

PERSPECTIVES ON MEDICAL RESEARCH CONDUCTED ON CHILDREN

Final Report of the Working group Appointed by the National Advisory Board on Health Care Ethics

Members of the working group on medical research on children appointed by the National Advisory Board on Health Care Ethics:

Salla Lötjönen, Chairperson, Secretary General, National Advisory Board on Research Ethics

Kalle Hoppu, Medical Director, Poison Information Centre, Helsinki University Central Hospital

Sirkku Kiviniitty, Parent Representative, Parents of Premature Infants Association

Eija Reen, Assistant Nurse Manager, Hospital for Children and Adolescents, Helsinki University Central Hospital

Outi Tammela, Chief Physician of the Neonatal Unit, Tampere University Hospital, Paediatrics Department

Ritva Halila, Secretary of the working group, Secretary General, National Advisory Board on Health Care Ethics

SUMMARY

A considerable proportion of the medical treatment of children is based more on estimates and assumptions than on clinical evidence. Enrolling children into research has been avoided because of the special status of children. The special characteristics of research performed in children are related to the physical size of children and their dependency on adults due to their level of development. While current legislation allows, on certain conditions, a 15-year-old to give independent consent to participate in a research study, a person must be 18 years old before he/she can make an entirely independent decision about participation. Children do not gain the same benefits from pharmaceutical innovations as adults, since so few clinical trials are conducted on children. On the other hand, many trials are conducted on children in some narrow sub-specialties, and both the parents and the health-care staff can be confused by repeated requests to participate in various research projects. The emotional stress of the parents and the fear of losing the child in serious situations makes giving a voluntary consent problematic.

On 5 June 2001, the National Advisory Board on Health Care Ethics (ETENE) appointed a working group to look for common rules to be applied to scientific research conducted on children. Representatives of paediatric clinical pharmacology, neonatology, nursing, law, and of parents were included in the working group. The members of the working group were: Kalle Hoppu, Docent of Clinical Pharmacology, Medical Director, Poison Information Centre, Helsinki University Central Hospital (HUCH); Sirku Kiviniitty from KEVYT ry (Parents of Premature Infants Association); Eija Reen, Healthcare student, Assistant Nurse Manager, Hospital for Children and Adolescents, (HUCH); and Outi Tammela, Docent of Paediatrics, Chief Physician of Neonatology Unit, Tampere University Hospital, Paediatrics Department. Salla Lötjönen, Master of Laws, Master of Arts, National Advisory Board on Research Ethics (TENK), acted as the chairperson of the working group. The secretary of the working group was Ritva Halila, Doctor of Medical Science, Specialist in Paediatrics, National Advisory Board on Health Care Ethics (ETENE). The finished report was extensively circulated for advisory comments and some additions were made on the basis of these comments.

The working group assembled eight times. The report of the working group focuses on clinical research of the intervention type, although most issues discussed in the report can also be applied to other research studies, such as research on medical devices, radionuclide and radiology, diagnostics, genetic screening, child psychiatry, and follow-up of normal growth and development. The scope of research studies conducted on children is so wide that it was impossible to take the special characteristics of each type into account. Even though the working group also gave some detailed recommendations, the main purpose of the report is to prompt discussion about ethical questions concerning research conducted on children rather than to give an exhaustive report of all viewpoints on the subject.

In the report, the working group decided to emphasise differences associated with different stages of life and development, and the ability of a child or an adolescent to decide whether or not to participate in research. A child or an adolescent should always be party to the decision-making that concerns him/her if possible. This can be promoted by telling the child or adolescent about the research in an understandable way. The number of children recruited should be kept as small as possible, but large enough to enable scientifically valid results. Children may be recruited to a research study only if there can be expectations of a direct benefit to their health or to the health of children having a similar condition or belonging to the same age group. The rule of thumb should be that the child participates in just one research study at a time. Special attention should be paid to the role of the person requesting the consent. For research that includes minor procedures, the consent of just one parent is sufficient. An additional risk of injury or stress associated with the research should be proportional to the child's individual situation and health benefits expected from the research rather than to a detailed classification of the procedures. It is recommended that researchers in the field receive training about the ethical questions relating to research conducted on children.

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BACKGROUND ON RESEARCH CONDUCTED ON CHILDREN

The development of medicine and biology has greatly benefited humankind, particularly during the last century. Life expectancy has improved, many previously fatal diseases have either been eradicated or medicines, vaccines and other preventive procedures have been developed against them. However, even during this time, research contained features that could never be accepted today. At the beginning of the 20th century it was still felt that, if animal studies could not be used for studying a problem, homeless children could be used as research subjects in clinical research; adults were used only as the last resort. Pharmacotherapeutic disasters of the 1950s and 1960s affecting particularly children (e.g. the thalidomide cases and hepatitis vaccine research in the USA) led to the development of the current international treaties and legislation concerning medicines. This history continues to contribute to the fact that people still feel a certain reserve about studying pharmaceuticals in children.

Childhood and adolescence are periods of vigorous growth and development. Children are not small adults, and this very growth and development make them mentally and physically different from adults. Scientific research must be conducted on children and adolescents that they could benefit from research-based development of medicine and biology like adults. Such research is the only way to find the best means to monitor and support the normal growth and development of children, as well as diagnose and treat any disturbances in them. Some diseases occur in children and adolescents but not in adults. Prevention, diagnosis and treatment of these diseases cannot be optimised without research conducted on children. Scientific research of diseases occurring in both children and adults is needed in order that, for example, treatments which have been found effective in adults could be applied to children and adolescents.

