Research with Minors in Germany

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Abstract
The European GCP Directive has been implemented into German law in sect. 40 ff. AMG (German pharmaceutical law). Unlike the Directive, German pharmaceutical law basically differentiates between three constellations of clinical trials on minors: clinical trials on healthy minors, clinical trials on ill minors with an individual benefit for the individual participant, and clinical trials on ill minors without direct benefit for the individual participant, but with a so-called "group benefit". Particularly the latter possibility of conducting clinical trials on minors even if no individual benefit can be expected is not a matter of course in Germany since due to historical experiences a sceptical attitude towards clinical research on humans prevailed for a long time. German legislature has availed itself of the option granted by Article 3 of the GCP Directive to establish a higher level of protection of clinical trial subjects than the European level.

Keywords
Benefit/risk assessment; clinical trial; consent; ethic committees; GCP Directive; group benefit; minors

Clinical trials on children and adolescents have been promoted in Germany for some time. As early as in the year 2000, the concept of a network of German paediatricians was established in order to develop an effective infrastructure for clinical drug trials on children and adolescents.[1] This led to the paediatric network PAED-Net which has since then participated in more than 100 studies covering a wide range of paediatric indications. Since autumn 2002 paediatric modules at six German universities have been sponsored by the German Ministry for Education and Research within the framework of this network.[2]

In Germany, clinical trials have to be approved by the Federal Superior Authorities, i.e. the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI). According to the BfArM about 6 % of all clinical trials in Germany which have been approved in this way involve minors. The disciplines most frequently concerned are neurology and psychiatry, respiratory tract and gastroenterology. In the year 2006, the BfArM filed 65 applications for clinical trials on minors (of a total of 1249 applications = 5,0 %), in the year 2005

1) Kuhlmann, DÄBl. 2008, A 257 (258).
2) See http://www.paed-net.org/.

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70 applications (of a total of 1093 = 6,1%) and in the year 2004 19 applications (of a total of 273 = 6,6%).[3]

I. The Implementation of Directive 2001/20/EC ("GCP Directive") into German Law

1. *Overview*

The European GCP Directive has been implemented into German law in sect. 40 ff. AMG (German pharmaceutical law) through the 12th AMG Amendment[4] and by the *Ordinance Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use* (GCP Ordinance).[5]

Clinical trials on children and adolescents are regulated by sect. 40 para. 4 AMG and sect. 41 para. 2 AMG. Sect. 40 para. 4 AMG establishes general provisions for clinical trials on all minors, i.e. non-patient volunteers and patients, sect. 41 para. 2 relates to the particular conditions of clinical trials on minors suffering from a disease. The protective provisions of both regulations go beyond the standards set by the EC Directive. The German legislature has thus availed itself of the option granted by Article 3 of the GCP Directive to establish a higher level of protection of clinical trial subjects than the European level.

2. *The Specific Regulations*

a) *Basic Structure of Regulations*

Unlike the GCP Directive, German pharmaceutical law basically differentiates between three constellations of clinical trials on minors:

- clinical trials on healthy minors
- clinical trials on ill minors with an individual benefit for the individual participant
- clinical trials on ill minors without direct benefit for the individual participant, but with a so-called "group benefit", i.e. direct benefit for other children suffering from the same disease.

The requirements for clinical trials on healthy minors are regulated by sect. 40 para. 4 AMG. In accordance with sect. 40 para. 4 no. 1 AMG, such trials are

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[3] Cf. BfArM, FAQ Klinische Prüfung — Klinik — Kinderstudien; download at www.bfarm.de.
[4] 12th AMG Amendment of 30 July 2004, BGBl I, p. 2031.
[5] GCP Ordinance of 9 August 2004, BGBl I, p. 2081.

