Non-therapeutic research with minors: How do chairpersons of German research ethics committees decide?

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ABSTRACT:

OBJECTIVES: Clinical trials in humans in Germany – like in many other countries – must be approved by local research ethics committees. The current study has been designed to document and evaluate decisions of chairpersons of research ethics committees in the problematic field of non-therapeutic research with minors. Our purpose was to examine whether for chairpersons non-therapeutic research was acceptable at all and whether there was certainty on how to decide in research trials involving more than minimal risk.

DESIGN: In a questionnaire, chairpersons of research ethics committees had to evaluate five different scenarios with (in parts) non-therapeutic research. The scenarios described potential, but realistic research projects with minors involving increasing levels of risk for the research participants. The chairpersons had to decide whether the respective projects should be approved.

SETTING: 49 German research ethics committees (return: 29 questionnaires).

PARTICIPANTS: Chairpersons of research ethics committees.

MAIN MEASUREMENTS: Approval or rejection of research scenarios.

RESULTS: Chairpersons of German research ethics committees generally tend to accept non-therapeutic research with minors if the risk for the participating children is supposedly low. If the risk is clearly higher than “minimal”, the chairpersons’ decisions differ widely.

CONCLUSION: The fact that there seem to be different attitudes of chairpersons to non-therapeutic research with minors is problematic from an ethical point of view. It points to a general uncertainty about the standards of protection for minor research participants in Germany. Therefore, further ethical and legal regulation of non-therapeutic research with minors in Germany seems necessary.

KEY WORDS: non-therapeutic research, minors, German research ethics committees
Ethical and legal regulations of clinical trials in Germany

For the last ten years in Germany, so-called non-therapeutic research with study participants not competent to consent has been a target of passionate criticism. For example, in 1997, the so-called “Eisingen Case” caused a stir when a trainee of the St. Josef’s Home for the Handicapped in Bavaria blew the whistle on human genetic research with mentally handicapped inmates that had taken place without informed consent or proxy consent. A doctoral candidate from the Institute for Human Genetics of the University of Wuerzburg had taken blood samples of 179 residents without informing the persons concerned nor their parents or legal custodies (Doerner & Spielmann [1]). Criticism focussed not only on the lack of consent but also and predominantly on the alleged immorality of research without potential direct benefit.

The public reaction was fuelled by a debate in Germany on the European Convention on Human Rights and Biomedicine, in particular on article 17 of the convention which deals with the “Protection of persons not able to consent to research.” Human rights activists objected to the permission of minimal-risk research with the non-competent. The churches and organizations for the disabled, in particular, warned against a deterioration of existing ethical and legal standards in Germany, should the convention be ratified. Moreover, for the same reason the revision of the Helsinki Declaration on Human Research (Edinburgh 2002), which allowed for this type of research, was received critically by German lawyers as well as the public (cf. Taupitz [2]). It is doubtful, however, whether Germany has reached high standards in the ethical and legal regulation of medical research (cf. Wiesemann [3], Wiesemann & Dahl [4]).

As in most industrialised countries, in Germany clinical trials involving humans must be approved by a local research ethics committee. The relevant law on the approval of prescription drugs (Arzneimittelgesetz/AMG) demands that researchers ensure the safety of participants in clinical testing. The law regulates clinical testing according to basic standards
in medical ethics: minimization of risks for study participants, informed consent, and good clinical practice. In addition, clinical research with minors has to fulfill the following requirements: the drug in question is designed for the diagnosis or therapy of pediatric diseases, clinical trials with adults are not expected to yield adequate results, and parents, and, if possible, the child, too, have to consent to study participation. However, the provisions in the AMG have been criticized for not being precise and detailed enough. It remains unclear, for example, whether the law allows for non-therapeutic research in minors or not (for a critical appraisal of this type of research see Nicholson [5], Brock [6]).

Further regulations are to be found in a statement of the “Central Ethics Commission” (Zentrale Ethikkommission) at the German Federal Medical Council “On protecting non-competent persons in medical research” (Zentrale Ethikkommission [7]). According to these guidelines, minimal risk or burden in certain cases of non-therapeutic research may be acceptable even for vulnerable groups. Only if a vulnerable person shows significant unwillingness to participate in a study, research has to be stopped. However, the status of these recommendations is unclear, since they might be in conflict with the existing laws. This situation creates a remarkable amount of uncertainty for the public as well as for research ethics committees.