A child needs the protection of adults because of his/her incomplete development. A small child's ability to evaluate and weigh the health risks and discomfort caused by the research study is limited. The child needs the protection and support of his/her parents or guardian in this evaluation. The child's possibilities to be party to decision-making can, however, be improved by various means. The child's perspectives and priorities may be different from those of his/her parents or guardian. In some situations, the family may receive considerable financial benefit from participation in research. The benefits may include, for example, free medicines or visits to the outpatient department even though paying actual fees for participation is prohibited by the Medical Research Act. The child, however, may see things differently. The child may be afraid of visiting the doctor or the hospital and of pain associated with the procedures. It is important that the investigator planning the research study, the person receiving the consent, and other staff participating in the research program think beforehand about how the voluntariness of the child's consent to participate in the research study can be ensured. Ensuring the well-being of the child is an obligation for everyone participating in the planning, realisation, and evaluation of the research study. The doctor responsible for the treatment must adhere to the obligation currently set by the Act on the Status and Rights of Patients: to provide the best possible treatment and to avoid all procedures that might put the patient's health at risk.

Ethics committees evaluating clinical research have an obligation to take into account the need of protection of special patient groups. The ethics of research performed in children involve finding a balance between the necessity of the research and the protection of the child. When searching for the right balance, the perspectives of the parents and staff treating the child must be taken into account in addition to medical and legal aspects. It is important to recognise and acknowledge the different interests of the different parties and find a balance between them. The most central principle is that the child should never be enrolled into a trial if participation is not in the child's best interests. It has been our goal to present the various viewpoints in this report on equal terms.

Creating an atmosphere of trust is of the utmost importance in the treatment of the child as well as in matters relating to research in particular.

Children are minors, but they enjoy the same rights as all other population groups. In Finland, this has also been emphasised in the constitution (the Constitution of Finland, 731/1999) § 6 paragraph 3). International agreements on human rights signed by Finland, such as the UN Convention on the Rights of the Child, also give children the right to the same level of health, health care and rehabilitation enjoyed by other citizens. The UN Convention on the Rights of the Child obligates the signatory countries to take into account as their primary consideration the best interests of the child (Article 3.1). Other obligations set forth in this convention include, for example, the obligation of the signatory countries to ensure the survival and development of the child to the maximum extent possible (Article 6.2). The convention also recognises the right of the child to have access to the highest attainable standard of health, the treatment of illness and rehabilitation services (Article 24).

Another important document relating to international law is the Convention on Human Rights and Biomedicine by the Council of Europe (ETS 164), which contains special regulations concerning scientific research in the field of medicine in subjects who are not able to give an informed consent independently. In the last few years, Finland has prepared for the ratification of this convention by bringing its national legislation closer to the convention. The most recent document relating to international law that applies to research in children is Directive 2001/20/EC of the European Parliament and of the Council (the so-called Clinical Trials Directive). This directive contains quite specific regulations for the protection of children, but also takes into account the necessity of research. On a national level, clinical research performed in children is controlled by the Medical Research Act (488/1999, later the Research Act). This report mainly refers to national legislation unless the requirements set forth in international documents outweigh those of national regulations.

Part I:

PERSPECTIVES ON RESEARCH CONDUCTED ON CHILDREN

Medical grounds of research conducted on children

A child's organs continue to develop from early foetal period to adulthood. Different organs develop at different rates and at different times. The threshold values of normal development in different age periods, which form the basis of diagnosis and treatment, have to be found with the help of research. Due to ongoing growth and development, the absorption, metabolism and elimination of a medicine, as well as its effect on the target organ and the rest of the body, are different in children than in adults, and they vary on the basis of the child's age and stage of development.

So-called children's diseases are those which rarely occur in the adult population or which must be treated in early childhood. Typical examples include, for example, several poxes, many infectious diseases occurring in children (such as ear infections), structural defects (anomalies), or CP. Children do, however, have diseases that more commonly occur in adults. These include asthma, chronic intestinal diseases (i.e. coeliacia, Crohn's disease, ulcerative colitis, migraine and epilepsy). Children with these diseases need treatment just like adults, although there may be differences in the nature of the treatment or the dosage of the medicine.

Research studies usually performed on children include vaccine research, which aim at finding preventive vaccines to diseases that commonly occur in children. Although the incidence of many of the most difficult and life-threatening infectious diseases has decreased or the diseases have been

entirely eradicated, vaccines are still being developed for, to name a few, chickenpox, diarrhoea, respiratory tract infections and ear infections. Most of the vaccines are directed at young children, but at the moment vaccines are also being developed for adolescents and adults (e.g. HIV and papilloma virus vaccines).

In principle, research conducted on children greatly resembles research conducted on adults. When children are participating in research, however, the child's level of development and ability to cooperate and understand must be taken into account. For example, in tasks that require cooperation from the research subject, such as respiratory research studies on asthma, the child's ability to act according to directions must be taken into account. In most research studies, various measurements and laboratory samples are required. The child's size is critical in determining how large a sample overall can be collected. For example, determining the maximum size of a single blood sample and the total volume of samples needed in the research study is important as early as at the planning stage so that blood transfusions would not be needed. One-percent of the child's blood volume can be considered a reasonable size for a single blood sample. Collecting samples larger than this is justifiable only in special circumstances (e.g. when studying premature infants). Sometimes the child's treatment necessitates simultaneous collection of several blood samples. The amount of blood lost must be replenished if the amount of samples collected is considerable in proportion to the child's total blood volume. Samples that are exclusively associated with the research should never be taken in such large amounts that the child needs subsequent blood transfusions. When performing other additional research-related procedures, such as collection of tissue and bone marrow samples or magnetic resonance imaging, x-ray imaging, radionuclide scans and other imaging, the additional stress and risks (e.g. anaesthesia) associated with the procedure must be taken into consideration. It is important to take into account the pain associated with various procedures. Repeated puncturing of the skin should be avoided, and every additional research-related puncture of the skin must be explained not only to the child's parents or guardian but also to the child, if at all possible.

