Evaluation of risk in research with children – it’s time to clear the misconceptions

Original article

Abstract

The current discussion on research with persons incapable of consent and consequently on research with children is obscured by four misconceptions. The «therapeutic misconception», by maintaining the notion that the primary goal of a research project does either include direct benefit to participants or not, obscures the fact that the primary purpose of research is not to benefit participants but to generate knowledge, and the ethical postulate that research must never put children at risk of serious harm, irrespective of whether it is performed in a context of patient care or not. Avoiding this and three additional misconceptions allows a unified and pragmatic approach to risk evaluation in all types of research involving children. Its cornerstone is the comparison of the likely outcome for participating children with the outcome for eligible non-participants in the light of the following conditions: research participation must not place the child at a net risk of serious harm, and the physical and psychological discomfort entailed by the study has to be readily tolerable according to the judgement of reasonable parents.

Keywords: Research ethics; research with children; risk evaluation

The debate on the necessity and the permissibility of research with children, which has been ongoing in the industrialised world for some time, has recently reached a new acuity in Switzerland. Within the same year in 2008 we have noted on the one hand that federal and international authorities have organized an international conference in Berne, promoting the conduction of clinical trials in children under the title «Better Medicines for Children – The Way Forward» (1), and on the other hand that a group of members of the Swiss parliament has proposed to inscribe a ban on research without direct benefit involving persons incapable of consent into the federal constitution (2).

In my opinion the debate on research with persons incapable of consent and in consequence with children is clouded by a set of widely held misconceptions. These preclude an unbiased view of the ethical and practical problems inherent in present day research with children for regulatory authorities, politicians and the public. In the following article I will try to analyse and dissolve these misconceptions and present a proposal for a unified and pragmatic approach to the evaluation of risk in any research involving children.

The therapeutic misconception

When research is performed in the context of medical treatment, the participating patients – and, not so rarely, also physicians and investigators – are under a strong psychological bias leading them to confound the purposes of the clinical study with the goals of their treatment. This therapeutic misconception has been described by Appelbaum and colleagues in psychiatric patients and shown to be quite resistant to explanations to the contrary (3). It seems to be very difficult to make the idea understood that the primary goal of research is never and can never be to provide an immediate benefit to the individual participants in clinical studies. On the contrary, as research aims to produce generalizable knowledge, it has to abstract from the individual needs of the patient. The primary beneficiary of research is not the patient but the scientific community and society as a whole, while the primary beneficiary of treatment must remain of course the patient. The therapeutic misconception is very understandable through the fact that, in clinical studies, participants who are also patients are investigated and at the same time treated by investigators who are also in charge of therapy. This conflation of the two relationships, investigator – research participant, and physician – patient, in the same persons and even sometimes in the same acts makes a clear distinction between them difficult. Nevertheless from a conceptual point of view this distinction is not only possible but, for an adequate ethical evaluation, mandatory. Risks and benefits derived from participation in research must be separated from those inherent to therapy. In practice, in this analysis it is useful to start from the primacy of the therapeutic relationship and to consider the research engagement as an add on. The patient has to be treated anyhow, whether he participates in research or not. The evaluation has therefore to compare the risk benefit balance between research participation and treatment outside the study. Only the diagnostic and therapeutic procedures and prescriptions restricted to study patients which are not used in the care outside of the study enter the risk benefit balance for research participation.
Unfortunately such a differentiated approach to the evaluation of research in the context of patient care has not prevailed during the past decades. On the contrary, the pervasive nature of the therapeutic misconception has led to an almost universal acceptance of a global distinction between «therapeutic» and «non-therapeutic» research or between research with direct or immediate benefit for the participant and research without such benefit. This distinction figures most prominently in the so-called Biomedicine Convention of the Council of Europe (4) and is also applied in the guidelines of the CIOMS (5). It is interesting and quite illustrative for the deeply ingrained nature of the therapeutic misconception, that the recent publication on research involving children by the Swiss National Ethics Committee criticizes the distinction between «therapeutic» and «non-therapeutic» research in the chapter on terminology but nevertheless uses the distinction between research with and without direct benefit throughout the rest of the paper (6). Unfortunately Switzerland is currently undergoing to enshrine this distinction in the federal constitution.

