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Research involving children

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Foreword

Research involving children? Can there be any ethical justification for carrying out research with children? Children have a special need for protection, and (adult) researchers have a responsibility to safeguard children's welfare. At any rate, they should not jeopardize children's welfare. So initially we hesitate to answer in the affirmative. But children also require medicine that is based on scientific findings, on knowledge about the origins and mechanisms of diseases which may affect children, about children's health and their physical, emotional and social development, and also about the various hazards that children face in society, about methods of prevention, and of course, quite specifically, about the efficacy of methods that are to be used in paediatrics. Saying no to research involving children would therefore deprive them of significant benefits and expose them to special risks.

If the answer cannot be simply either yes or no, the question is transformed into a question of how. Whether it is ethically acceptable and reasonable to carry out research with children depends on how the research is performed, i.e. how a child is affected by research activities. There is a need for sound regulations on research involving children that provide an ethically acceptable answer to the question of how. This is not to be understood minimalistically, in the sense of a few essential conditions for the protection of children. To be ethically acceptable, the best possible regulations are needed, judged by children's best interests.

This is the framework within which legislators' task of creating laws on research involving children is to be understood. The Swiss National Advisory Commission on Biomedical Ethics (NEK-CNE) found that relatively few materials are available as yet in Switzerland dealing broadly with the ethics of research involving children and with regulations on research practice. Since 2006, prompted by the drafting of – and public debate and parliamentary deliberations on – the Human Research Act, the Commission has closely examined the topic of research involving children, and its findings are presented in this Opinion. They are naturally addressed, in the first instance, to legislators and to the circles concerned with the implementation of the Human Research Act – in particular, the authorities, ethics committees, researchers and parents or other people who represent children's interests. However, the Opinion is also conceived as a contribution to a wider ethical debate within society, extending beyond the circles of those directly involved.

The NEK-CNE wishes to help to identify, interpret and clarify the ethical issues arising in connection with the regulation and oversight of research involving children. Ultimately, it resolutely, with incisive arguments, adopts a position favouring the necessity of research involving children, opposing the use of children as means to the attainment of benefits for others, supporting careful interpretation of the principle of minimal risks and burdens for "non-therapeutic" research (in the sense of reasonableness for the child itself), and also acknowledging the value of empirical medical knowledge.

Christoph Rehmann-Sutter, Chairman – 11 November 2008

1 Background and goals

If children[1] are to be involved in research projects, great caution is required. Children are vulnerable and particularly in need of protection in various respects. At the same time, children should be able to benefit from medical progress and from the advantages of scientific research. New knowledge of health and disease is needed to improve medicine and healthcare overall, e.g. in order to develop new methods of diagnosis and treatment. Research can also help to make children's life-world, rearing and schooling, and the various institutions that they encounter more responsive to their needs. Scientific research can underpin and deepen our knowledge of children's development, their social life and psychology. While children may benefit from the findings of research, research involving children raises a number of particularly challenging ethical questions, which cannot be answered with reference to the concept of voluntary informed consent – the key legal notion in the legitimation and approval of research involving competent adults since the adoption of the Nuremberg Code. As legal minors, children are dependent on proxy decisions and are frequently incapable of adequately assessing the implications of a planned study themselves. In the consent process, they therefore rely on the protection provided by the adults responsible for their care.

The present Opinion was prepared against the background of efforts by legislators to regulate human research at the federal level by means of a constitutional article on research involving human subjects (draft Article 118a, Federal Council's Report dated 12 September 2007) and a corresponding Human Research Act (HFG, preliminary draft dated 1 February 2006). Both drafts have already given rise to contentious, but fruitful, debates. These have centred, not least, on ethical demands for the protection of human dignity and rights to personal integrity. Attention needs to be paid to the preservation of these goods while pursuing the goals of freedom of research and medical and social progress. In the course of the consultation procedure in 2006, the Swiss National Advisory Commission on Biomedical Ethics (NEK-CNE) commented on various points in the preliminary draft HFG and made specific recommendations and suggestions for amendments.[2]

In addition, with regard to research involving children, the NEK-CNE sees a major need for ethical clarification, since on the one hand there is a serious lack of scientific knowledge concerning disease and recovery processes in children and on the other hand research involving mentally incapable subjects is particularly complex and difficult to justify from an ethical perspective. This Opinion seeks to clarify the ethical basis for research involving children and to highlight a number of particularly crucial points. The text is conceived as a background paper to support public and political discussions and is addressed to legislators, ethics committees, researchers, physicians and parents or other people who represent children's interests.

[1] The term "children", as used by the Commission, covers persons from birth to the age of 18 years. This corresponds to the legal term "minors". Where distinctions need to be made, the terms applied in normal usage are used (e.g. infants, adolescents).

[2] http://www.bag.admin.ch/nek-cne/04229/04233/index.html?lang=de (last accessed 26.11.2008).

2 The specific problems of research involving children

2.1 Children – therapeutic orphans?

While pharmaceutical research has made great strides in developing treatments for adults over the past 50 years, this is not the case for children's medicines. According to an article published by the American Academy of Pediatrics in 1995, about 80% of all drugs administered to children had not been studied in children.[3] Although more recent statistics indicate a degree of progress, many drugs are still used off-label (i.e. outside the terms of the licence) and others are even prescribed off-licence (i.e. without regulatory approval). A survey of five European hospitals published in 2000 showed that 67% of children had received drugs prescribed off-licence or off-label, and that 39% of 2262 drug prescriptions given to children were off-label.[4] In a 6-month prospective study at a Swiss paediatric university hospital, published in 2006, 24% of prescriptions were found to be off-licence and 25% off-label.[5] Overall, it is apparent that the use of drugs in children remains inadequately studied, and a large number of newly introduced products are not tested in the relevant paediatric age groups. This prompted Harry Shirkey in the late 1960s to describe children as "therapeutic orphans".[6]

The lack of approval for paediatric use means that children are exposed to a higher risk of adverse effects than adults. However, pharmaceutical research is not the only area where failure to pay sufficient or any attention to the specific situation of children may mean that effective new treatment modalities cannot be introduced in paediatrics since the information required is not available for this age group.

The official regulatory procedure required for authorization of a medicine involves an assessment of the risk/benefit ratio; efficacy and the required level of safety have to be demonstrated for specific indications in controlled clinical trials. However, the conduct of such trials is associated with a wide variety of problems.

2.2 Medical, methodological and economic difficulties for clinical trials involving children

As well as being susceptible to almost the whole spectrum of adult diseases, children may be affected by typical paediatric conditions. In addition, dosages need to be adapted for specific age groups, as drug absorption, metabolism and excretion processes vary widely in the course of child development.

The principle that children are not small adults is also applicable in pharmacotherapy, especially with regard to the administration and dosage of medicines. Internationally, for medical purposes, childhood is divided into five stages:

- Preterm infant: 20th to 36th week of gestation
- Newborn: 36th week of gestation to 28 days after delivery
- Infant and toddler: 28 days to the end of the 2nd year
- Child: 3rd year to the end of the 11th year
- Adolescent: 12th year to the end of the 17th year

[3] Cf. American Academy of Pediatrics Committee on Drugs 1995.

[4] Cf. Conroy et al. 2000.

[5] Cf. Ermindo et al. 2006.

[6] Cf. Shirkey 1968.

In pharmacotherapy, the various developmental stages are associated with specific physiological, pharmacological and toxicological characteristics. These are summarized in the tables below:[7]

Physiological characteristics:

Preterm infants and newborns:
- Immature organ systems
- Extremely premature infants mainly affected by cardiovascular and pulmonary disorders
- Newborns generally affected by infectious, neurological and metabolic conditions

Infants and toddlers:
- Rapid growth and maturation of all organ systems
- Changes in function of liver, kidneys, immune and nervous system
- Typically numerous common infections (childhood diseases)

Children:
- Increased propensity to infectious diseases
- Higher risk of accidents with increased mobility and independence
- Intellectual and psychosocial maturation

Adolescents:
- Rapid changes in hormone metabolism, autonomic nervous system and mental state
- Somatic and emotional instability

Pharmacological characteristics:

Preterm infants and newborns:
- Increased susceptibility to adverse effects due to substantial differences in pharmacokinetics
- Influence of maternal disorders

Infants and toddlers:
- Hepatic and renal maturation (clearance capacity)
- Frequency of disease largely determined by viral and bacterial infections
- Function tests requiring the patient's cooperation (e.g. spirometry) frequently impracticable

Children:
- Possibly adverse effects of pharmacotherapy on bone development and weight gain

Adolescents:
- Changes in pharmacokinetics and pharmacodynamics associated with developmental physiology
- Influence of pharmacotherapy on growth, sexual and mental development (contraceptives, psychotropic agents)

[7] Cf. Brochhausen/Seyberth 2005, 17-66.

Toxicological characteristics:

Preterm infants and newborns:
- Greater sensitivity of central nervous system to many drugs due to increased permeability of the blood-brain barrier
- Influence of drugs on transition to postnatal circulation, and on carbohydrate and electrolyte and mineral metabolism

Infants and toddlers:
- Risk of hepatotoxic effects of drugs and efficacy affected by high clearance capacity
- Paradoxical effects of drugs on the nervous system

Children:
- Risk of accidental poisoning by drugs (increased mobility)
- Sensitivity of the central nervous system to drugs
- Impairment of skeletal growth (glucocorticoids, tetracyclines)

Adolescents:
- Physical, emotional, cognitive and sexual maturation affected by long-term pharmacotherapy
- Varying reliability of adolescents in compliance with drug treatment
- Effects on fitness to drive
- Potential hepatotoxicity of pharmacotherapy in female adolescents

In addition to these considerations, given the age-related biological diversity of children, clinical trials can only operate with small populations; in other words, one has to accept either the risk of inconclusive results or the very high costs involved in enrolling a sufficient number of subjects. This gives rise to specific methodological problems: clinical trials involving children usually have to include a number of different hospitals (multi-centre studies), which leads to high costs, additional efforts, a prolonged study period and less scope for possible publications than with laboratory-based research. The conduct of such trials also tends to be less routine than with adult subjects.