In addition to children being a special group with regard to clinical research, they may have certain additional characteristics that should be taken into account. For example, children with cancer who are in poor condition, or children who have, or whose family members have, substance abuse problems should not be subjected to the additional stress caused by research unless the purpose of the research is to influence the well-being of such children. Particularly in these research studies, acting in the child's best interests and evaluating on a case-by-case basis are of the utmost importance.

Particularly in departments treating a small number of patients, there are often several simultaneously ongoing clinical research studies that apply to the same patients. There is a need for rules that state how many research programs a child can participate in at the same time. As a general rule, participation in more than one research study at a time should require special grounds and the approval of the head of the unit. The opinions of the other personnel and the parents should also be taken into account in decision-making. In these situations there should also be an evaluation as to what are the times when different research projects can be combined. Doctors responsible for the children's treatment and other staff members should be informed about the research project before it is launched. In addition, when research permits are being granted, the head of the treatment unit, who is responsible for the availability of unit resources as well as the recruitment effort directed at patients, should be heard. Depending on the study, it should also be considered whether the child's day care centre or school should be informed of the study. Since participation in a research study is as strictly confidential as all other health care the child receives, contacts and any information sheets, as well as information on the child's participation in the research, should be conveyed primarily via the child's parents or guardians, unless other arrangements have been made with them.

Children and clinical trials on medicinal products

In clinical trials on medicinal products, an investigational medicinal product is given to the research subjects. This medicinal product is often compared either to a known medicine in the market or to placebo. In clinical research performed in children, the composition of the investigational product is important. Different dosage ? forms are often needed for children, and absorption of the medicine may vary. This may cause problems not only for the investigator but also for the manufacturer of the medicine.

Clinical trials on medicinal products have some special characteristics in comparison with other scientific studies. A medicine is either an alien substance to the body or differs quantitatively from substances produced by the body (e.g. hormones), and therefore it may also cause adverse effects. Research on adults can only provide estimations about the incidence of adverse effects on children, since the passage of the medicine in a child's body and the body's response to the medicine may be different due to growth and development. Since children cannot be subjected to unnecessary risks, clinical research can be performed on healthy children in exceptional cases only. In research performed on children, the same principles must be applied to the use of placebo as in research performed on adults. Placebo use in children can sometimes be considered acceptable and, at times, even necessary. For example, if the results of a treatment currently in use are unclear, the use of placebo may be justified.

After the requisite studies, new medicines are usually first approved for use by adults. Usually, it is also in the best interests of children that the effect, efficacy and safety have been first evaluated with adults. When the medicine is available in pharmacies or used in hospitals, its use for children is often also possible without authorisation for use by children. According to various research studies, 20–90 % of the medicines used for children in Europe are not authorised for use by children, or the dosage deviates from the approved guidelines. If the medicine represents major progress in the treatment of a certain illness, it should be made available for children with this illness as soon as possible. Today's examples include AIDS medicines which have not been tested with children but which are the only possible medicines for those children who have received the HIV infection from their mothers.

Also when treating a critically ill child, a situation may come about in which using a potent medicine or treatment without previous clinical evidence is desired in order to save the child's life. When is initiation of such a treatment ethically justified? From the perspective of the child needing treatment, it is always preferable if the treatment can be given within the framework of scientific clinical research and not as an individual experiment. It would be good, however, if hospitals had the possibility to ask for an evaluation by a neutral external party on an emergency basis in such cases. Whether this external party would be an ethics committee or a medical-judicial group, remains a topic for discussion. The line between experimental treatments and clinical research is unclear, but for example ethics committees and drug authorities are more effective at monitoring clinical research than experimental treatments. The follow-up, combination of research data and systematic analysis associated with good clinical research help optimise the treatment and detect any adverse effects as early as possible.

It is hard to justify researching similar or parallel medicines on children unless the new parallel product is expected to be clearly superior to those already on the market. On the other hand, similar medicines that differ with regard to adverse effects or pharmaceutical forms provide more options in the treatment of children. It is impossible to define in general terms how many similar medicines should be available. It is, however, important to minimise the number of children enrolled in research while making certain that the research yields, however, sufficient data on the efficacy and safety of the medicine.

Medical research conducted on children and legislation

In legislation, children, as well as handicapped adults, are considered a special group in need of protection, and performing medical research on such groups is restricted. The reason for this is the limited ability of children to give an independent informed consent to research procedures. If participation in the research is considered possible, the consent of the parents or guardian and minimisation of research-related risks are, as a general rule, required. Furthermore, children can only be enrolled as research subjects if it is not possible to achieve the same results with adult subjects. The research must also be of direct benefit for the child's health or of particular benefit to persons of similar age or state of health. If a minor is able to understand the significance of the research procedure to be performed, a written consent from him/her is also required (Medical Research Act § 8, paragraph 1).

