circle of people. It seems then reasonable, against this background, to ask children to participate in medical research which cannot be carried out without child subjects.

Need for research involving children

There are a number of reasons why research conducted in infants and children is necessary. Physiology and pathophysiology in infants and children is in many respects different from that in adults. Although physiological principles will be the same in children compared to adults, the way they are regulated might be different. Secondly, a number of diseases are unique for children and therefore cannot be studied in adults. Thirdly, the infant is in a period of growth and development. Diseases which might not be of any harm to the adult, can have serious consequences for the developing individual. Also the pharmacokinetics of drugs can be very different in children compared to adults as well as the reaction of children to drugs. It is often impossible to draw guidelines regarding safe and optimal drug dosages in infants from results obtained in adults. Studies often will have to be performed at all different ages. Not conducting this research in children will be to the disadvantage of them. Not only will insight into their physiology and metabolism, needed for optimal treatment, not be available, but also drugs either cannot be prescribed or will be prescribed in incorrect dosages.

Based on these considerations, we must conclude that research in children is not only necessary, but essential for the improvement of health care in infants and children.

Types of research in children and infants

Research in children can be divided in non-therapeutic and therapeutic research. The non-therapeutic research can further be divided in observational research and non-therapeutic interventional research.

Non-therapeutic research

In observational research, the researcher does not attempt to change the existing situation, but only to describe it as accurately as possible. Such research can provide "standard data" or can improve understanding of the way a given characteristic is distributed through a certain group or of the way a certain illness progresses. So, for instance, observational research might be conducted to establish the concentration of a given substance found in the body under normal or certain pathological conditions, or its purpose might be to establish what a "normal" electrocardiogram or electroencephalogram looks like for a particular group. Another common reason for carrying out observational research is to compare the distribution of a given characteristic in one group or population with its distribution in another group, whose circumstances differ. Such studies can improve understanding of the origins of certain diseases. It should be noted that normal values in children can often not be taken from samples collected in adults.

In non-therapeutic interventional research, the investigator intervenes within the normal situation without the aim to improve the situation of the patient. The following are examples of these studies. First, the administration of a non-radioactive label to measure the metabolism in a healthy or sick infant. The aim of these studies is to provide a better understanding of physiology and pathophysiology. A second example is the early phase of studies with drugs. For instance, a new and promising antibiotic might be important for use in children and infants, but data on pharmacokinetics are completely lacking. Then it will be not appropriate to give this drug as treatment in a child with an infection. Therefore one dose might be given to a healthy child or to a child with an infection in addition to regular amtibiotic therapy and blood samples are taken.

Therapeutic research

In therapeutic research, the direct aim of the study is to improve the case and treatment of the group involved in the study. The ethical dilemma in this type of studies lies with the control group. Whenever possible these studies should be placebo-controlled double-blind studies. This involves a group that might benefit from the new intervention, but also a group which will not receive the new treatment or drug. This group therefore has no direct benefit. As results of these studies will benefit ultimately

children with the disease at stake, it is acceptable to include a group without the new treatment, although the infants cannot have given their consent for the studies. Not involving a proper control group will make the study useless.

Consent versus assent

Consent describes the positive agreement of a person, assent refers to acquiescence. The application of general principles indicate that when children have sufficient understanding and intelligence to understand what is proposed, it is their, and not their parents' consent that shall be required. Refusal by a child to participate in research, also when no clear reason for the refusal is given, could be evidence of such understanding and it then would be incorrect to rely on parental consent. Some conduct in children, however, should be regarded as a normal healthy reaction which does not necessitate not involving the child in the study. If the child is insufficiently mature to consent, then a valid parental consent should be obtained. It can generally be assumed that parents will protect the best interests of their child. On the other hand, this also means that parents can speak for their children and that the interests of the children can be protected by the parents.

Regulatory aspects

Among others, two international agreements are of importance for judging medical research in humans: The Helsinki Declaration and the International Covenant on Civil and Political Rights.