Decisions on whether, and for what situations, development programmes and studies are to be initiated often rest with pharmaceutical companies. However, in the paediatric field, many unanswered questions relate to diseases with a low incidence (in Germany, for example, more than 300,000 adults develop cancer each year, compared with only 1,800 children and adolescents). While the costs of clinical studies required for regulatory purposes are at least as high in the case of children as for adults, the revenues generated by drugs for children are usually far lower, given the lower incidence of the diseases in question. As a result, companies are frequently unable to recoup the development costs of paediatric drugs after registration or to make a profit with such products. Accordingly, for economic reasons, pharmaceutical companies have little interest in carrying out studies with infants and toddlers.

The economic interests at stake in drug registration and efforts to ensure that the results of studies are not compromised by sponsors' interests have led to the current complexity of the regulatory regime and to an explo-

sion in the costs of such studies. The question arises: who is to be responsible for initiating and bearing the costs of a study, or who should have an interest in clinical studies if children are not to be excluded from pharmacotherapeutic developments.

Another notable consequence of the current situation – as demonstrated by the above-mentioned figures for off-label and off-licence drug use in children – is that clinicians frequently face a conflict: are a child's interests best served by prescribing a drug that has been tested on children and is thus safe but may be less effective than a treatment that has not been appropriately studied? Or should the child receive a treatment that has been shown to be effective but has not been sufficiently investigated with regard to dosage or biological effects in children? Both cases ultimately give rise to a paradoxical situation in which, as a result of gaps in scientific knowledge, children are treated de facto as research subjects, without however being placed within the controlled framework of a proper research project – with the appropriate guarantees regarding procedure and information.[8]

In the view of the NEK-CNE, the need for medical research involving children is clearly demonstrated by the fact that children may be permanently harmed by the administration of unsuitable medicines, and that, owing to the lack of knowledge about child-specific factors, they are much more likely than adults to be exposed to the risk of inappropriate or inadequate medical care.

3 Key principles for research involving children, and their codification in legislation and guidelines

Ethical requirements for research projects involving children are discussed against the background and on the basis of a series of principles that are increasingly well established in the international debate and are widely accepted. In this section, an overview is given of these key principles (3.1); this is followed by an examination of their origins and their codification in international (3.2) and national (3.3) legislation and guidelines on biomedical research. The most important principles are discussed from an ethical perspective in Section 4.

3.1 Key principles

3.1.1 Consent of the child's legal representative(s)

Since the adoption of the Nuremberg Code, the fundamental requirement for any human research has been that the subjects concerned should provide voluntary informed consent to participate in the project. This principle is based on every individual's right to self-determination; it became prominent in particular through the World Medical Association's Declaration of Helsinki (cf. Section 3.2.2). Children, being essentially incapable of consenting to participate in research, are not in a position to fully satisfy the informed consent requirement; accordingly, all the relevant regulations call for proxy consent or permission to be granted by legal representatives, i.e. by parents or other duly appointed persons. It is generally required that consent is to be given in the presumed interests of and for the benefit of the child. In the case of more mature children who are in a position to assess a study and their own situ-

[8] Cf. Magnus 2006, 17f.

ation themselves, but are still regarded as legal minors, certain regulations require the minor's assent in addition to the *consent* given by the legally authorized representatives (cf. Section 4.4).

3.1.2 Refusal by the child

A principle related to that of voluntary informed consent is the principle whereby any potential research subject is entitled to refuse to participate in or to withdraw from a project at any time. This principle, highlighted for example in the Convention on Human Rights and Biomedicine (cf. Section 3.2.3), also applies for legal minors, irrespective of whether they are mentally capable or not. However, especially in the case of young children, it is difficult to define what is to be interpreted as refusal (cf. also Section 4.5).

3.1.3 Subsidiarity

A key role is played by the principle of subsidiarity, under which research involving children is only permissible if equivalent results cannot be obtained by means of research projects with persons capable of giving consent. This requirement is applicable for all research subjects who are particularly in need of protection and is especially significant with regard to research involving children: in view of children's lack of decision-making capacity, the fact that research interventions in children may only be undertaken for scientifically compelling reasons represents the most important protective condition.

3.1.4 Independent review of the research project

One of the generally recognized requirements, finally, is that every project involving research in humans is to be reviewed by an independent body (ethics committee). These committees are responsible for approving or rejecting research studies, taking into account the principles mentioned above (e.g. procedures for obtaining consent or minimizing risks and burdens). In assessing proposed studies, the committees focus on protecting human dignity and personal integrity, which are not to be violated even for the sake of freedom of research or its benefits for health and society. The independence of the review procedure is of great importance in the case of children in particular, as ultimately they cannot themselves decide whether or not to participate in a study. Alongside parents or other legal representatives, ethics committees offer an additional safeguard for the child's interests and welfare. Remarkably enough, the call for an independent review originally derives from sets of rules such as the Declaration of Helsinki (cf. Section 3.2.2), in which physicians and researchers sought to regulate their own activities.

3.1.5 Special principles for research with no prospect of direct benefit to the child

Among the generally acknowledged principles for research involving children are two which are applicable to the question of whether and under what conditions research projects should be permissible if they offer no prospect of direct benefit to the child concerned. Such projects, often termed "non-therapeutic research", are extremely controversial.[9] These principles are as follows:

[9] Accordingly, research offering no direct benefit to subjects who lack the capacity to give consent is not infrequently rejected wholesale. Consequently, the principles mentioned below are only relevant if such research is deemed to be justified under certain conditions.

a) *The research project must offer the prospect of a group benefit:*
Under this principle, the participation of a child in a research project providing no direct individual benefit is considered to be justifiable if the project is designed to substantially expand medical knowledge concerning the specific situation (e.g. disease) of the group to which the potential research subject belongs.

b) *The risks and burdens for the participants must be minimal:*
The relevant regulations reflect a basic consensus that the risks and burdens for children involved in research projects with no direct individual benefit must be minimal. However, as will be discussed below (Section 4.7), opinions differ as to how this requirement should be interpreted.

3.2 Selected supranational agreements

3.2.1 Human rights treaties

The *European Convention for the Protection of Human Rights and Fundamental Freedoms* (4 November 1950) is not directly concerned with the question of human research, but it does specify two rights closely related to this issue: the right to life (Article 2) and the right to respect for private and family life (Article 8). The United Nations *International Covenant on Civil and Political Rights* (ICCPR, 16 December 1966), as well as specifying the rights to life (Article 6) and liberty and security of person (Article 9), includes the following provisions (Article 7): "No one shall 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." At first glance, this wording would appear to rule out any possibility of children being involved in research projects, since free consent cannot be obtained from those incapable of giving it. However, from the comments accompanying this article it is apparent that, under the terms of the ICCPR, research may indeed also be carried out on subjects lacking the capacity to consent, provided that their need for special protection is taken into account and the subjects' integrity is preserved.[10]

3.2.2 The Declaration of Helsinki

Of fundamental importance among the international regulations governing medical research is the *Declaration of Helsinki,* which was originally adopted by the World Medical Association in 1964 and last revised in October 2008.[11] Although the Helsinki Declaration does not have the status of binding international law,[12] it has attained major significance in all national and international legislative processes as a self-imposed code of medical ethics. The Helsinki Declaration is of outstanding importance insofar as it defines the principle of voluntary informed consent as a mandatory requirement for human research projects. In response to the inhuman research practices of the Nazi regime in Germany, this requirement was first explicitly stated in the Nuremberg Code of 1947; with the adoption of the Helsinki Declaration, it was subsequently established as a fundamental precondition for any medical research involving human subjects. In addition, however, the Helsinki Declaration includes special provisions for the protection of research subjects who cannot give consent and, by way of a self-imposed obligation, requires researchers to have each human research project reviewed by an in-

[10] Cf. Sprecher 2007, 90.

[11] Cf. www.wma.net/e/policy/b3.htm (last accessed: 20 November 2008).

[12] Cf. Magnus 2006, 92.

dependent ethics committee. With regard to research involving incompetent subjects, the latest version of the Declaration specifies that, while informed consent is always to be obtained from the legally authorized representative, assent must also be sought from subjects who are able to give it.[13] The Declaration thus acknowledges the right to self-determination that is also enjoyed by children and adolescents, who belong to the group of subjects incapable of giving consent.[14]

3.2.3 The Council of Europe Convention on Human Rights and Biomedicine

Detailed provisions concerning human research are to be found in the Council of Europe *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (4 April 1997, hereinafter the Biomedicine Convention[15]) and the *Additional Protocol concerning Biomedical* Research (25 January 2005)[16]. The Biomedicine Convention is the first binding international treaty containing regulations on biomedical research and the application of medicine that are to be transposed into national law as soon as a party has ratified the treaty. Although the Convention was signed by the Federal Council on 7 May 1999, it was only ratified by Switzerland in the summer of 2008 after lengthy parliamentary deliberations, which were suspended several times (a decision on ratification of the Additional Protocol is still outstanding). The Convention finally came into effect on 1 November 2008.[17] The Biomedicine Convention specifies the conditions under which research projects can be carried out with persons not capable of giving consent and the exceptional conditions under which research is permissible when the results will not be of direct benefit to the health of the person concerned. However, rather than referring specifically to research involving children, the Convention distinguishes between persons who are able and those who are not able to consent to research, with children belonging to the latter group. Under the Convention, research on this group is only permissible if the results have the potential to produce direct benefit for the individuals concerned, if the principle of subsidiarity is complied with, and if written consent has been obtained from the legal representative and the child does not refuse to participate in the project. Research projects offering no direct benefit to the child are only permissible under the Convention if they meet the group benefit requirement. This means that the research must aim to significantly improve medical knowledge of the specific condition of the group to which the potential research subject belongs.[18] In such cases, the Convention also requires that the risks and burdens for the individuals concerned should be minimal.