As a general rule, the guardian(s) of a young child may give the consent for research participation on behalf of the child. Who is considered guardian in the legal sense? The Child Custody and Right of Access Act (361/1983) defines a child's guardians to be his/her parents, or persons to whom custody of the child has been entrusted (§ 3). If the child's parents are married when the child is born, both are considered as the child's guardians. If the child's parents are not married when the child is born, only the mother is considered to be the child's guardian. The father can become the child's guardian by marrying the mother, by a joint parental agreement validated by the social welfare board, or by a court order (§ 6–9). If a research study needs to be performed in a newborn infant on an emergency basis, the father can give consent for the research only if he is married to the child's mother, since there has been no time to take action to affirm the father's role as a guardian. The situation is problematic, as approximately half of the children in Finland are currently born outside of marriage. While the initiation of the research requires the consent by the guardian, it is important to consider how more information could be given to the child's parents preferably before the child's birth, and how the mother could authorise the child's father to make the decision for the child in a situation where she is unable to give her consent to research directed at the child.

According to the above act, the child's guardians generally make decisions concerning the child together (§ 5) if there are more than one guardian. An exception to this can be made on the basis of travelling, illness, or another reason, if delay in reaching the decision may cause harm to the child. If the matter is of considerable importance to the child's well-being or future, however, the guardians must make a joint decision unless the best interests of the child requires another approach. This also applies to parents with joint custody who are separated. In routine health care procedures, for example, the consent of one parent is nevertheless considered sufficient. This can also be said to apply to medical research, if the required procedure is minor (e.g. collecting a blood sample). The Child Custody and Right of Access Act (§ 1) requires that the parents must take the child's best interests and well-being into account in matters concerning the child's care.

But how is one to act if the parents cannot be reached, for example in a case of an accident, or if they are unable to give their consent on behalf of the child due to their physical or mental state? The Medical Research Act (488/1999) allows the initiation of research without a written informed consent if the consent cannot be obtained because of the urgency of the matter and the patient's state of health, and if the procedure is expected to be of immediate benefit to the patient's health (§ 6 paragraph 1). This regulation can probably be applied to minors whose guardians cannot be reached in time, or if the guardian has, for example, been injured in the same traffic accident as the child. In these cases the guardians must be informed of the research as soon as possible, and at this or at a later time the guardians can prohibit the child's participation in the research. This is also the standard approach for emergency research on adults. However, if the research can be performed using other research subjects or waiting for the parents' consent is possible, this exception should not be applied. Enrolling newborn premature infants into research is facilitated if the parents have

already received information on such a situation beforehand. Additional information should be available, preferably in written form, in maternity hospitals and research units. Research that is started without delay can sometimes be of considerable importance to children's well-being. For example, the hazards of 100 % oxygen in reviving neonates would never have been noticed if a written consent of the parents had been needed before enrolling the children into the research. The current form of the EC Clinical Trials Directive (2001/20/EC) does not appear to allow research in any situations without the consent of the guardian or another legal representative, so the Medical Research Act will be revised during the implementation stage of the directive.

Children who have been taken into custody are in a special situation, and should be spared additional hazards and stress. On the other hand, children who have grown up in a family with substance abuse problems, for example, may have special characteristics that are of particular need for further research (e.g. effects of alcohol use during pregnancy), which may be of considerable benefit to the children themselves. In cases of custody, the right to make decisions about the child's care, upbringing, supervision and other welfare are normally transferred to the social welfare board (Child Welfare Act (683/1983) § 19 paragraph 1). The right to decide about the child's participation in clinical trials remains with the child's parents, unless other arrangements have been made in connection with taking the child into custody or on the basis of a court decision. If the research is for example connected to the child's care and is in accordance with the purpose of taking the child into custody, the social welfare board and those responsible for the child's care are usually in the best position to evaluate what is in the interests of the child. However, when considering the participation of a child who has been taken into custody, it is important to consider on a case-to-case basis who has the best qualifications to oversee the welfare of the child.

As the child grows and develops, his/her statutory right of self-determination increases. It is also worth bearing in mind that the ability of chronically ill children to decide about their care is generally better than that of children who are not used to the hospital environment. The Medical Research Act states that if the child is able to understand the significance of the procedure to be performed, his/her personal consent is required to perform the research. According to the Medical Research Act, the guardian's consent is needed in addition to the minor's consent if the child is less than 15 years old or the research is not expected to produce any direct health benefits to the child. Only when the child is 15 years old does he/she have the right to make independent decisions concerning participation in research. This right, however, is restricted to research from which direct health benefits can be expected. In addition, the child's guardians must be informed of the matter. The Act on the Medical Use of Human Organs and Tissues (101/2001) states that, in the case of minors, consent is to be received primarily from their legal representatives. The current form of the EC Clinical Trials Directive does not appear to allow research to be performed without the consent of the guardian or another legal representative even when the minor is over 15 years old. During the implementation stage of the Clinical Trials Directive, the Medical Research Act may have to be revised for this part as well.

The Medical Research Act allows only minor risk or stress to be caused to an underaged research subject. The problem is the definition of minor risk. Can minor risk be determined with strict classification of procedures, or should it be relative to the situation of the individual patient or to the benefit expected from the research? Collecting five millilitres of blood may be a minor procedure to an adolescent, but it is life-threatening to a premature infant weighing 500 grams. Children also have individual differences. Children who are used to the hospital environment and who know what the procedure entails, may suffer less from minor procedures than children who are not familiar with the procedure. On the other hand, repeatedly painful experiences in the past may cause a great deal of fear towards painful procedures. The concept of minor risk is relative also in research studies where a risk of considerable adverse effects is associated with the treatment of a serious illness. In such cases, minor risk refers to the additional hazard and discomfort that the paediatric

patient is subjected to when he/she participates in the research in addition to regular treatment. When evaluating stress caused by the research, the number of additional visits, for example, and the stress caused by travelling and restrictions to normal life must be taken into consideration.