On the other hand, the distinction between «therapeutic» and «non-therapeutic» research has had its critics for many years already (7); the World Medical Association abandoned the distinction in its 2000 revision of the Declaration of Helsinki but reintroduced it into one sentence of the latest version of 2008 (8). Obviously, the negative consequences conferred by the application of this dichotomy are more easily appreciated by physicians directly involved in clinical research than by regulatory authorities or the public. In so called therapeutic research, fully informed consent and optimal protection from research related risks can be hampered by the therapeutic misconception (9). For «non-therapeutic» research the risks of many completely innocuous studies in physiology, pathophysiology or epidemiology tend to be overemphasized because they are grouped together with research on experimental procedures involving human subjects (10). In France, the practical difficulties in rigorously applying this distinction, which is far from obvious in many studies combining different therapeutic and diagnostic elements, have apparently led to considerable obstacles for legitimate research (11).

The fact that, on conceptual grounds, research can never have the benefit of the individual participant as its primary objective does not, of course, preclude study subjects from deriving a range of benefits from their research participation. These various possibilities for benefit arising as side effects rather than study goals from research projects have been described elsewhere (12). Abandoning the therapeutic misconception does not mean disregarding these benefits but, for every study, to weigh them individually against the specific risks of research. This is far more meaningful than to maintain an arbitrary dichotomy, where on the one hand, apparently more than «minimal risk» from research participation should be allowed in «therapeutic» research, while on the other hand «non-therapeutic» research is regarded as suspect and placed under severe restrictions or even a complete ban for children and other persons incapable of consent.

There is no good reason, why the net risk-benefit-balance for research participation versus non-participation should be different for a child with a life-threatening disease eligible for an experimental treatment or a healthy child asked to participate in a research project. Of course absolute risks and benefits differ widely between these two cases, but there is no justification to put either of the children at a significant net risk derived exclusively from research participation.

The «standard therapy is safe – research is dangerous» misconception

In an ideal medical world, one or more standard therapies with known benefits and risks would exist for each disease. Unfortunately, in everyday medical practice, and especially in pediatrics this is the exception rather than the rule. There is a widespread lack of data on many therapies applied in everyday practice (13) and the use of unlicensed and off label drugs is very common in Switzerland (14) and in other countries (15). In view of this there is often little reason to consider standard therapy as safe and research as a departure towards unknown dangers and unproven benefits.

Traumatic experiences from the past, with thousands of babies severely harmed by the application of unproven therapies such as uncontrolled oxygen application for premature babies or therapy with sulfisoxazole in newborns with jaundice (16), have led paediatricians to consider treatment within research trials as the safer alternative in many instances. In paediatric oncology inclusion into a research protocol has become the standard of care, and treatment outside a current study protocol occurs far more often because the patient is not eligible for the study than because of lack of parental consent.