3.2.4 The CIOMS Guidelines

In 1993, the Council for International Organizations of Medical Sciences (CIOMS, a body established by the WHO and UNESCO) published its *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (last revised in 2002).[19] Unlike the Biomedicine Convention, these guidelines are not legally binding; however, they are duly considered in current national legislative processes.[20] Of particular relevance in the present context is Guideline 14, which is explicitly concerned with research involving children. In accordance with the provisions mentioned above, this Guideline specifies

[13] Cf. Article 28 of the Helsinki Declaration.

[14] Cf. Sprecher 2007, 101.

[15] Cf. http://conventions.coe.int/treaty/EN/Treaties/Html/164.htm (last accessed: 25 October 2008). This treaty is also frequently known as the Oviedo Convention.

[16] Cf. http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm (last accessed: 25 October 2008).

[17] Cf. SR 0.810.2.

[18] Similar provisions are included in the Helsinki Declaration and in the relevant Swiss legislation (Therapeutic Products Act).

[19] Cf. www.cioms.ch/frame_guidelines_nov_2002.htm (last accessed: 25 October 2008).

[20] For Switzerland, cf. for example the Explanatory Report on the preliminary draft HFG, 68 (February 2006).

that – especially in the case of older children – not only is assent required but a refusal to participate in a research project is to be respected. According to the commentary on Guideline 14, parents and medical personnel may only override the child's wishes "if an investigational intervention shows promise of preserving or prolonging life and there is no acceptable alternative treatment".[21]

3.2.5 EU Directive 2001/20/EC

As discussed above, the problems of research involving children (or rather the lack of such research) are particularly apparent in the field of pharmaceutical research. Finally, therefore, mention should also be made of the *Guideline for Good Clinical Practice* adopted in 1996 by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[22] and of ICH Guideline *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (2000).[23] Also relevant in this respect – given that Swiss regulations are closely harmonized with those applicable in Europe – is the implementation of ICH Guidelines in European law, especially *Directive 2001/20/EC*[24] of 4 April 2001.[25] The EU Directive explicitly invokes the above-mentioned principles and specifies in Article 4 (a) that the legal representative's informed consent must represent the minor's presumed will. In addition to the established protective principles, Article 4 (e) states that clinical trials on minors may only be undertaken if there is some direct benefit for the relevant group of patients. Research involving healthy children is also permissible, provided that the clinical trial of the drug in question can only be carried out on minors.[26]

3.3 Legal regulations in Switzerland

3.3.1 Current national legal situation and the preliminary draft Human Research Act

As mentioned above, the preparation of this Opinion was occasioned in particular by the ongoing discussions concerning federal legislation on human research. This legislative process, launched by a parliamentary motion in 1998, springs from the fact that only limited areas of research involving human subjects or human material are covered by existing regulations at the federal level.[27]

The most relevant provisions at the federal level are contained in the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, HMG).[28] Article 55 of this Act specifies the conditions under which clinical trials involving subjects incapable of giving consent (including children) are permissible. Here, the established principles mentioned above are invoked, i.e. subsidiarity, consent of the legal representative and respect for the child's refusal to participate. In the case of clinical trials offering no "direct" benefit to the child, it is specified that they may be carried out "in exceptional cases" if they "are expected to produce important knowledge concerning the status, illness or suffering of the trial subjects, and if this knowledge would bring long-term benefits for the trial subjects concerned or for persons of the same age group, or for persons suffering from the same illness or presenting the same characteristics" (principle of group benefit). In addition, the trial must involve only minor risks and burdens for the subjects concerned. Finally, the Ordinance on Clinical

[21] Cf. www.cioms.ch/frame_guidelines_nov_2002.htm (last accessed: 25 October 2008).

[22] Cf. www.ich.org/LOB/media/MEDIA482.pdf (last accessed: 25 October 2008).

[23] Cf. www.ich.org/LOB/media/MEDIA487.pdf (last accessed: 25 October 2008).

[24] Official Journal of the European Communities 2001; L121:34-44 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML

[25] For the implementation of the ICH Guideline in Swiss legislation on therapeutic products, cf. Section 3.3 below.

[26] Cf. Sprecher 2007, 118.

[27] Relevant provisions are to be found in the Reproductive Medicine Act (FMedG), the Therapeutic Products Act (HMG), the Stem Cell Research Act (StFG), the Transplantation Act and the Human Genetic Testing Act (GUMG).

[28] SR 812.21.

Trials of Therapeutic Products (VKlin),[29] which fleshes out the Therapeutic Products Act, specifies in Article 4 that clinical trials of pharmaceuticals must comply with the above-mentioned ICH Guideline for Good Clinical Practice (1 May 1996).

These provisions from the therapeutic products legislation will also be included in the federal legislation on human research, the scope of which, however, will go beyond pharmaceutical research, covering additional areas of research involving human subjects. This extension of the scope is important, as there are many other areas of research involving adults and children where regulation is required to protect the subjects concerned. This may be the case, for example, for research projects in the fields of surgery, psychology, behavioural psychology, sociology, public health or psychiatry.

The principles mentioned in the draft constitutional article on human research, which at the time of the adoption of this Opinion is being considered in Parliament, and those included in the preliminary draft of the Human Research Act,[30] which has been issued for consultation, correspond to the established principles discussed above. Moreover, as the Biomedicine Convention has now been ratified by Switzerland, the principles specified therein have binding force for national legislation. At the time of the adoption of this Opinion, it is not possible to estimate when or in what form the constitutional article or the Human Research Act will come into effect. Outside those areas that are already regulated at the federal level (especially in therapeutic products legislation), responsibility for the regulation of human research will remain with the cantons until the new Act enters into force. The cantonal provisions, however, are not uniform.

3.3.2 Cantonal regulations and guidance from the Swiss Academy of Medical Sciences[31]

Human research is not specifically regulated in all cantons. Those cantons that have adopted legal regulations in this area also adhere to the established principles enshrined in international agreements and guidelines. In certain cantons, however, research projects offering no direct benefit for the mentally incapable subjects involved are currently prohibited. To date, the requirement for an independent review of research projects by ethics committees has also been implemented through cantonal regulations. Some cantonal regulations refer exclusively to the Guidelines of the Swiss Academy of Medical Sciences (SAMS) for research in human subjects, while others declare these to be applicable in addition to cantonal laws.[32] The SAMS Guidelines, adopted on 5 June 1997, and conceived as an aid to decision-making for researchers and ethics committees in the absence of comprehensive federal legislation on human research, were withdrawn in November 2008. They are to be replaced by a practical guide for research involving humans, which is expected to be published by the SAMS in 2009.

4 Ethical questions and problems in the area of research involving children

There is an ethically justified demand for research involving children, which is particularly striking in the pharmaceutical field. Given the lack of relevant

[29] SR 812.214.2.

[30] At the time of the adoption of this Opinion, the submission of the Human Research Act to Parliament is scheduled for the first half of 2009. As a Commission independent of the Federal Administration, the NEK-CNE has no knowledge of the results of the revision of the preliminary draft.

[31] For this section, cf. also the discussion in the Explanatory Report on the preliminary draft HFG (49-52) and Sprecher 2007, 138-159.

[32] Cf. www.samw.ch/docs/Richtlinien/d_Forschungsunters.pdf (last accessed: 25 October 2008).

data concerning safety, efficacy and dosage, the large-scale administration of medicines to young patients as currently practised is essentially of an "experimental" nature. This deficiency cannot be fully remedied by paediatricians' ample empirical knowledge. Children thus pay the price for the lack of research concerned with this population.

At the same time, there are good ethical reasons for keeping research involving children to a minimum: as children's limited or non-existent mental capacity means that they cannot decide for themselves whether to participate in a study and are unable to defend their own interests, they are particularly in need of protection and liable to be exploited for the benefit of others.

Both positions are based on ethically justified interests – hence the moral conflict. The aim of the following discussion is to examine in detail a number of ethically sensitive issues.

4.1 Terminological questions

4.1.1 "Child"

The use of "child" as a general term is problematic. A 17-year-old teenager no longer sees himself as a child and is, moreover, capable of making major decisions, e.g. concerning career choice, independently. The question therefore arises whether specific regulatory categories are required for "minors" in different age groups. This would also give rise to different requirements for consent to participate in a research project (cf. Section 4.4). This approach is adopted in the preliminary draft HFG, which introduces a distinction between "mentally incapable" and "mentally capable" minors or legally incapacitated persons and, on this basis, specifies different requirements for consent to participate in a research project.

4.1.2 "Therapeutic" vs "non-therapeutic" research

The classification of research involving children often invokes a distinction between "therapeutic" research on the one hand and "non-therapeutic"/"altruistic" research on the other. A categorical distinction between two different types of research has, however, been increasingly criticized in the bioethical literature.[33] As research is designed, by definition, to generate knowledge rather than to cure the trial subject, it is to this extent always "non-therapeutic". Individual interventions undertaken within the framework of a study may indeed provide a therapeutic benefit for the subject; however, since the outcome of research is open and the potential therapeutic benefit of an intervention for a group of patients has yet to be demonstrated, the occurrence of any such benefit is more uncertain than with a recognized form of treatment.

The distinction drawn in the preliminary draft HFG between "research offering a direct benefit" (Article 18) and "research offering no direct benefit" (Article 19) does not avoid the problem that it is not possible to distinguish categorically between different types of research.

The NEK-CNE assumes that there is a continuum between research offering no therapeutic benefit for the trial subject and research that is very likely to provide a therapeutic benefit for the subject. From an ethical perspective, reference to a potential therapeutic benefit for the subject concerned is not sufficient to legitimize a study. The decisive factors in an ethical assessment are the risk/benefit ratio and respect for the principles of subsidiarity, consent and lack of dissent.