Paediatric patients and health-care personnel

Doctors, nurses, and other health-care personnel participate in scientific research projects ever more often. In clinical trials, the doctor often acts not only as the investigator but also as the child's treating physician. Similarly, a nurse may be involved in the realisation of the trial as a research nurse and be responsible for the paediatric patient's care. On the other hand, they may be responsible for the child's treatment only, or be involved in tasks relating to research only.

Scientific research must not interfere with the child's regular care. Research that requires handling of the child, collection of samples etc. should be accommodated with the child's other care. When performing the research, the child's needs and resources should be taken into account whenever possible. Among other things, painlessness and uninterrupted, sufficient periods of rest between procedures should be guaranteed to the child. Examinations must not cause unreasonable stress or additional suffering to the child or anxiety and uncertainty to the parents.

The basic task of the treatment staff is to take care of the comprehensive care of the ill child and his/her family. The doctor treating the child is responsible for the realisation of medical treatment. The nurse responsible for the child's care at a given time acts as the interpreter or advocate for the child and his/her family. Parents' resources are limited, and worry about the child's situation may impair their ability to receive information concerning research, the purpose of the research, their participation in it, and the informed consent. The nurse works in cooperation with other personnel treating the child, giving support to the parents without trying to influence their decisions.

To the parents, the nurse often represents a more neutral party with regard to the research; a person with whom they can discuss research-related fears and uncertainties without having to consider the effect of their opinions on the medical treatment their child receives. In addition, the nurse often has a different relationship to the child and his/her parents than the treating doctor or the investigator, who often has no part in the clinical treatment of the child.

There may be one or more research nurses in units with several ongoing scientific research projects. The research nurse acts as a link between the unit staff and the investigators. By participating in the collection of research samples, the research nurse thus frees the staff to treat the patients. Among other things, the research nurse coordinates the studies conducted on the unit, takes care of research documents, writes operating instructions, trains personnel and assists in the collection and handling of samples. In research studies where the results of measurements may be influenced by technical performance, one extra person taking measurements increases the reliability of the results (e.g. head circumference, length).

The doctor and nurse treating the child may be faced with several ethical problems in connection with research. Performing scientific research on children may cause feelings of anxiety for the treatment staff as well, especially if the child is very ill or in terminal treatment, or if the prognosis is poor. Questions may arise concerning the purpose and necessity of the research and the giving of false hope. Ethical conflicts concerning clinical research may arise e.g. in cases where placebo is used in clinical research, or in the evaluation of the effects of the medicine in open clinical research studies when the nurse or the doctor knows what medicine the child is receiving and does not consider it the best option for the child in question. Discussing these questions openly in the work community is important.

Using limited resources for scientific research can sometimes be felt to be ethically wrong. The time required by scientific research is time taken from other activities, and as resources become more

scarce, conflicts and ethically difficult choices emerge more and more often. The nurse and the doctor treating the child have to weigh the patient's concrete treatment against the research, as well as to evaluate the quality of their work and factors influencing it. Even when resources are limited, using them for scientific research is necessary in order to gain new knowledge which may improve treatment of patients.

Cooperation with the investigator, other research staff and treatment staff is important. It is the investigator's duty to inform the staff responsible for the child's treatment about the ongoing research at its various stages regardless of whether the staff form part of the research group or not. Sometimes samples are collected by someone not belonging to the department staff, in which case the child's personal nurse guarantees the flexibility of the work and looks after the child's best interests. Successful teamwork and good interaction skills are important also with regard to the development of research compliance. The success of research studies and their flexible conduct also benefit the patient.

The genuine voluntariness of the consent is influenced by who gives the information concerning the research, who requests the consent, and how the consent is requested. Nurses often do not have enough information about research-related details, and therefore, asking for the consent should not be left to the nurse. The treating physician or on-call physician giving the initial information may not necessarily have detailed information about the research unless he/she is part of the research group. The investigator has the most information about the research. However, it is important to discuss whether the interests of the investigator to recruit research subjects make it more difficult for him/her to give neutral information about the research. On the other hand, if the information is given and the consent requested by the child's treating physician who is acting as the investigator, fear about the consequences of refusal on the child's treatment may influence the voluntariness of the consent in a more direct way.

Research on children from the viewpoint of the parents

It is always a shock to parents when their child falls seriously ill. The child's illness, pain, and suffering are often harder for the parents to accept than a personal illness. When the child is chronically ill, the parents often experience all crisis-associated emotions, since they must adapt to a new situation, often without a warning.

Parents can make good decisions if they have received enough comprehensible information. Parents make a decision concerning the child's participation in a research study mainly on the basis of the information given by the person requesting the consent. Information sheets and other material must be given to the participants and/or their parents in a language they understand well. Medical terms should be avoided, and there should be enough opportunities to ask questions. The parent information sheet and written consent must state the name of the research and the person conducting the research, contact information of the responsible investigator, and detailed information about the content, benefits, adverse effects, long-term effects, and any unknown risks of the research. The parents must know what they are agreeing to when signing the consent. Whenever possible, enough time should be reserved for giving the consent. The person requesting consent must not put pressure on the parents.