The research ethics committee at Goettingen University, for example, in 2002 received a total of 13 research protocols dealing with minors. 11 of the 13 protocols had elements of non-therapeutic research. So far, little is known about decisions German research ethics committees actually make in the case of non-therapeutic research with minors: How do chairpersons decide in these cases? Are they willing to accept studies with no direct benefit for the participants? Which type of risk do they think is acceptable in research with minors?

In the present study, we do not intend to present an ethical solution for the problems involved. We are well aware of the fact that a normative problem cannot be tackled by analyzing empirical data. However, we want to examine how those ultimately responsible for the ethical
evaluation of research with minors in Germany decide and whether their answers show ambiguity or certainty in decision-making. We will also compare their answers to what is internationally perceived as acceptable risks. Our results will show whether German ethical standards in non-therapeutic research can in fact be judged to be comparatively high.

Description of the study design

In order to answer the questions mentioned above, a research group at Goettingen University designed an empirical study to assess the decisions of chairpersons of German research ethics committees in case of non-therapeutic research with minors. In accordance with Kopelman [8: 2293], by non-therapeutic research we understand study elements performed to seek “generalizable knowledge and not intended as therapy to benefit the individual directly”. 49 chairpersons of research ethics committees were contacted and asked to complete a questionnaire. In the questionnaire we asked for an evaluation of five realistic research scenarios, all examples of non-therapeutic research in paediatrics or child psychiatry with no direct benefit for the children concerned (Table 1). The risk and burden involved for the study participants gradually increased from scenario 1 to 5 (see Table 1). We recorded 35 reactions (71%), 29 questionnaires were filled out and sent back (59%). 90% of those who answered were men, 53% were older than 60 years, and 40% were between 41 and 60 years old.
90% of the respondents were medical doctors, 21% of whom worked in the field of paediatrics. 73% of the respondents had extensive experience in the field of decision-making in research ethics committees, i.e. they had taken part in more than 50 meetings of a committee; another 24.3% had participated in at least 10 to 50 meetings. 93% of the respondents had children of their own.

We asked whether the research scenarios depicted would be evaluated positively by the chairperson (“Do you think the study is justifiable and would you support a positive decision of the research ethics committee?”) For their answers, the respondents had four options: “Yes, without restrictions”, “Yes, with restrictions (please explain)”, “I don’t know / I have no opinion” and “No, under no circumstances”.

<table>
<thead>
<tr>
<th><strong>Table (1): Research Project Scenarios</strong></th>
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<tr>
<td>(1) Using an additional 5 ml blood from a blood sample primarily drawn for diagnostic / therapeutic reasons.</td>
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<tr>
<td>(2) Various tests with healthy children: neurological examination, electroencephalogram, hearing test, questionnaires (duration: 7-8 hours over a period of 3 days).</td>
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<td>(3) Additional myocardial biopsy in the course of a heart operation performed for therapeutic purposes.</td>
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<tr>
<td>(4) Additional bone marrow biopsies in leukaemia patients (6 out of 10 exclusively for non-therapeutic reasons).</td>
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<td>(5) Controlled clinical trial with toddlers involving a placebo group which would have to undergo several intra-muscular injections of sodium chloride solution.</td>
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Results

The answers of the respondents are given in table (2). From the respondents’ point of view, there was a significant difference between the appraisals of studies (1) and (2), and studies (3), (4), and (5). While research scenarios (1) and (2) would have been approved by all research ethics committee chairpersons (although sometimes with slight restrictions), trials (3) to (5) were strongly rejected by a number of participants. In our view, this division of opinions is caused by the far more invasive character of the latter research projects. While the study design of research projects (1) and (2) involved only a very small risk for the participants’ health, the medical interventions in studies (3)-(5) were far riskier and could have caused severe side-effects.