Especially difficult are situations where no satisfactory standard treatment for a disease exists but innovative approaches appear hopeful. Paragraph 35 of the declaration of Helsinki (8) stipulates for these cases: «In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.» Contrary to a widespread intuition, especially among non-physicians and non-patients, the declaration does not consider the innovative treatment to be motivated by a research interest but by the desire to help the individual patient. Research is recommended for these cases in order to make the innovation available to other patients. Whether an innovative treatment is applied within a research context or isolated on an individual basis, two premises must be respected in the same way: Informed consent by the patient or in the case of children by the parents or legal guardians must be obtained and a very careful analysis of the expected risks and benefits of the planned intervention must be car-
ried out. Whereas for a research project evaluation by an Ethical Review Committee is mandatory, this is not the case for an innovative approach in an individual patient. On a voluntary basis a clinical ethics consultation can be sought for an independent opinion. From the standpoint of scientific progress it would be preferable that most innovative treatment would be carried out in a research context and its results could be published. To realize this goal it would be important to have review procedures adapted to the special circumstances. The administrative burdens required to pass a large drug trial through ethical review are easily handled by drug companies but may possibly deter individual innovative physicians who want to test a new idea in a few selected patients. Clinical studies currently undertaken in children differ widely as to the extent to which standard therapy is altered by study participation. Trials testing an entirely new therapeutic approach are in a small minority, whereas a great number of studies deal with improvements in standard therapy and carry little, if any, research related risk for the patient. A good example for this study type is the systematic comparison of two standard treatment approaches, which outside of the research context are used at the discretion of the physician. Also in this situation, adapted requirements for ethical review and registration at the drug regulation authority would be very helpful. On this subject, the European Science Foundation has recently issued an interesting position paper proposing a «risk-based» approach to the regulation of investigator-driven clinical trials (17). Abandoning the «standard therapy is safe – research is dangerous» – misconception would mean recognizing, that in the same way as standard therapies differ widely in their proven efficacy and safety, clinical studies differ in the risks they confer to study participants. Just as it would be unwise to trust all standard therapies as safe, it is unreasonable to regard all clinical research as inherently dangerous and to apply the same severe administrative regulations irrespective of the actual risks a study confers.

The conflation of risks and burdens and the minimal risk standard

Whereas the first two misconceptions treated in this article concern an inadequate dichotomy, the next subject is the frequent failure to consider a relevant distinction. When speaking of potential negative consequences of research, the declaration of Helsinki always uses the terms «risks and burdens», but does not explain the difference between the two, except for the mention in paragraph 32, where risk is qualified as «risk of serious or irreversible harm» (8). In my opinion a clear distinction between risks and burdens is paramount for an adequate ethical evaluation of research involving children. Under «risk» I understand the danger to incur serious harm, permanent impairment or death as an unintended complication of research participation, whereas by «burden» I mean any negative physical (e.g. pain, nausea, physical strain, restriction of movements etc.) or psychological (e.g. fear, embarrassment, separation etc.) experience of a transient nature inherent in study participation.

The enormous difficulties of attempting to classify all negative consequences of research in a unified approach along the two axes of likelihood of harm and magnitude of harm is illustrated by the ongoing debate on the application of the federal minimal risk standard in paediatric research in the United States of America (18). The recommended approach is to multiply the likelihood and the magnitude of harm and compare the result to risks encountered by children in everyday life (19). However, Ethical Review Committees have encountered considerable difficulties in determining which interventions represent a minimal risk or a minor increase over minimal risk and differ widely among themselves in their judgement (20). The difficulties derive from two main problems. First, the concept of comparing risks for serious harm of very low likelihood directly to risks for minor or moderate harm of higher likelihood may be mathematically correct but it is very difficult to handle for the intuitions of moral judgement. Can a very small increase in the likelihood of death be compared to an almost certain but small increase in discomfort of limited duration? The second difficulty is the necessity of an absolute standard of minimal risk to compare research risks with. The «risks of daily life standard» has been criticised on several grounds (6) but alternatives encounter similar difficulties (20) as long as the conflation of risks and burdens and an absolute standard for acceptable risk is maintained.

These difficulties could be avoided by evaluating risks and burdens separately and to compare them not to an absolute standard but to the situation for eligible persons not participating in a given study. In my opinion children should never be exposed knowingly to risks of permanent serious harm for the sake of research whereas it is morally acceptable to let them suffer from limited discomfort for the obtaining of beneficial insights pertaining to the health of children that cannot be procured in another way. The distinction between risks and burdens is also very pertinent to questions of assent to study participation. Whereas children are not able to judge risks of serious harm until up to a rather advanced age, their capacity to assent to enduring a moderately unpleasant procedure matures much more rapidly.