[33] Cf., for example, Spriggs 2004 and Kind 2007. According to Spriggs, criticism of the distinction between "therapeutic" and "non-therapeutic" research was one of the factors that led to a revision of the Helsinki Declaration (cf. Sprecher 2007, 177).

4.2 Children's special need for protection

As trial subjects, children are particularly in need of protection, since they are reliant on the decisions made by and protection provided by their legal representative, dependent on care and supervision, and not fully capable of representing or safeguarding their own interests.[34] In addition, owing to their emotional and physical dependence, children are not always able to assert themselves or influence their situation within a research setting. As children are still growing and undergoing physical, emotional and social development, burdens imposed on them during a study may have more serious and longer-term effects than for adults.[35] In addition, knowledge – e.g. concerning a genetic predisposition – may have a lasting adverse impact on their future life and on the development of their personality. Children, however, as argued by Joel Feinberg, have a right to an open future.[36]

In the view of the NEK-CNE, the ethically relevant distinctive characteristics of children, which make them especially vulnerable, can be summarized as follows:

- They are dependent on the decisions, protection and care of adults.
- They have little scope to influence the framework of a study, which determines their own situation.
- Their physical, emotional and social development has yet to be completed.
- The development of their personality has yet to be completed.
- They can be readily manipulated.
- They are susceptible to emotional stress.
- They generally still have most of their lives in front of them.
- Harm and burdens associated with research may have a lasting impact on their future life, growth and personality.
- They are themselves oblivious of the future; i.e. they cannot assess the possible effects of research on their future life.

At the same time, children are entitled

- to have an open future,
- to have their capacity for independent decision-making and action promoted,
- to have decisions made on their behalf that promote their welfare.

In the view of the NEK-CNE, these characteristics make children a vulnerable group of research subjects. Following Hurst, the NEK-CNE considers vulnerability to be an increased likelihood of suffering wrong or harm.[37] Whether such wrong or harm could actually occur will depend on the design and purpose of a specific study. The NEK-CNE takes the view that the vulnerability of children should not mean that they are automatically excluded from research. Rather, special duties of care need to be formulated not only for parents or other legal representatives but also for researchers (e.g. safeguards against third-party interests adversely affecting the child's welfare).

4.3 Assessment of mental capacity

For research involving children, assessment of subjects' mental (in)capacity is essential if they are to be given the possibility of assenting to or refusing research (or a research intervention) and thus to participate in decision-

[34] Cf. Sprecher 2007.

[35] Cf. Dahl/Wiesemann 2005.

[36] Cf. Feinberg 1980.

[37] "I propose that vulnerability as a claim to special protection should be understood as an identifiably increased likelihood of incurring additional or greater wrong" (Hurst 2008,195).

making. Mental capacity is always defined in relation to a particular object. For example, the requirements specified for consent to participate in a study involve more stringent conditions than refusal of a research intervention. The implications of this are already apparent at the formal level. While the consent of parents and of mentally capable minors is legally required to be given in writing, a minor's assent may be oral and refusal may also be expressed non-verbally.

What makes children a special case is the fact that their mental capacity is in the process of developing. The stage of development attained in a specific case needs to be taken into consideration in assessing the child's capacity and to ensure that management is appropriate to the child's age. Adults have a responsibility to promote the child's development into a mentally capable person. Signs of opposition to a research intervention should generally be respected (also in order to foster the child's independence).

In the view of the NEK-CNE, age is less crucial than the child's maturity for an assessment of mental capacity and the capacity to consent. Competence to consent depends on cognitive abilities, which in turn may be promoted or impaired by emotional, social and motivational processes and factors, and by experiences of illness.[38] Accordingly, rather than being guided by fixed age boundaries, it would be desirable to assess the child's maturity or competence to consent on an individual basis.

The NEK-CNE also emphasizes that information needs to be given in a manner appropriate to the child's age. If the physician provides an oral explanation, the interactive situation makes it possible to check whether the child and parents have understood the relevant information.

4.4 Consent to participate in a research project

Since the adoption of the Nuremberg Code in 1947, the subject's consent to participate in a research project has been a fundamental prerequisite for its legitimacy. With the development and strengthening of patients' rights to self-determination, this requirement has become increasingly important in biomedical ethics. The concept of informed consent involving four criteria (disclosure, understanding, voluntariness and competence), as articulated by Faden and Beauchamp,[39] reflects the core conception of autonomy in medical practice and ethics. It is associated with the requirement that autonomy in this sense (the basis of voluntary informed consent) is to be respected.

This conception of autonomy is inadequate with regard to decision-making processes in the case of children, since the ethics of paediatrics involves a structural peculiarity.[40] Paediatric decision-making processes are based on a triadic relationship (child – parents or legal representative – researcher), in which the person concerned (i.e. the child) cannot – at least not independently – make the decision on whether to participate. In the case of mental incapacity or if a research project offers no direct benefit, with risks and burdens rated as more than minimal, a child can only participate in a study with the consent of its parents or legal representative. This requirement is designed to protect the child, who is not yet able to recognize and defend its welfare and interests to a sufficient extent. This protective measure addresses the fact that the child cannot itself give informed consent to participate, which – by invoking the principle of autonomy – would provide an ethical foundation for the conduct of the research project.

[38] Cf. Spangler 2005. The social scientist Priscilla Alderson showed that children with chronic diseases were already competent to make decisions at the age of six or seven Alderson 1993. See also Collogan/Fleischman 2005.

[39] Cf. Faden/Beauchamp 1986.

[40] Cf. Kodish 2003.

The NEK-CNE believes that it would be a mistake, on the basis of these considerations, to declare the principle of autonomy to be irrelevant for research involving children, or to regard this type of research as fundamentally illegitimate from an ethical perspective. Instead, the concept of autonomy described above should be modified in paediatric ethics, and researchers should in practice pursue the goal of maximizing the freedom of the children concerned and avoiding a paternalistic approach to children.[41] A modification of the concept involves distinguishing between two forms of consent in paediatric ethics which can – and in practice also should – accommodate the principle of autonomy: consent given on behalf of the child by parents or other legal representatives (proxy consent/permission) and the agreement that can be given by mentally capable children (assent/child consent).

4.4.1 Consent of parents or other legal representative(s)

As the child's legal representatives, parents or other duly appointed persons should be guided in their decision-making by the child's interests and welfare (cf. Section 4.6). Parents are also responsible for assisting the child in determining and expressing its wishes.[42] Wherever possible, the parents' decision-making process should involve an examination of the child's individual wishes and interests. In other cases (e.g. for newborns and infants), decisions are to be guided by the "objective best interests" standard. The parents should seek not to exercise control over the child but to make decisions in its interests, as this is the only way of doing the child justice.

Since participation in a study is optional and the primary aim is not to optimize the individual child's welfare but to generate knowledge so as to improve paediatric medicine for future patients (cf. Section 4.1.2), it is essential that the acceptability of the study should be carefully examined by an ethics committee. A question that may arise for an ethics committee reviewing proposed research is from what perspective the members should deliberate on or assess projects. It has been proposed that committees should act *in loco parentis,* evaluating the risks and burdens associated with research projects involving children from the perspective of "informed and scrupulous parents whose children are being invited to participate in research".[43] The NEK-CNE supports this interpretation of the principle of consent.

4.4.2 The child's assent

The child's assent is to be obtained as soon as the child is able to provide it, given the development of its mental and decision-making capacity. Assent is more than the absence of opposition (cf. Section 4.5): it involves affirmation, expressed either verbally or non-verbally. In psychological and sociological research,[44] it has increasingly been emphasized that mental capacity is to be assessed independently of age, and that it is present more often than is generally assumed in clinical practice (cf. Section 4.3).[45] Since it tends to be assumed in medical research that children (unlike adults) have no or only limited mental capacity, particular attention should be paid to recent findings from research on the development of maturity in children, and there should in future be greater openness to the possibility of children being capable of decision-making. This capacity must also be promoted through the provision of information in a child-friendly manner.[46] This involves the communication of relevant, appropriately presented information through interviews

[41] Cf. the discussion of the approaches of Nathaniel Laor and Janusz Korcazks in Dahl/Wiesemann 2001, 99.

[42] Gill et al. 2003.

[43] Freedman et al. 1993.

[44] Cf. Alderson 1993 and 2007.

[45] Cf. Signorelli 2004.

[46] Cf. Gill et al. 2003.

rather than in writing. During such discussions, the child is not to be put under pressure, and it must be confident that its privacy will be protected – also vis-à-vis its parents. Especially in studies on sensitive topics (e.g. sexual behaviour, drug use), this confidence is indispensable, both for the conduct of the research and for the quality of the results.

For the ethical quality of a research protocol, the design of the process whereby the child's assent is sought is more decisive than reference to a form documenting this assent.[47] It is also important that the child's rights to be involved should not depend categorically on the presence of the mental capacity that would be required for informed consent. The fact that the capacity for autonomy and judgement is in the process of developing in children means that these abilities are a matter of degree.[48] Children should therefore always be involved in decision-making processes as soon as they can form and express an opinion.

Ethical problems are raised by cases where mentally capable children agree to participate in research while their parents are opposed to their participation. While some authors[49] argue that the minor's wishes should be respected, the preliminary draft HFG maintains a requirement for parental or proxy consent in cases where the conduct of a study is expected to involve more than minimal risks and burdens. The adoption of this position restricts the child's rights to personal integrity despite the recognition of mental capacity. This restriction can be justified on the basis of the vulnerability that still applies in the case of adolescents who are already mentally capable. For example, adolescents might participate in studies from financial motives and in so doing adversely affect their long-term welfare by incurring higher risks and burdens. As parents or other legal representatives are responsible for protecting the welfare of adolescents, the requirement for proxy consent can be seen as an additional protective condition for minors.