One of the first international agreements to regulate the conduct of medical research involving human subjects was the Helsinki Declaration, effected in 1964, by the World Medical Association. Very recently the Declaration was revised. An article pertaining research in children was included (Article 24). According to this article, research in children is not allowed unless "the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons". Therefore, according to the World Medical Association, responsible for the Helsinki Declaration, research in children is acceptable under these, strict, conditions. The Helsinki Declaration has no formal status, it is the free decision of the state authorities to acknowledge them as guidelines or even as compulsory for their territory.

Article 7 of the International Covenant on Civil and Political Rights states: "no one should be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation." Interpreted quite literally, this article appears to outlaw all medical research involving persons who lack the capacity to personally consent to participation. On the basis of such an interpretation, such research would not be allowed even if it was likely to be of direct benefit to the subjects. However, no one believes that it was the intention of the Covenant's authors to curtail activities of vital importance to humanity. Therefore, the intention of the law should be followed instead of taking it literally. What the issue is, is not the general legality of non-therapeutic research involving children and infants, but the legality of the kind of research identified as medically necessary if carried out in accordance with generally accepted guidelines.

When these general guidelines are taken into account, and the Medical Ethics Committee has given consent and the parents have given consent for the study, there seems legally to be no argument not to carry out studies in infants when there is a clear benefit for infants in the short or long run.

The role of Medical Ethics Committees

Each study conducted in infants and children should be sent to a proper Medical Ethics Committee for approval. It is unethical to carry out studies which can not give proper answers. It is important that these committees should consider the following questions:

1. Does the study have a real question or questions?
2. Is the study designed in the best possible way to answer the questions?
3. Will the study work in practice?
4. What are the risks and burdens for the children involved?
5. Are the results of the study to be published?

When the Medical Ethics Committee is convinced that the study is properly designed and the risks for infants will be low or minimal, the study can be approved of. A Medical Ethics Committee should consist of different members with different backgrounds including experts in law, a psychologist, an ethicist, nurses and doctors including paediatric nurses and paediatricians involved in research. The committee should have members with experience in paediatric research.

Risks and discomforts involved in studies

In the determination of the balance between benefits and risks of research, one has to consider also which risks are potentially acceptable. Risks can be defined as minimal, low or high. Minimal risks include both observing and questioning children and taking urine and blood samples, provided that all measures are taken to prevent unnecessary harm to the infant. Observing and questioning children should be done in a sensitive way. Taking urine samples by applying a urine bag or blood samples when a venipuncture or heel prick is done for clinical reasons, is also beyond doubt. We feel that

Table 2 Guidelines regarding the approach of research in children

Guidelines for research in children
1. Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner
2. Children are not small adults; they have an additional, unique set of interests
3. Research should only be done in children if comparable research in adults could not answer the same question
4. A research procedure which is not intended directly to benefit the individual child is not necessarily either unethical or illegal, if it is likely to yield generalised knowledge of vital importance
5. All proposals involving medical research in children should be submitted to a research ethics committee involving experts in paediatric research
6. Legally valid consent should be obtained from a child, parent or guardian as appropriate. When parental consent is obtained, the agreement of school-age children who take part in research should also be requested by researchers

taking blood samples by either venipuncture or heel prick especially for a study is also acceptable, provided that measurements cannot be done without taking these blood samples and that all possible precautions, as for instance applying anaesthetic creme, are used. Low risk can be procedures that cause brief pain or tenderness. Examples are injections. High risk are procedures that go beyond taking blood or giving injections.

In our opinion, procedures including minimal risks are acceptable in children, provided that all other restrictions regarding research in children are met. Low risk procedures can be acceptable provided that the information acquired is of high importance for children and this cannot be obtained without these procedures. High risk procedures are not justified when done for research purposes only. Crying on performing a venipuncture in children is not considered an abnormal reaction and in principle no reason not to carry out the study. In accepting the risks involved, one should realise that important research ventures into the unknown. A prohibition on such research involvement would be to the detriment of children, just as prohibition of new experience is harmful to children in the long-term.

Conclusion

We believe that medical research involving children is not only acceptable, but also necessary, given that a strict number of guidelines are being followed, as summarised in Table 2. If these guidelines are being followed, the Ethics Committees can give approval for a study and consent of the parents can be sought.

Further reading

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