admissible if the drug for trial is intended for the diagnosis or prevention of diseases affecting minors and is of benefit to the individual participant of the clinical trial. Sect. 41 para. 2 AMG specifies additional prerequisites for clinical trials on minors suffering from a disease. Para. 2 sentence 1 no.1 refers to clinical studies offering an individual benefit for the individual participant. Even stricter requirements are defined by para. 2 sentence 1 no. 2 for clinical trials which do not offer any individual benefit for the individual participant but only a benefit for the group of patients suffering from the same disease. Further requirements for all kinds of clinical trials are specified by sect. 40 para. 4 no. 2-5 AMG.

b) *Clinical Trials Offering a "Group Benefit"*

The possibility of conducting clinical trials on minors even if no individual but only a group benefit can be expected is not a matter of course in Germany. Following experiences made under the Nazi regime, a sceptical attitude towards clinical research on humans prevailed for a long time,[6] resulting in considerable reluctance when weighing research interests against individual patient interests, in particular in the case of persons incapable of giving their consent. Research interests were of secondary importance in such cases and the subject's consent could not be replaced by a third party's consent.[7]

However, this approach was not satisfactory either. Although it prevented the ethically questionable instrumentalisation of individual minors for research purposes, this protection led to significant deficits of research on paediatric diseases in Germany and, in consequence, to deficits of the every day practice of the administering of drugs to minors. This result was equally questionable and the "ethical dilemma" of research on minors was frequently discussed. There was an increasing willingness to attach more importance to research interests in this ethical dilemma, always provided that the protection of minors in research would be guaranteed.

Finally, the legal situation in Germany changed with the implementation of the GCP Directive by the 12th AMG Amendment of 30 July 2004. Clinical trials on minors are now admissible — though under strict conditions — even if they do not entail any immediate benefit to the participants. The prerequisites are defined specifically by sect. 41 para. 2 no. AMG and in general terms by sect. 40 para. 4 no. 2-5 AMG: Apart from providing some direct benefit for the group of patients, the research must be essential to validate data obtained in other clinical trials; the research must relate to a clinical condition from which the minor concerned is suffering and the risk and level of distress of the trial subject have to be minimised (see also f) below).

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6) Zentrale Ethikkommission bei der Bundesärztekammer (Central Ethics Committee at the German Medical Association), Stellungnahme zur Forschung mit Minderjährigen, DÄBl. 2004, 329.

7) Jachertz, DÄBl 2005, A 546.

c) *Minors and Legal Representatives*
The GCP Directive does not provide a definition for the term minor. According to German law, a person is regarded as „minor", if he/she is capable of holding rights, but is still under age. The legal capacity of a human being begins at birth (sect. 1 Civil Code). Majority is attained at the age of 18 (sect. 2 Civil Code).

In accordance with German law, the legal representatives of a minor are the parents (sect. 1629 para. 1 Civil Code). The right of custody of a minor is generally shared by both parents; the consent to the clinical trial must therefore be given by both parents. The parents may give each other power of attorney for the custody of the child. In cases of routine medical treatment, the physician may generally assume that the parent which is present acts with the consent of the other parent. The consent to the participation of the child in a clinical trial, however, is not one of these routine cases.[8] It requires a power of attorney which should expressly state in concrete terms that consent is given, especially so in clinical trials intended for group benefit.[9]

d) *The Requirement of Consent*
As in the case of Art. 4 of the GCP Directive, the provisions on consent set out within the framework of sect. 40 para. 4 AMG are very extensive. Consent is regulated in sect. 40 para. 4 no. 3; the provisions correspond more or less to those of Art. 4 a-c of the GCP Directive. German law goes beyond the protective requirements of the Directive, however, in so far as, in the case of a minor who is capable of assessing information about the trial and of forming an opinion („capacity to understand"), not only the minor's *refusal* to participate in the trial has to be taken into account, but instead her *consent* has to be obtained in order to be allowed to conduct the trial. At what age a minor is regarded as having the „capacity to understand" depends on the individual case and cannot be generally specified. The view is held that minors can be presumed to have the „capacity to understand" at the age of twelve; according to others, at the age of 14 the minor's consent is deemed to be "mandatory in all cases".[10]

Sect. 40 para. 4 AMG does not refer to the revocability of consent which is explicitly stated by Art. 4 a of the Directive. However, sect. 40 para. 2 AMG stipulates for all clinical trials that consent can be revoked at any time; naturally, this principle also applies to the consent of minors.