The «use as a means for the benefit of third parties» misconception

People who want to ban or severely restrict «non-therapeutic» research involving children proffer the Kantian prohibition to use a human being solely as a means to the ends of other persons as their main argument. If a research project would offer no individual benefit to a child, she would be used in this project only as a means to the benefit of third parties and not be respected as an end in herself and thereby her human dignity would be disrespected (21). This argument is compelling against abuse, where vulnerable subjects, such as children, are deliberately exposed to risk of serious harm to the benefit of other persons, e.g. the investigators or society as a whole. However, against biomedical research, as it is currently practised with children, the argument is inappropri-
A unified and pragmatic approach to risk evaluation

Avoiding the misconceptions described above, any research project involving children can be evaluated by a unified and pragmatic approach. For this evaluation the following points are important:

1. For the eligible children as a group and for each individual child the most likely outcome with research participation must be compared directly to the most likely outcome outside of the study.

2. Risk, i.e. the likelihood of serious harm, permanent injury or death, must be evaluated separately from burden, i.e. foreseeable physical or psychological discomfort derived from study participation.

3. The net risk of serious harm, permanent injury or death for a given child participating in the study must never be higher than the risk a child faces if she does not participate, but it can of course be lower.

4. The burdens placed on children by study participation must appear readily tolerable according to the judgment of a reasonable parent acting in the child’s best interest.

5. Study protocols must ensure that the developing autonomy of the child is respected and the child is allowed to decline or withdraw from study participation.

6. The evaluation has to be performed both at a group level by the Ethical Review Committee and at an individual level by the consenting parent or legal representative, in the case of research in the context of patient care together with the treating physician.

Of course, a favorable risk evaluation alone is not sufficient to make conducting a research project with children ethically acceptable. It has also to be scientifically valid with regard to research questions and methods applied, and to offer the prospect of gaining valuable insight into questions relevant to children’s health, which could not be obtained in a way not directly involving children.

The apparent simplicity of this approach should not obscure the fact, that in practice a comprehensive analysis of risks and burdens of a given research project is not always easily achievable. But the difficulties no longer lie in theoretical misconceptions but in the difficulties of estimating likelihoods and magnitudes of possible risks, benefits and burdens of individual study procedures. The crucial questions that have to be answered positively by the ethical review committee in order to allow parents to give consent to participation of their children in a given study are simple:

1. Is the study safe for participating children and does it not put them at the danger of serious harm?

2. Would a reasonable parent expect that the burdens imposed by the study are readily tolerated by the children?

However, these questions cannot be addressed by regulations but have to be answered individually for every study by persons with adequate scientific and moral expertise and intimate experience with the particularities of children.

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Résumé

Evaluation du risque de la recherche impliquant des enfants – il est temps d’abandonner les fausses idées

La discussion actuelle sur la recherche impliquant des personnes incapable de consentement est obscurcie par quatre idées fausses. En maintenant l’idée que le but primaire d’un projet de recherche doit soit impliquer un bénéfice direct pour les participants, ou non, le « malentendu thérapeutique » empêche de voir le fait que le but primaire de toute recherche n’est jamais d’apporter du bénéfice au participants mais de gagner des connaissances, ainsi que le postulat éthique que la recherche ne peut jamais exposer des enfants à un
Risikoevaluation in der Forschung mit Kindern – Es ist an der Zeit, falsche Annahmen zu verlassen

Die aktuelle Diskussion über Forschung mit Personen, die unfähig zur Zustimmung sind, und damit über Forschung mit Kindern, wird durch vier falsche Annahmen behindert. Dadurch, dass das «therapeutische Missverständnis» davon ausgeht, dass das primäre Ziel eines Forschungsprojektes entweder einen direkten Nutzen für die Teilnehmenden beinhaltet oder nicht, verstellt es den Blick erstens auf die Tat- sache, dass der primäre Zweck von Forschung nie ist, den Teilnehmenden zu nützen, sondern Erkenntnis zu gewinnen und zweitens auf das ethische Postulat, dass Forschung beteiligte Kinder nie der Gefahr einer ernsthaften Schädigung aussetzen darf, unabhängig davon, ob sie im Kontext von Patientenbetreuung durchgeführt wird oder nicht. Wenn diese und drei weitere falsche Annahmen vermieden werden, kann für alle Typen von Forschungsprojekten mit Kindern ein vereinheitlichter und pragmatischer Zugang zur Risikoevaluation gewählt werden. Der entscheidende Punkt ist dabei der Vergleich zwischen den wahrscheinlichen Folgen für Kinder, die an der Studie teilnehmen, und den Folgen für Kinder, die für die Studie in Frage kommen, aber nicht eingeschlossen werden. Für diesen Vergleich sind die folgenden Bedingungen massgebend: Die Teilnahme am Forschungsprojekt darf für das Kind kein Nettorisiko einer ernsthaften Schädigung beinhalten und die forschungsbedingten, unangenehmen körperlichen oder psychischen Erfahrungen müssen, nach dem Urteilsvernünftiger Eltern, dem Kind gut zugekommen werden können.