When a written consent is given, the parents can always check what they have agreed to and what kind of a research study it is. It is also extremely important for the parents to know how the treatment their child receives during the research differs from the child's regular treatment, and whether it is possible that their child is randomised into the control group or, if a medicine is being studied, into the placebo group, in which case the child may not receive a certain treatment. If new research-related adverse effects appear later, the parents must be informed. The parents must be

able to monitor whether the research is being carried out as described in the information sheet. If extending the research is necessary, a new consent must be requested from the parents.

When requesting consent, a negative decision from the parents must be respected. The viewpoint of the parents may be different from the viewpoint of the investigator with regard to the child's situation. The Medical Research Act and ethics committees require genuine voluntariness from participants in a research study, and the participating children and their parents must have been told that refusal to participate will not affect the child's regular treatment. Despite this, the parents may give their consent to the child's participation because they are afraid that refusal will affect the child's treatment.

The parents may consider the request to participate in a research study confusing, and it may also arouse contradictory feelings. Even though the medicine or treatment to be studied might benefit other children in the future, the parents may not necessarily want to add to their own child's suffering. The parents are worried about the pain and suffering their child experiences. The stress caused by pain or a procedure may cause additional injury, e.g. due to changes in blood pressure. Repeated pain may later lead to pain sensitivity or psychological effects. The parents are also often concerned about whether the chosen research arrangement is necessary or whether the answers to the questions could be found in another way. These matters should be discussed with the parents prior to the signing of the consent form, and again during the study if necessary. Discussion eases the stress associated with making a difficult decision.

Part II:

EFFECT OF AGE AND STAGE OF DEVELOPMENT IN RESEARCH CONDUCTED ON CHILDREN

Children can be divided into different age groups according to growth and physical changes, and also according to the capacity for self-determination and to the mental development it is based on.

The neonatal period and infancy

The ability of a neonate to express his/her feelings and experiences is very limited. The guardians of the child must then consider what is in the best interests of the child, and on that basis, make the decision about agreeing or refusing to let the child participate in a research study. The child's guardian or guardians give the consent concerning the participation of a neonate in the research, but even the child's parents may find it difficult to put themselves in the position of the child. Making the decision is often made more difficult by parents' lack of basic information about special characteristics of a neonate's vital functions.

The neonatal period is associated with a process of change and adaptation from intrauterine to extrauterine life. The metabolism of several medicines is influenced by postnatal changes in the circulation and the low content of carrier proteins in the blood, which must be taken into account in clinical research. The dosage for many medicines is different in infants aged under one week. In premature infants, the dosage of many medicines is different from the dosage for full-term children. The smaller the patient, the greater is the proportion of water and extracellular space in total body volume. The same applies to skin surface area in proportion to body weight (about six-fold in an infant weighing less than 1000 g in comparison with adults). The functions of the liver and the kidneys are inadequate, and the skin of a very small premature infant is thin and sensitive, thus

making the collection of a bag urine sample a potentially damaging procedure. The immaturity and vulnerability of the body increases the risk of damage and unexpected adverse effects.

A neonate may react strongly to handling, touching, and pain. Moreover, research may interfere with the child's rhythm of sleeping and being awake. Aids needed for evaluation include tried and proven pain and discomfort indicators. An experienced nurse may be of considerable help in evaluating when it is the appropriate moment for performing a research-related procedure from the child's point perspective.

The medicines the mother used during pregnancy, and any problems during pregnancy may have long-term effects on the health of the baby. Via the mother, a neonate may have been involved in a randomised clinical trial as early as in the foetal period. In such a situation, the child generally cannot be enrolled into another randomised clinical trial during the neonatal period.

The small blood volume of a neonate places restrictions on the collection of blood samples. If the blood sample collected in association with the trial can amount to no more than one per cent of the total blood volume of the research subject, the largest allowable blood sample from infants weighing 1000 g and 600 g would be approx. 0.9 ml and 0.5 ml, respectively. In the case of small premature infants, blood samples may be needed several times a day to check the child's condition. For this reason, it is important to agree upon the largest acceptable total volume of blood samples when samples are collected repeatedly.

Clinical and therapeutic research should also involve long-term follow-up of neonates participating in the research, since for example the potential adverse effects on growth and development may not be revealed until later, sometimes years after the study. For example, the adverse effects of dexamethasone (a cortisone preparation) treatment, used to mature an infant's lungs in case of imminent premature birth and after premature birth, were observed only after the medicine had been widely used for several years. It was observed that premature infants who had received dexamethasone had a three-fold risk of neurological injury in comparison with premature infants who had received another treatment.

Emergencies requiring fast action and decision-making may emerge in particular in the treatment of neonates. Research-based treatment practices must be developed for emergencies as well. The birth of a new family member represents a substantial change in itself, and the parents have to adjust to it. The situation of the parents is particularly fragile if the newborn is ill or in a poor condition. The physical and mental state of the parents, and the mother's recovery from childbirth or caesarean section should be taken into account when asking for the parents' consent to a trial to be performed on a neonate. Only in exceptional situations and after thorough deliberation can initiation of the trial without the parents' consent be considered. The course of action in such situations must be pre-approved by an ethics committee. Also in these situations, the parents must be informed of the research as soon as possible, at which time they have the right to discontinue the child's participation. To enable parents to make informed decisions in such situations, possibilities should be discussed concerning the distribution of information to maternity clinics and hospital staff about emergency research in neonates. If there is a risk of prematurity, the parents could be informed of a possible research already before delivery. In specialised health-care units treating neonates, information about emergency research could be made available to parents who may need it. In this way, the parents could better prepare themselves for the request for their consent and also take care of any consent-related authorisations beforehand.