The NEK-CNE assumes that the development of mental and decision-making capacities in children is variable and a matter of degree. Consequently, the decision as to whose consent is to be sought for participation in a study should depend on the child's developmental status. For purposes of legislation, it may not be helpful to note the existence of a continuum of cognitive and volitional capacities. However, ethics committees reviewing research projects would be in a position to decide what conditions minors would generally have to fulfil for it to be necessary to seek their consent to participate in a study. A question to be assessed separately would be whether the consent of the mentally capable minor is sufficient, or whether the parents' consent would also need to be obtained. To permit a study-specific assessment of mental and decision-making capacity, legislators would have to give ethics committees sufficient legal leeway to find an arrangement appropriate for the study in question. In practice, however, the NEK-CNE believes that a consensus between parents and children will always facilitate the conduct of a study.

4.5 The child's right of refusal

Parents' proxy consent for a child to participate in a study is a necessary but not a sufficient condition for participation. It does not deprive the child of the right to refuse to participate ("right of veto").[50] This right has also been included in the draft constitutional article on human research, where it is applicable for all children – irrespective of their mental capacity.

[47] Cf. Kodish 2003.

[48] Cf. Fegert et al. 2005, 118.

[49] Cf. Gillick, cited in Alderson 2007, 2273.

[50] Taupitz 2003, 40 and Sprecher 2007, 266ff.

Children's refusal is generally unproblematic if their non-participation does not give rise to any adverse consequences for the minors in question. However, a refusal needs to be examined much more carefully if non-participation could have serious consequences for those concerned. Faced with certain discomforts, a (seriously ill) child could relatively easily forget that declining the treatment offered in a clinical study would mean rejecting the best available treatment. Accordingly, the weight attached by adults, parents or legal representatives to a child's refusal should be determined by the significance of the research project for the child itself. For this reason, most legal provisions recognize the need for exceptions, at least with regard to young children, in order to address this specific issue.

Controversy could, however, arise in cases where it is difficult to determine the object of a sign of opposition. In practice, for example, signs of a child's opposition to blood sampling could possibly be interpreted, not as refusal of the research intervention, but as the expression of a general fear of "white coats".[51] A child's crying would thus not have to be interpreted as a binding expression of refusal to participate in research.

The NEK-CNE finds this approach problematic, as it potentially weakens the child's right of refusal. It is true that parents also regularly make and implement decisions against the wishes of a child (e.g. forcibly administering medicines when the child is ill). However, their forcible action must be justifiable, generally with reference to the child's welfare, and this is not applicable in the case of research offering no direct benefit to the child. In addition, a child's fear, even of a "white coat", may represent an unreasonable burden.

In the view of the NEK-CNE, it is therefore essential that the child's right of refusal should be taken seriously and strengthened. An important measure in this connection is a child-friendly explanation of the potential subject's rights concerning participation in a study. In practice, according to Leikin, such explanations are often inadequate, as participants are not always aware that they are entitled to withdraw at any time.[52] Such misunderstandings are to be prevented in research practice.

4.6 Determination of the child's welfare and interests

Proxy decisions should be guided by the child's welfare and interests, rather than by the child's hypothetical agreement.[53] In the first instance, the NEK-CNE assumes that the child's welfare or interests are best represented by the parents. As mentioned above, it is a misinterpretation of the child's special situation if one treats the child as a mentally incapable adult for whom the criterion of informed consent is to be applied merely by requiring proxy consent to be given by the parents or the legal representative. Likewise, as a hypothetical construct, the child's presumed wishes that are to be taken into account in parents' decision-making bear no relation to the actuality of the child, especially the infant or toddler. Whereas, in the case of adults who have become mentally incapable, presumed wishes can be constructed with recourse to previously expressed desires, values and interests, children lack mental capacity when they are born and only develop values as a result of experience, upbringing, education and other factors. Consequently, children are initially "value-neutral individuals".[54] In order to make decisions on the child's behalf, it is therefore more appropriate to be guided by the criteria of the child's welfare and best interests. In the eyes of the NEK-CNE, this offers the following advantages.

[51] Cf. Federal Council's report of 12 September 2007 on the constitutional article concerning human research (4.4.2.3), 6736.

[52] Cf. Leikin 1993.

[53] Cf. Maio 2002.

[54] Maio 2002, 171.

As well as having an objective (medical) content, the welfare of a human being is shaped by subjective elements, such as individual preferences, values and personal experience. In children, these subjective elements are present only to a limited extent or – in the case of newborns – have yet to develop, and they are not apparent to third parties. In this case, parents are guided by the objectively ascertainable ("enlightened") welfare of the child. Here, consideration is to be given to the child's potential for development and future prospects.[55]

The NEK-CNE believes that, if the child is able to express desires, these should be taken into account in assessing the child's welfare, so as to respect the child's right to have a say as part of its rights to personal integrity. However, cases may arise in which the child's views conflict with its objectively determined welfare, for example if a seriously ill child refuses further treatment within the framework of research offering a possible direct benefit, while the parents favour such treatment for the sake of the child's welfare. In such a case of conflict, the NEK-CNE recommends an examination of whether the parents' determination of the child's welfare could possibly be distorted by their own interests, and whether the child already has the necessary maturity to decide for itself whether to participate in the research (cf. Section 4.3).

4.7 Determination of risks and burdens

The draft constitutional article on human research includes a principle of proportionality between the possible risks and burdens for participants and the benefits to be expected (Paragraph 2 Letter b). Additionally, in the case of research offering no direct benefit to mentally incapable subjects, only "minimal" risks and burdens are permissible according to the draft constitutional article and the preliminary draft HFG. The Federal Council's Report on the constitutional article, echoing Taupitz[56], offers the following definition of minimal risks and burdens: "research leads at most to a slight and temporary impairment of health (risk) and is expected to produce only mild and temporary symptoms or discomforts (burden)".[57] A precise specification of minimal risks and burdens is to be left to legislators.

However, what is to be viewed in practice as "minimal", i.e. a short-term, non-serious impairment of well-being, is a controversial issue. For example, in its guidelines,[58] the Ethics Advisory Committee of the Royal College of Paediatrics and Child Health rates as minimal only non-invasive procedures such as observing and questioning, (non-invasive) urine sampling, or using blood for research purposes that has been taken as part of treatment; others, however,[59] also consider additional venous blood sampling to be a minimal burden. Diagnostic procedures such as radiography may also be burdensome and raise the question whether the radiation exposure involved is to be regarded as "minimal" or more serious.

In assessing the risks and burdens assumed by research subjects, it is first important to distinguish between three different dimensions:[60] 1. the probability of a subject suffering harm, 2. the magnitude of the harm and 3. the reasonableness of the harm. However, this conceptual distinction does not in itself yield a definitive definition of the nature of minimal risks and burdens. Further gradations invoked in justifying research involving mentally incapable subjects – "minimal risk", "minor increase over minimal risk",

[55] Cf. Sprecher 2007, 266.

[56] Cf. Taupitz 2002, 67.

[57] Federal Council's Report of 12 September 2007 on the constitutional article concerning human research (Section 4.4.4), 6738.

[58] Cf. Royal College of Paediatrics and Child Health: Ethics Advisory Committee 2000, 179.

[59] Cf. Dahl/Wiesemann 2001, 100.

[60] Cf. Dahl/Wiesemann 2001, 107 and Kopelman 2004, who refer to the regulations governing human research in the US. Subpart A § 46.102i of the Code of Federal Regulations ("Basic HHS Policy for Protection of Human Research Subjects") defines "minimal risk" with reference to "probability" and "magnitude" of harm or discomfort, as well as everyday hazards: "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

"more than minor increase over minimal risk" – tend to exacerbate rather than solving the fundamental problem of how a threshold or range of "minimality" is to be defined.

In regulations on human research in the US, the risks and burdens of research are now often compared with everyday hazards.[61] However, these are not precisely quantifiable and the comparison is ethically problematic. Kopelman, for example, points out that the term "everyday hazards" can denote a variety of situations that may differ dramatically with regard to the probability of occurrence, and magnitude, of harm.[62] In addition, the determination of "everyday" hazards is strongly dependent on the specific circumstances of the subject's life.[63]

Apart from the conceptual fuzziness, what makes the comparison especially problematic is that this approach ignores the normative question of whether it is ethically *permissible* and *should be socially* acceptable to expose children in everyday life to – sometimes major – risks and burdens.[64] The fact that children encounter risks and burdens in daily life cannot provide a justification for their also being exposed to such hazards in other areas, e.g. research. In the view of the NEK-CNE, such reasoning would overlook a crucial difference between everyday hazards and those arising from research: while one is exposed to many everyday risks and burdens – irrespective of their magnitude – *involuntarily* (e.g. road traffic) without thus acknowledging the legitimacy of these risks, hazards associated with a study can be *voluntarily* avoided, by refusing to participate. Such powerlessness in the face of everyday circumstances applies in particular to children, who do not themselves choose the conditions under which they lead their lives. Parents or other legal representatives have a duty as caregivers, and ethics committees have a responsibility, not to extend this powerlessness into the domain of research, where children are also dependent on the decisions made by adults.

Another dubious consequence of seeking to justifying research on the basis of a comparison with everyday risks is that children who are already exposed to greater hazards than other children in their daily lives would also have to accept higher risks and burdens in studies.[65] This would be contrary to the dictates of fairness. With the goal of permitting objective measurement of minimal risks and burdens and thus facilitating ethics committees' assessment of research risks, Wendler et al. endeavoured to quantify minimal risks and burdens in relation to everyday hazards (risk of dying in a road accident, risk of sustaining sports injuries).[66] Objecting to this approach, Nelson and Ross argued – rightly, in the NEK-CNE's view – that quantification is not a satisfactory solution because it leaves unanswered the normative question of which risks and burdens are ethically permissible.[67] In addition, quantification overlooks the subjective component in assessment and in how risks and burdens are experienced by the research subject. Subjective perceptions, however, are crucial in determining whether a risk or burden is "minimal" or greater for the research subject.[68] Even among medical professionals, there is no consensus on what scales or instruments should be used for measuring risks, or on the "objective" risks or burdens associated with specific procedures.[69] For these reasons, the NEK-CNE considers everyday risks and burdens to be problematic "quantities" in comparisons designed to justify research.