The design of study (1) found the highest acceptance (28/96.6%). It included the use of an additional 5 ml blood from a blood sample drawn for diagnostic reasons from children suffering from Rett Syndrome, a neurological disorder which can cause mental retardation, autism, epilepsy, and other neuropathological symptoms. Although the study design as far as risks are concerned strongly resembled the German “Eisingen Case” (see above), it seemed quite acceptable to chairpersons. The respondents could give comments to their evaluation of the respective research projects. Most of the comments on the evaluation of study (1) correctly referred to the necessity of obtaining the parents’ or children’s informed consent or assent.
The proposal for study (4) received the highest number of rejection. Children at the age of 6-11 suffering from acute lymphatic leukaemia were supposed to participate in a randomized, two-armed study. Its purpose was to compare the outcome of a new chemotherapy with standard therapy. In the course of the study, weekly bone marrow biopsies were to be performed in both study groups. 6 out of 10 bone marrow biopsies were intended for purely scientific purposes, without direct benefit for the participant involved. Correspondingly, a majority (17/58,6 %) of the respondents refused approval of the study. The most frequent comment on the study design was the rejection of additional, non-therapeutic bone marrow biopsies. Other frequent comments were critical of the high burden it put on the study participants, and of the treatment plan for the biopsies. One respondent referred to the additional biopsies as “a kind of child abuse”. However, 6 chairpersons (20,7%) saw no problem to approve the study without further restrictions.
Scenario (5), too, elicited a wide range of reactions. The study would aim at the treatment of children aged 2-5 with congenital cardiac defect. These patients have an increased risk to suffer from myocardial inflammation caused by RS-viruses (respiratory syncytial virus). The research programme proposed a randomized, two-armed, placebo-controlled study to prove the prophylactic effect of immunoglobin against heart muscle inflammation. The children in the placebo group were supposed to receive intramuscular injections of sodium chloride solution. In the course of the study, cases of myocarditis in each group would be counted. Study participants with myocardial inflammation were supposed to receive standard therapy. As the chart in table (2) shows, the placebo-controlled study (5) was more easily accepted by chairpersons than study (4). Seven of the respondents (24.1%) would have approved the study without further restrictions, while 12 (41.4%) would have rejected it.

Conclusion

The results of our study show that in the case of non-therapeutic research with minors involving a higher than minimal risk, decisions of chairpersons of German research ethics committees vary to a disturbingly high degree. In contrast to widespread public criticism, chairpersons do not on principle object to non-therapeutic research with only minimal risk or burden (for a critical discussion of the notion "minimal risk" see Kopelman [9], Maio [10]). There seems to be a kind of consensus among chairpersons with regard to the evaluation of less invasive interventions for non-therapeutic research, as the undisputedly positive evaluation of studies (1) and (2) has shown. More invasive interventions like those involved in studies (3)-(5), however, are seen more controversial. This reflects the ethical discussion about non-therapeutic research with minors in Germany. Disturbing from our point of view is the fact that research ethics committees in Germany seem to come to widely differing decisions where more invasive interventions are concerned. Whereas 4 out of 29 committees,
according to the vote of their chairpersons, would probably have refused the approval for at least 3 of the 5 studies, 2 committees might have approved all studies without any restrictions. From our point of view, this situation is not acceptable. We are aware of the fact that the opinion of chairpersons cannot simply be equated with the decision of the committees as such. However, chairpersons are usually experienced and well-informed members of ethics committees as far as ethical and legal regulations are concerned. Their interpretation of what is legally and ethically acceptable on the basis of current German regulations should, where more than minor risks are at stake at least not differ to such a wide extent. The European Convention on Human Rights and Biomedicine, for example, strictly rules out this type of research. That the opinions of German chairpersons on these issues vary to such a high degree reveals significant uncertainty as to the ethical standards in non-therapeutic research. This creates problems for study participants, researchers, and the public who are left uncertain about the standards of protection of research participants and in risk-benefit analyses. This problem is particularly prominent in multi-centre research projects where several local research ethics committees are involved. Our conclusion is that there is an urgent need for a more detailed, comprehensive, and unambiguous regulation of research with the non-competent in Germany that does not permit such a wide range of interpretation. Meanwhile, the ratification of the European Convention on Human Rights and Biomedicine seems to be a good way to guarantee at least minimal ethical standards in these cases in Germany.

REFERENCES