Even if the parents give their consent to emergency research before it is started, receiving new information may be difficult in a state of shock. The parents may have difficulty remembering that they have given their consent to the research at all. Discussing matters relating to the research as well as matters relating to other treatment given to the neonate is important also after the consent has been given.

Preschool age

The organs of a preschool-aged child develop quickly. During this period, the body weight doubles and considerable energy is spent on the development of bones, muscles and nerves. The blood volume of the child no longer sets such strict restrictions to research as it does in the neonatal period, and performing the procedures is technically easier. In many ways, the metabolism of medicines in preschool children is similar to that in older children and thus allows for more adult-type research. On the other hand, the effects of medicines on growth, bones, and metabolism must be taken into consideration in treatment and research alike. Long-term effects may be caused, for example, by steroids (possible growth retardation) and tetracyclines (discoloration of developing teeth).

The understanding of a baby or a preschool child regarding the procedures to be performed on him/her increases as the child grows. The child reacts strongly to pain and is often afraid of procedures that cause pain. The child's right of self-determination should already be respected at an early stage. The child begins to understand matters relating to his/her life as early as the preschool age. The child's ability to understand speech and causal relationships improves. The child expresses his/her own feelings and sentiments by words, gestures and play, for example, and reacts to treatments and research on the basis of his/her own feelings.

Although a preschool child is physically able to resist a procedure, it should be asked if such resistance means that the child refuses to participate in the research entirely. As a rule, a preschool child is not yet developed enough to understand the significance of the research on a rational level, but should the child's fear be accorded the same significance as an adult's informed refusal? The final responsibility for evaluating the child's ability to understand lies with the doctor evaluating the child's level of development, but in reality, the decision concerning the child's participation in a research study is made together with the guardians, who are often the best people to interpret the child's feelings and understand the child's reactions, whether based on understanding or fear. A preschool child who resists a procedure should not be forced to participate in a research study even if the refusal is based on an emotional reaction. The child's fears can be eased in many ways, for example by pictures, games and fairytales, and various means should be used to inform the preschool child about the research and make the research more understandable to him/her. Giving the child time and space also gives him/her an opportunity to make decisions.

The principle of respecting the child's right of self-determination has also been taken into account in legislation. When the Medical Research Act was being prepared, it was planned that even a 5-year-old should have the right to refuse to participate in a research study. There is no age limit in the final version of the Act, and the right to refuse was proportioned to the child's age and level of development. The child's level of development will be evaluated by the doctor giving the information about the research, who will also evaluate whether the consent is informed and voluntary.

Pre-pubertal school age

Physical growth and development continue rather steadily in school age. In addition to physical growth, the child's ability to understand, think in abstract terms, and thus take responsibility and make personal decisions increases. The process of becoming independent affects not only the child's right of self-determination but also the success of the research if the procedures require the collaboration of the child (e.g. swallowing tablets or using medical devices). This should be taken into account when discussing participation in the research with the child. As a rule, the simpler the procedure, the younger the child who is able to understand the content and the effects of the procedure. The same applies to procedures the child is already familiar with.

After learning to read, the child also learns to understand information given in written form. Therefore, at this time he/she should also have a separate information sheet, since the information sheet for adults contains not only complicated descriptions of procedures and phrases of foreign derivation but also less meaningful issues from the child's point of view, such as information about registers and the coding, storing and transfer of data. Information sheets for young school-aged children do not need to fulfil every requirement set by laws and ethical codes about what research subjects should know about the research. A child less than 15 years old also cannot give his/her consent independently, since the consent of at least one guardian is needed in addition to the child's consent. This is why the guardians should have a separate information sheet, on the basis of which they give their consent.

The significance of a child's expression of his/her wishes becomes greater when the child is better able to understand the significance of the procedure. If a minor understands the significance of the research, his/her written consent is required for participation. Ensuring the child's continuing willingness to participate and cooperate is important at different stages of the research. If the child refuses to continue to take part in the research, the previously given consent will be cancelled.

Pre-puberty and puberty

Physical changes occurring in pre-puberty and puberty include pubertal growth spurt, hormonal changes and sexual development. Physically, the adolescent begins to resemble an adult. The most important physiological change occurring in this age group is hormonal in nature. Psychologically, the adolescent starts to become independent and wants to make decisions about his/her own life to a greater extent. Therefore, adolescents should be given the opportunity to decide whether they want to participate in a research study or not. Although, according to current legislation, an adolescent can make an independent decision about participating in a research study only at the age of 15 years, and then only in situations when he/she is expected to have direct benefit from the research, many younger adolescents are able to understand the course and significance of the research. The opinions of 15-year-olds, and even younger adolescents who are at a sufficiently high level of development, should be accorded authoritative importance with regard to participation. However, the guardian has the right to receive information about a clinical research study performed on a minor, if necessary.

The right of self-determination of children and adolescents should be respected to the greatest extent possible. A teenager should never be forced to participate in a research study against his/her wishes. Youth is associated with rebellion, and adolescents are often more interested in their appearance than their health. The treatment compliance of adolescents is, however, an essential starting point if the research is to succeed. Because puberty is associated with the need to belong in groups, emphasising that the adolescent is in any way different should be avoided in planning the research.