[61] Cf. footnote above.

[62] Cf. Kopelman 1989.

[63] Cf. Kopelman 1989.

[64] Cf. Nelson/Ross 2005 and Ackerman 1980.

[65] Cf. Spriggs 2004, 179.

[66] Cf. Wendler 2005 and Wendler et al. 2005.

[67] Cf. Nelson/Ross 2005; Ross/Nelson 2006.

[68] Cf. Kopelman 1989.

[69] Cf. Janofsky/Starfield 1981.

Modifying a definition given by Ackerman,[70] Nelson and Ross propose that the acceptability of procedures should be assessed with reference to the risk of physical or psychological harm to which it is appropriate for a scrupulous parent to intentionally expose a child for educational purposes in family life situations.[71] This definition of minimal risks and burdens has one obvious advantage: it is normative, insofar as the determination of minimality is guided by a moral ideal, namely appropriate education by scrupulous parents who make decisions as caregivers for the benefit of the child. This definition could, however, give rise to a misunderstanding. It could create the impression that a child's participation in research offering no direct benefit serves an educational purpose, e.g. practice in altruistic behaviour. However, in the view of the NEK-CNE, an educational goal of this kind should not be adduced as a primary justification for research offering no direct benefit to the child (cf. Section 4.11).

Given that the assessment of hazards in research is situation- and subject-dependent and includes a normative component, it does not appear to the NEK-CNE to be possible to define in general terms what level of risks and burdens is minimal and hence tolerable in furtherance of scientific and social interests. Rather than the use of fixed or even quantitative standards for the measurement of risk, the NEK-CNE would welcome a situational assessment on the part of ethics committees, taking into account the context of the study and the specific characteristics of the subjects concerned. Here, ethics committees should be guided by the principle of proportionality between potential harm and benefits, which is to be understood in the sense of "reasonable" risks and burdens for the child (on the question of reasonableness, cf. key conclusion C). What counts as reasonable depends, in part, on the above-mentioned dimensions of the probability and magnitude of harm. A study-specific assessment of burdens makes it possible to take into consideration the child's particular situation (e.g. developmental and health status) and also the type and extent of benefits anticipated (individual/social, minor/major).

4.8 Determination of benefits

According to the Federal Council's Report on the constitutional article concerning human research, research involving mentally incapable subjects must offer the prospect of benefits either for the individual concerned or for third parties. As well as group benefits (cf. Section 4.11), third-party benefits include "social benefits" and "public health benefits".

"Benefits" is a normative concept, based on conceptions of the good life. The normative element is revealed by efforts to differentiate between health benefits and types of performance enhancement. The determination of benefits also depends on the specific context (research aims, subject's health status, etc.). Participation in a research project does not necessarily entail benefits for the subject concerned, as study interventions are not geared to the specific needs of individual patients. For a physician, it may be difficult to invite a patient to participate in a study where no direct benefit is anticipated. In the view of the NEK-CNE, particular caution is required in cases where only third-party benefits are expected (cf. Sections 4.10 and 4.11).

[70] Cf. Ackerman 1980.

[71] Cf. Ross 1998, 77-110 and Nelson/Ross 2005.

4.9 Risk/benefit assessment

Since the risk/benefit assessment can only be carried out by proxy for mentally incapable subjects, it involves a risk of incorrect attribution, for the child may experience risks or benefits differently than is presumed in adults' assessments. For example, it is controversial whether the collection of highly personal (e.g. genetic) data represents more than merely a "minimal" or reasonable burden.[72] On the one hand, it can be argued that knowledge of such data is irreversible and may prove burdensome for the child in later life. In addition, the child is deprived of the liberty of deciding for itself as an adult what it wishes to know about itself and its genetic predispositions or carrier status. On the other hand, genetic testing may also give rise to individual benefits. Genetic screening could lead to early detection of a curable disease and the initiation of appropriate treatment at an early stage. Which arguments are more convincing and which solutions are chosen (e.g. data to be withheld until the age of majority) can only be determined for a specific research project on a case-by-case basis.

The levels of risks and burdens deemed acceptable will depend on the type and extent of benefits. In accordance with the principle of proportionality between risks and benefits, the more serious a child's illness, the greater the risk that may be incurred if its life could be saved or its quality of life significantly improved by participation in a study. However, the same does not apply for benefits that could be derived by third parties from research (cf. Section 4.10).

The NEK-CNE takes the view that utilitarian considerations (helping as many children as possible by developing new diagnostic or therapeutic options) must not be used to legitimize unreasonable impairment of a child's well-being or violation of a child's rights to personal integrity or dignity. In addition, in the risk/benefit analysis, it should be ensured that the benefits which could arise for the child from participation in a study are not prevented by other – financial or social – factors.[73]

4.10 Difficulties of justifying research offering no direct benefit to the child

Under the preliminary draft HFG, research involving mentally incapable subjects and offering no direct benefit would be permissible under certain conditions (Article 19). In the case of children, allowing such research is ethically controversial, as they cannot themselves decide whether to participate in a study – at most they can exercise a veto. However, if children cannot derive any direct benefit from the research – i.e. if it does not (also) advance their well-being – then it can be seen as using children as a means to serve the ends of third parties ("instrumentalization").[74] According to Seelmann,[75] this would violate their human dignity, which is constitutionally protected. Regardless of the benefits that the research could provide for third parties, a violation of this kind would have to be avoided.

However, the soundness of this line of argument needs to be investigated. Does participation in a study with no prospect of direct benefit for the subject automatically represent an impermissible instrumentalization? Maio answers this question firmly in the negative, as he considers research offering no direct benefit to the child to involve only "partial", rather than "essential", instrumentalization.[76] For him, such research is comparable to types of

[72] On ethical issues in paediatric genetics, cf. also Ross 2008 and Rehmann-Sutter et al. 2004.

[73] Cf. Spriggs 2004, 179.

[74] For this line of argument deriving from the Kantian tradition, cf. the accounts given in Seelmann 2007 and Taupitz 2004, 41.

[75] Cf. Seelmann 2002.

[76] Cf. Maio 2002 and 2007.

instrumentalization that occur in daily life without representing a violation of human dignity. Taupitz raises the additional objection that depriving children of any possibility of participating in research with no direct benefit could itself amount to a violation of human dignity, or discrimination.[77] For Fischer, too, equating respect for human dignity in a research context with respect for the subject's volition involves discrimination against those people who are not capable of decision-making or of self-determination.[78] The exclusion of subjects not capable of giving consent would impede the progress of paediatric medicine, e.g. in the refinement of diagnostic procedures for which investigations in healthy children are required so as to obtain normal and reference values, which represent indispensable standards for the diagnosis of abnormalities and diseases.[79] Likewise, severely ill children who could not hope to derive any direct benefit from participation in a study would be excluded from research, with efforts to improve the diagnosis and treatment of precisely such life-threatening conditions being hampered as a result.

The NEK-CNE, equally, does not question the importance of the possibility of research offering no direct benefit to the child. Arguments seeking to justify such research are examined more closely in the following section.

4.11 Solidarity and group benefit – justifications for research offering no direct benefit to the child?

In the debate on the preliminary draft HFG and the draft constitutional article on human research, the principle of solidarity was claimed to provide a justificatory framework for research with no prospect of direct benefit to the child. This raises the question of whether the solidarity of third parties (in this case, children) may be enlisted if only proxy consent is available (in this case, that given by parents or other legal representatives).

According to Seelmann, proxy consent is not sufficient to justify such research, since the decisions made by the child's legal representatives should be guided primarily by the "child's welfare" and "interests", but research offering no direct benefit does not advance the "child's welfare". Seelmann sees the attempt to attribute an interest in solidarity to the child – so as to justify research offering no direct benefit – as misguided, since according to his interpretation this infringes the right to personal integrity, under which individuals can only decide themselves whether they wish to behave altruistically or egoistically.[80] This right, he maintains, is also enjoyed by children.

Contrary to Seelmann's view, the NEK-CNE contends that, among children in disease situations, a sense of solidarity towards other children, but also towards adults, can indeed be perceived. In addition, empirical evidence indicates that, among sick children and their parents, there is a high degree of readiness to participate in research offering no direct benefit.[81] However, for the NEK-CNE, the fact that children are already capable of solidarity does not give rise to a duty to behave altruistically. Such a duty – here the Commission agrees with Seelmann – cannot be formulated, but research offering no direct benefit may indeed – contrary to Seelmann's view – be permissible.

In order to justify such research, the concept of *group benefit,* taken from the Biomedicine Convention, was introduced as an additional condition in the preliminary draft HFG. While group benefit is based on the idea of solidarity, it also circumscribes this idea. Under the preliminary draft HFG,

[77] Cf. Taupitz 2004.

[78] Cf. Fischer 1999. See also Seelmann 2002, footnotes 42 and 43.

[79] Cf. Wiesemann/Dahl 2003, 268.

[80] Cf. Seelmann 2002, 576. In a later publication, however, Seelmann maintains that – subject to controls for the prevention of abuses – research with only the prospect of a "third-party benefit" is permissible for the sake of "minimal civic solidarity" in the case of "trivial" interventions (e.g. cheek swabbing) (cf. Seelmann 2007). However, this raises the difficult question of what is to count as trivial. For example, if the saliva sample is used for genetic testing, this procedure could be "non-trivial", given the need to protect sensitive personal data.