Zusammenfassung

Risikoevaluation in der Forschung mit Kindern – Es ist an der Zeit, falsche Annahmen zu verlassen

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L'éthique de la recherche s’est développée comme une branche spécifique de la bioéthique dès les années soixante. Elle se construit sur un large éventail de documents de référence dont la déclaration d'Helsinki constitue la pierre angulaire. Mais elle a également été complétée par une réglementation et un ensemble de normes légales au niveau national et international. Même si la Suisse ne dispose pas d’une loi spécifique relative à la recherche impliquant des êtres humains, preuve en est le débat actuel visant à adopter une disposition constitutionnelle en la matière, il serait faux de conclure à l’absence de droit et de règles sur le sujet. Au contraire, l’éthique et la réglementation de la recherche souffrent sans doute aujourd’hui davan
tage d’une pléthore de normes de référence que d’éventuelles lacunes de son cadre normatif. La principale difficulté consiste ainsi, surtout, à harmoniser les normes existantes et leur mise en œuvre plutôt qu’à développer des règles originales pour répondre à des questions nouvelles. Une autre difficulté, évidemment, est de maîtriser ce système complexe en connaissant sa structure et ses différents éléments avec leur valeur propre et leur portée spécifique. A observer certains, pratiquer l’éthique de la recherche consiste ainsi trop souvent à développer des arguments en se servant de nombreuses références ciblées, mais disparates, puisées dans autant de documents nationaux et internationaux, connus ou moins connus. Les principes de base sont ainsi parfois oubliés, au profit d’un formalisme que ne renieraient pas certains juristes. La formation et l’expérience permettent toutefois de limiter le risque de dérives.

On notera ainsi que l’ordonnance sur les essais cliniques de médicaments (OClin) exige depuis 2004 que les chercheurs justifient d’une formation ou d’une expérience suffisante en matière de bonnes pratiques des essais cliniques (art. 8 al. 1 lit. b). Cette exigence s’applique également aux membres des commissions d’éthique de la recherche (CER) selon l’art. 31 OClin. Entrées en vigueur depuis 5 ans, ces dispositions impliquent que des formations spécifiques soient offertes aux investigateurs et aux membres de CER. Différents programmes existent, du simple séminaire de 1 à 2 jours, à des formations académiques pouvant être étalées sur deux ans. Cela n’est cependant pas sans poser problème au vu des agendas surchargés des uns et des autres.

Il est intéressant de noter à propos des membres des CER en Suisse, qu’interrogés sur leur degré de formation en éthique et réglementation de la recherche, ils ne sont que 58% à indiquer avoir suivi un cours ou l’autre en la matière. Pour la plupart (89,5% des répondants), leur formation a consisté dans la participation à des séminaires, le plus souvent de 1 à 2 jours. Ces chiffres sont tirés d’une enquête sur les besoins en formation dans le domaine de l’éthique de la recherche bio-médicale réalisée en 2007–2008 en Suisse, ainsi qu’au Mali, au Cameroun et en Tanzanie. Il s’agissait d’évaluer les besoins et les attentes des membres des CER par rapport à leur activité avec pour objectif de développer une formation en ligne qui permette justement de les satisfaire de manière ciblée. L’ensemble de cette démarche s’inscrivait dans le projet

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**Point de vue**

**Formation de base en éthique de la recherche: retour aux sources avec le projet TRREE**

Dominique Sprumont

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