When the adolescent approaches maturity, the questions concerning his/her right of self-determination emerge in a more concrete way. The adolescent is treated as an individual, and his/her guardians are not informed of the treatments if he/she forbids it, for example in matters concerning contraception or abortion (Act on the Status and Rights of Patients (785/1992)). On the other hand, if a minor is asked to participate in a clinical trial evaluating the effects of oral contraceptives on a developing hormonal system, the guardians of the minor must always be informed of the research. This may, however, make the recruitment of research subjects considerably more difficult. Although the procedure, i.e. prescribing oral contraceptives to the research subject, is exactly the same as when treating a patient in clinical practice, and although the minor would not face any more substantial risks than in standard treatment, research is considered to be different. Although an adolescent from 15 to 18 years of age understands many issues that

concern him/her, he/she can still be influenced by the opinions of his/her friends, for example. If complications occur in research studies on contraception, for example, the child may be left too much alone with feelings of responsibility and guilt.

RECOMMENDATIONS OF THE WORKING GROUP

- 1. As a rule, the child should not participate in more than one invasive scientific research study at a time.** The participation of a child in a clinical research study is always an exception from the main rule set down in law, according to which research should not be performed on children if the same results can be achieved with adult research subjects. Since research data from research performed on children are needed, however, it should be ascertained that the exceptional provisions are not interpreted in such a way that the well-being of individual children is endangered. For this reason, it is the opinion of the working group that, as a rule, a child should not participate in more than one invasive research study at a time. Questionnaire studies have not been taken into account in this case. When requesting consent to participate in a research study, it should always be ascertained that the child is not participating in other research programs at the same time. Since the scope of research studies and the complexity of procedures vary, exceptions to the main rule should be made possible with appropriate grounds. It should also be considered in research units whether different trials and consent procedures can be adapted to each other and combined. The doctor responsible for the unit (and, during on-call hours, the on-call backup person) bears the responsibility for the compatibility of research as well as other treatment given to the children. In outpatient treatment and prevention studies, the child's personal doctor can evaluate the strain centering on the child and the parents. The doctor in charge of the research is responsible for the well-being of research subjects during the research, as stipulated by the Research Act.
- 2. The working group proposes that, in the future, more thought should be given to who should provide the necessary information about the research and request the consent needed for the research from the child and the child's parents.** The investigator conducting the research has the best knowledge about the details of the research. The investigator's neutrality with regard to recruiting research subjects may, however, be made more difficult by his/her research-related interests or the need to recruit the child into the research for other reasons. On the other hand, the physician or nurse treating the child may not know all the details of the research study and may not be able to answer questions the child or the child's parents wish to ask. In emergency situations, the neutrality of the doctor on call may be jeopardised by the rush and the stress associated with treatment. The ideal situation would be if the investigator and the doctor who is treating the child could give the information about the research together. Additional information can also be given by the research nurse, if there is one in the research unit. However, depending on the circumstances, other methods of action are often needed. It is important that the research subject or his/her guardian has the opportunity to request additional information about the research from the investigator. Varied and neutral information about the research must be available, on the basis of which a decision about participating or refusing to participate can be reached. It is also important to give the parents enough time to consider their decision, whenever possible.
- 3. When evaluating the child or adolescent's level of development, and the consent associated with this, as well as when carrying out the research, the investigators must have sufficient expertise concerning the growth and development of children.** In order

to ensure a sufficient level of expertise, the working group proposes that special courses in research conducted on children be organised at the Faculties of Medicine. The course could be taken at the stage of specialisation, in association with a doctoral dissertation, or as supplementary education. Ethics committees should have sufficient expertise in paediatrics to evaluate research conducted on children.

4. **In routine research procedures, a consent from one guardian is sufficient.** If a child or an adolescent under 15 years of age is to participate in a research study, the consent of his/her guardian is required. As a rule, the child's guardians should make the decisions concerning the child together. In practical treatment situations, the consent of one guardian is sufficient if the child is to be subjected to a minor or routine procedure, or if the situation can be considered exceptional as stipulated by law. Similar exceptions should also be applied in association with research if the risk of injury or stress to the child is equally small.
5. **The right of self-determination of minors should be expanded.** To ensure that the right of self-determination is realised, it is recommended that a brief summary of the purpose, nature, benefits, risks and adverse effects of the research be made for children who are able to read. If such a summary is not considered necessary, the reasons must be given to the ethics committee. Information about the research can also be given to children who cannot read in the form of fairytales, games and stories. At the pre-planning stage of the research, it is also important to emphasise the significance of oral information and ways to ensure that research-related information is understandable to children of different ages. The resistance of a child younger than school age must also be respected even if the reaction is based on fear, for example, and is not in accordance with rational behaviour models. If a minor is able to understand the purpose of the research, his/her consent is required before the research can be realised. When implementing the Clinical Trials Directive, the possibility accorded by Finnish law to adolescents over 15 years of age to give an independent consent should, at the very least, be maintained, if possible.
6. **Any additional research-related risk of injury or stress should be proportional to the child's individual situation and the health benefits the research is expected to have, rather than to a strict classification of procedures.** The Medical Research Act requires that a minor can only be subjected to minimal research-related risk of injury or stress. Such procedures include, for example, collection of a small blood or stool sample, painless imaging that does not involve any additional risks, etc. On the other hand, the risk and injury associated with the collection of blood samples may be considerable, for example, in small premature infants. The child's suffering must always be minimised. Pain associated with procedures can often be effectively alleviated topically or by means of anaesthesia. The evaluation of benefits and risks associated with each research study should always be made on a case-by-case basis.

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- Act on the Status and Rights of Patients (785/1992)
- Act on the Medical Use of Human Organs and Tissues (101/2001)
- Child Custody and Right of Access Act (361/1983)
- Child Welfare Act (683/1983)
- The Constitution of Finland (731/1999)

International agreements:

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