[81] Cf. Wendler/Jenkins 2008.

subjects involved in such research only display solidarity with people in the same condition (e.g. same age category) or in the same disease or disorder situation. In addition, there must be a prospect of a benefit in the long term.

For the NEK-CNE, several aspects of this approach appear to be problematic. Firstly, the concept of a "group" is elastic and can be interpreted in various ways (grouping by age ranges, by social, economic or geographical criteria, etc.). If the concept is restricted to age and disease categories, then the group benefit clause excludes studies that could be advantageous for the investigation of adult diseases. Such research could, however, be in the child's interest, as it will subsequently be an adult itself. In addition, it is difficult to explain on what grounds solidarity with "one's own group" (rather than with "all humankind") should be attributed to children. The group-benefit argument appears collectivist, since it understands "one's own group" as a kind of community of fate with which solidarity is, as it were, "naturally" displayed. However, the definition of "a group" is undertaken by researchers, not by those directly concerned, which represents a kind of heteronomy. Alternatively, group benefit could be interpreted as an extension of "self-interest", as the group-specific benefit from the perspective of group members is oriented towards their individual welfare.[82] However, the NEK-CNE also finds this argument unconvincing, since for the *individual* child, the group benefit remains a third-party benefit.

In order to strengthen the ethical legitimacy of research offering no direct benefit to the child, it could be helpful to appeal to an "objective interest" in the performance of such research as a way of improving paediatrics or medicine overall. In this context, "objective" means that the interest is a universal one, which can automatically be attributed to each individual. In view of the possibility of future illness, the child has an interest in medical progress, e.g. in relation to diseases from which it could itself suffer. An "objective interest" of this kind could be attributed to children if this is permitted by the specific study design and the child's situation (reasonableness of interventions). Thus, rather than prohibiting research offering no direct benefit wholesale, it would be possible to assess on a case-by-case basis whether a study should be permitted and which subjects should be allowed to participate. It should be emphasized, however, that the appeal to an "objective interest" in research involves a hypothetical assumption, which can also be falsified (e.g. by signs of opposition from the child).

For the protection of children, the following normative criteria are crucial: observance of the subsidiarity principle, respect for the child's right of refusal, consent given by parents or by the mentally capable minor, and the reasonableness of risks and burdens. However, in the view of the NEK-CNE, appeals to group benefit, a sense of solidarity or an "objective interest" are not among the criteria required for the acceptability of such studies, although they may indicate the value of the research. To maintain compatibility with the Biomedicine Convention, it would however be advisable to leave the group benefit clause in the HFG. The NEK-CNE believes that, in order to expand protection for children, it would be desirable to specify additional conditions. For example, children's right to veto their participation in research with no direct benefit should be subject to less stringent conditions than in the case of studies with a prospect of direct benefit.[83] In addition,

[82] This argument is advanced by Taupitz 2004, 39.

[83] Reusser, cited in Sprecher 2007, 301.

child protection would be facilitated by a monitoring process, in which for example a trusted individual could serve as a contact and supervisor.[84] The determination of "minimal risks and burdens" should be adapted to the situation of the subject concerned in accordance with the specific context so as to ensure reasonableness.

4.12 Should a research project offering no direct benefit be carried out if a child dissents?

In its submission to the consultation on the draft constitutional provisions and Federal Act on Human Research (7 June 2006), the NEK-CNE noted that "research interests" should take precedence over "personal freedom" only in "extremely well-justified cases".[85] As an example of such an exception, it cited "cases where young children undergoing cancer therapy can only be treated in a study and therefore treatment is carried out for their own benefit, even if they do not wish to be hospitalized."[86] Assuming that the child does not yet have the cognitive capacity to come close to understanding its illness and treatment options (or the lack thereof), the preservation of the child's objective welfare can be regarded as more important than respect for its right to personal integrity and its right of refusal. In this case, participation in the research is no longer optional, but – from the perspective of the child's welfare – mandatory.[87] However, the risks associated with participation in the study must be minimal compared with the risks of the child's disease.

4.13 Emergency research

For emergency research, a rule has become established whereby under certain conditions the consent of the person concerned is not required for the conduct of a study, as implicit consent can be assumed.[88] This rule is not directly applicable to emergency research involving children, since the child's legal representative is capable of making a decision. To clarify the question of how far the above-mentioned rule can replace parental permission for emergency research, three situations[89] need to be distinguished: 1. The parents are not present and cannot be consulted in good time. 2. The parents are present, but in view of the narrow therapeutic window it is not possible to obtain their voluntary informed consent. 3. The parents are present and there is adequate time for discussion.

Situation 1 corresponds to the emergency situation for adults, in which the rule is applicable, i.e. the implicit consent of the person(s) concerned is taken for granted. However, Situations 2 and 3, which differ only in degree, are more difficult to evaluate. The parents are in a highly emotional and vulnerable state. The hectic environment of the emergency room and intense time pressure are further stress factors that may adversely affect decision making. Communication is also complicated by the medical team's lack of any prior relationship with the parents, together with their dual role as treating physicians and investigators. This dual role may also create anxieties in the parents, who want their child to be seen as a human being in dire need of help rather than as an "object of research".

Nonetheless, there are good reasons for permitting emergency research in children. In order to develop effective emergency treatments and avoid the use of (unproven) innovative therapies, there is a need for more research that also includes at-risk children.[90] To protect children – especially

[84] Cf. Taupitz 2004, 42.

[85] http://www.bag.admin.ch/nek-cne/04229/04233/index.html?lang=de (last accessed 26.11.2008).

[86] http://www.bag.admin.ch/nek-cne/04229/04233/index.html?lang=de (last accessed 26.11.2008, own translation).

[87] Kodish takes the opposing view that participation in research is, by definition, optional. Cf. Kodish 2003, 90.

[88] Cf. Nelson 2006, W1.

[89] Cf. Nelson 2006.

[90] Cf. Nelson 2006.

in the case of research where no direct benefit is anticipated – the proxy consent requirement must be fulfilled as far as possible. The NEK-CNE believes that, for the problematic situations mentioned above, this entails the following possible courses of action: in Situation 2, the planned measure (already applied in practice) could be carried out in the emergency setting within a research framework, with the parents subsequently being given the option of determining whether the data collected can be used for research purposes (retrospective informed consent).[91] The requirement here would be that the measure was taken in the child's best interests, with primarily therapeutic intent. However, if the measure is of an experimental nature, the therapeutic gains are highly uncertain, and no standard treatment is available, the parents' permission should be sought in advance, even if this cannot – for reasons of time – meet the standard of informed consent. Here, likewise, the option of subsequently withholding data collected for research purposes would have to be available. In Situation 3, parental consent should always be obtained.

4.14 Placebo-controlled research

Placebo-controlled, double-blind trials are regarded as the gold standard for assessing the efficacy of a new drug or a new therapeutic measure. In a placebo-controlled trial, a placebo (inert substance) is administered to one group of patients (the control group). A double-blind trial is one in which neither the subjects nor the investigators know who receives the active substance and who receives the placebo. A placebo effect is a positive response observed in a subject who has received the inert substance. This effect is based on the benefits associated with receiving treatment and thus care and attention from medical and nursing staff. A placebo effect is experienced by 35% to 75% of all study participants.[92] In a trial, knowledge of the placebo effect can help to identify the true pharmacological effects of the medical intervention under investigation.

Placebo-controlled trials are generally considered to be ethically acceptable if no proven standard prophylactic, diagnostic or therapeutic intervention currently exists, or if a study concerns minor conditions, where any adverse consequences of non-treatment would be negligible.[93] In such cases, the placebo treatment is equivalent to the experimental treatment (therapeutic equipoise). Some bioethicists go further, considering placebo controls to be ethically required whenever new therapeutic agents and methods are tested, since – from the perspective of evidence-based medicine – placebo-controlled studies produce the most scientifically sound results. However, the use of placebos in studies involving paediatric populations raises particular problems, which necessitate more stringent conditions.

Firstly, children lack the cognitive abilities required to understand the highly complex design and aims of a placebo-controlled trial. Studies have shown that even adult subjects find it difficult to grasp that a trial in which they are participating is not pursuing therapeutic goals, but research interests – focusing not on their "best interests", but on the generation of knowledge. This so-called "therapeutic misconception",[94] together with the misunderstanding of terms such as "randomization", "placebo" and "double-blind", often persists even after subjects have been fully informed. In children, this problem is exacerbated, owing to their intellectual immaturity. Even in a placebo-

[91] Cf. Gill et al. 2003.

[92] Cf. Berg 2005, 295.

[93] Declaration of Helsinki, Article 32, Cf. www.wma.net/e/policy/b3.htm (last accessed: 20 November 2008). However, as pointed out by the European Agency for the Evaluation of Medicinal Products (EMEA) and the Committee for Proprietary Medicinal Products (CPMP): "Forbidding placebo-controlled trials in therapeutic areas where there are proven prophylactic, diagnostic or therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest as there is a need for both new products and alternatives to existing medicinal products." (EMEA/17424/01, 2001. EMEA/CPMP Position statement on the use of placebo in clinical trials with regard to the revised Declaration of Helsinki http://www.emea.europa.eu/pdfs/human/press/pos/1742401en.pdf).

[94] Appelbaum et al. 1982 and 1987.

controlled trial posing no risk to their health, the limited intellectual capacity of children means that they are more likely to suffer an injustice, namely whenever they labour under the misapprehension that they are receiving an active substance. However, this would be a breach of the investigators' duty of honesty towards children and could possibly lead to a subsequent loss of confidence in the healthcare system.[95] Such misunderstandings should be prevented as far as possible through child-friendly explanations.

Secondly, the participation of children in placebo-controlled trials depends on decisions made by their parents or legal representatives. However, parents may also have difficulty in understanding the research protocol. In addition, given the lack of a standard treatment, they are highly concerned about their child and may be inclined to underestimate the risks. This means that their decision will not necessarily be in the child's best interests. In assessing placebo-controlled trials, ethics committees would need to pay special attention to the risks involved.

Finally, mention should be made of a problem which, though it concerns all placebo-controlled trials, is especially relevant to research involving children. It is difficult to determine whether an existing treatment is of "proven efficacy", removing the need for a placebo-controlled trial. Particularly in paediatrics, the efficacy of many standard treatments has not been tested in clinical studies, and many drugs are prescribed off-label. However, despite the need for research, caution is required in the use of placebo-controlled trials. Non-administration of medication, e.g. in the field of psychopharmacology[96] or antihypertensive therapy,[97] may involve high risks. The NEK-CNE is convinced that priority must always be accorded to the welfare of children participating in trials, rather than to research interests.

5 Key conclusions

A) There is an ethically justified demand for research involving children

Children require special protection because they are particularly vulnerable. The question arises whether this need for protection is even compatible with the conduct of research involving children. The immediate aim of research interventions is not to advance the welfare of the research subjects. When children are involved in a study, they serve to generate valid insights for the purposes of the study. What is characteristic of scientific knowledge is that it can be generalized beyond individual cases. Accordingly, research involving children requires ethical justification. The question is whether and on what grounds it can be justified.

On the one hand, children are inherently vulnerable. This vulnerability includes their dependence on the adults who take care of them. While adults make decisions that affect children, they cannot or cannot always involve them in these decisions, in the sense of obtaining voluntary informed consent. Children, at least while they are young, cannot themselves fully assess the situation in which they are placed by a study. Their capacity to evaluate certain aspects of the situation increases as they develop and therefore requires appropriate consideration. In addition, children are both physically and mentally vulnerable and have their own particular needs. A special need for protection also arises from children's unique individual constitution, situ-

[95] Cf. Berg 2005, 305f.

[96] Cf. Scahill et al. 2008.

[97] Cf. Flynn 2003.

ation and biography, which must also be taken into account when considering the justifiability of research.

On the other hand, children are disadvantaged if scientific knowledge concerning this age group is deficient (cf. Section 2 above).

The application of evidence-based medicine also calls for more research on the use of drugs in children of various ages. This is required in particular for drugs that are new or newly prescribed for children.

In everyday medicine, in both hospital and practice settings, many drugs are prescribed to children in doses corresponding to those used in adults, i.e. in proportion to the child's body weight. Insufficient attention is paid to the absorption and metabolism that are specific to the child's stage of development. Such empirical use of drugs may well be appropriate in the case of familiar medicines, but it no longer meets current requirements for treatments in the case of newly developed products.

Qualitative and quantitative social scientific and psychological research involving children should be assessed by different criteria than pharmaceutical research. For example, an evaluation of qualitative research must consider to what extent it can accommodate and give a voice to the actual experience of the research subjects, while avoiding prejudiced interpretations. An improved knowledge of children's needs, cognitive and emotional development, and social behaviour is certainly indispensable if children's adult-made life-worlds are to be improved. In medicine, qualitative social scientific research can also be helpful in giving children a voice in discussions about the design of treatments.

It would, however, be wrong for these arguments in favour of research involving children to be weighed against any harm suffered by children participating in studies. The correct approach is to design studies in such a way that children receive appropriate protection, ensuring that they are not harmed by the research. The NEK-CNE is therefore convinced that it would not be ethically acceptable vis-à-vis children to forgo research that involves or concerns them.

If a child is seriously ill and there is no other way of providing effective help than by administering a drug of unproven efficacy in a study setting, it may be acceptable to take this risk following an assessment of the individual case. This applies both to the conduct of a study and to the decision to include a specific subject. As well as the risks, however, the inevitable burdens associated with the intervention are to be assessed.

To be distinguished from the above are research situations outside the therapeutic context, in which an intervention is not designed to relieve a child's suffering or avert a threat but may produce a benefit of another kind. This may give rise to a different basis for ethical justification.

In both cases, the following is to be noted: the benefits that may arise for other children in a similar situation cannot be adduced to justify from an ethical perspective the risks or burdens for the individual concerned. This is a consequence of the principle of each child's personal integrity. It must be protected for its own sake and must not be the object of utilitarian calculations. Human dignity requires that individuals are never to be treated merely as means, but always also as ends in themselves.

B)
In "therapeutic" research involving children, benefits/ burdens and opportunities/ risks must be appropriately balanced for the individual child concerned.

The risks and the therapeutic benefits of research for the child must be appropriately balanced. It is difficult to calculate the benefits of a research intervention for a child precisely, as the outcome of research is always open, i.e. it is carried out in order to fill gaps in knowledge. The anticipated therapeutic benefit must be inferred from earlier study phases. If the therapeutic benefit anticipated is substantial, no suitable alternative treatments are available and the patient's condition is serious, greater risks may also be acceptable.

The determination of acceptability and the weighing-up of opportunities and risks is a task calling for the involvement of a child's parents or other legal representatives in an informed consent procedure. The child itself – being the individual most directly concerned, who will subsequently have to live with the consequences – must also be acknowledged and respected in this process. As far as possible, therefore, the child should also be involved.

C) Research with no direct benefit to the child is not to be ruled out on ethical grounds, but it calls for the utmost caution. The requirement that risks and burdens in research projects without the prospect of direct benefit should be no greater than "minimal" is to be interpreted in the sense of "reasonableness" for the children concerned.

The central ethical challenge raised by research in children is to assess the conditions under which children may be involved in research projects offering benefits, not for the individuals concerned, but for others. Whether "non-therapeutic" research can be ethically justified at all depends on whether a satisfactory solution can be found to this question. Under what conditions is it permissible for a child to participate in a project that does not serve its own (enlightened) interests?

The matter is relatively straightforward in cases where the research is not burdensome from the child's perspective and does not pose any significant risks. This will be the case with most social scientific and psychological research. Examples of risk- and burden-free research are also conceivable in the medical field – anonymous evaluation of patient data, or systematic documentation of investigations or treatments that are justified on other grounds and would have been performed anyway.

More difficult are research projects where a certain burden or risk cannot be ruled out. If interpreted in quantitative terms, the frequently used formula "minimal risk" or "minimal burden" can be misleading. After all, risks and burdens are not experienced as measurable quantities by the child concerned.

Comparisons with "risks encountered in daily life" fail, partly because some of the risks accepted there are very high, and partly because some of these risks are faced involuntarily, without being recognized as acceptable. Thus, the risks associated with road traffic are not to be used for purposes of comparison, since parents do not voluntarily expose their children to these risks (i.e. they are unavoidable).

The Commission prefers to speak of the reasonableness of the risk or burden. For if a risk or burden has to be "reasonable", the ethical question arises in each individual case: is this specific risk or burden reasonable for this particular child in this particular situation? Here, reasonableness also depends on the aims and design of the study. If a risk/burden is deemed to be reasonable, one can ask for the reasons that apply in this specific case. The assessment is not based on a general standard, or rather the general standard specifies that the assessment has to consider the individual case.

The Commission therefore recommends that the "minimality" requirement, as found in various regulations, should be interpreted in the sense of reasonableness, and those concerned should ask whether this child can reasonably be exposed to this risk and this burden.

The consequence is that there is no generally definable level of risk or intensity of burden that is held to be acceptable. The determination of reasonableness must be undertaken on a case-by-case basis by the persons responsible for the child's welfare – in particular, the parents or legal representative. Assessing what is reasonable in a specific case calls for judgement and keen intuition. For the person making the assessment, the following aspects and questions may be relevant:

- Can I explain to the child what the research will involve?
- Has the child already had similar experiences and found them acceptable? For example, has it learned that a needle prick is only painful for a short time?
- Comparisons will be needed, but they will have to be comparisons with something as similar as possible (e.g. a prick with a prick or a comparable pain)
- The subjective perspective on the intervention is crucial.

The parents play an important role in the communication that leads to an assessment of reasonableness. They are responsible not only for giving consent, but also for evaluation and assessment. The competent ethics committee must assess whether, from its viewpoint, it is reasonable for children that parents may possibly consent.

The aim of this explanation is to facilitate interpretation for practical purposes of the legal standard of minimal risks and minimal burdens. It remains for legislators to clarify the question of whether it would also be better for the Human Research Act to refer explicitly to "reasonableness" "or giving no cause for concern".

For research with no direct benefit to the child, as well as the criterion of reasonable risks and burdens, the condition of subsidiarity must be satisfied, and voluntary informed consent must be given by a legal representative. In addition, the child must not be forced to participate in the research project, but must be able to refuse. The child's desire not to participate must be respected, even if it is incomprehensible or not rationally justified: being forced to participate in research is itself a burden and may produce adverse psychological effects in the child. It undermines the child's confidence in its parents or legal representatives and in healthcare professionals. Exceptions may be made in cases where non-participation in a study would be seriously detrimental to the child.

A general prohibition on research offering no direct benefit to the child is not ethically justifiable, since it is only with the aid of such research that a variety of needs which are self-evident among children can be addressed. Examples can readily be cited in the fields of developmental psychology, educational research (school/didactics), or anthropological and sociological research on the realities of life for children in disadvantaged situations. This would include, for example, research on the particular sensitivity of children to anthropogenic environmental degradation.

D) Not every use of drugs in children necessarily requires a clinical trial. Drug use is also justified by long-term therapeutic experience in clinical practice.

A drug that has been used successfully for decades in the treatment of children is not to be handled like a new drug, even if it has never been studied in accordance with the criteria of evidence-based medicine. It would not be desirable for such proven drugs and treatment methods to have to be additionally tested on children in trials so as to meet regulatory requirements. Practical experience and evidence may sometimes be considered equivalent to a clinical trial. However, this does not rule out a systematic, retrospective review of experience in clinical practice.

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