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8) Kloesel/Cyran, Arzneimittelrecht, sect. 40 annot. 107.
9) Arbeitskreis der Ethik-Kommissionen der Bundesrepublik Deutschland, Empfehlungen zur klinischen Prüfung von Arzneimitteln bei Minderjährigen / Working Group of the Ethic Committees of the Federal Republic of Germany, Recommendations for clinical drug trials on minors.
10) Kloesel/Cyran, Arzneimittelrecht, sect. 40 annot. 112.

e) *Incentives and Financial Inducements*
According to German as well as European law, no incentives or financial inducements must be given, except compensation (which, according to German law, has to be "adequate").

f) *Benefit/Risk Assessment*
Art. 4 of the GCP Directive states that clinical trials have to be designed to reduce the degree of distress and the risks involved as much as possible. This corresponds to sect. 40 para. 4 no. 4 AMG. In addition to the Directive, German law also stipulates that a clinical trial intended for group benefit should only involve „minimal" risks and level of distress („minimal" defined as insignificant risks and distress occurring only temporarily; sect. 41 II 1 no. 2 d AMG). According to the legislator, such measures involving „minimal" risks or distress would include e.g. measuring, weighing, questioning or observing, or the taking of a small additional blood sample if a catheter has already been placed.[11]

Compared to European law, the German legislator has thus established stricter protective requirements for the benefit/risk assessment of those clinical trials which offer only group benefit. This cautious approach can be better understood if one considers that clinical trials on minors offering only group benefit were not admissible at all in Germany before the 12th AMG Amendment in 2004, which in turn reflects the experience of research on humans under the Nazi regime (see above b).

II. Application of Law by Ethic Committees: Implementation through Interpretation

The function of ethic committees has undergone a fundamental change with the implementation of the GCP Directive in national law: without the approval of the ethic committee — and without the approval of the Federal Superior Authority — a clinical drug trial cannot be conducted (sect. 40 para. 1 p. 2 AMG).[12] The assessment of the ethic committee is an administrative act resulting in approval or refusal which may be subject to judicial review.[13] The ethic committee has thus turned from an advisory into a decision-making institution, from an "advisory body under professional law into an authority-type institution for the protection of patients".[14]

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[11] Committee Report (Recommendations of the responsible committee of German Parliament) on sect. 41 para. 2 p. 1 AMG; printed in Kloesel/Cyran, Arzneimittelrecht, sect. 41 AMG preceding annot. 1.
[12] The procedure is regulated by sect. 40 para. 1 AMG and the GCP Ordinance based on sect. 42 para. 3 AMG.
[13] Cf. Hart, Klinische Arzneimittelprüfung, in: Rieger (ed.), Lexikon des Arztrechts, 2nd ed. 2002, last update Dec 2007, BVZ 2880, marg. no. 9 ff.
[14] Cf. Annotations of the Draft of the 12th AMG Amendment, BT-Drs. 15/2109 of 1.12.2003, sect. 42 (re. no. 28).

Before the adoption of the 12th AMG Amendment,[15] i.e. prior to 6 August 2004, the non-observance of an ethic committee's vote would only be relevant under liability law, while today, the conduct of a clinical trial without the approval of the ethic committee will have consequences under criminal law, too (sect. 96 no. 11 AMG).

To our knowledge, the introduction of regulations for clinical trials on minors has not led to a significant increase in the number of assessments made by ethic committees, although the Working Group of Ethic Committees reports a general rise of clinical trial applications. The Ethic Committee of Bremen for example had to review four clinical trials on minors in 2005, four in 2006, four in 2007, and up to now three in 2008 (1st quarter). Some of these trials had to be reviewed in accordance with the former regulations. Most of these trials related to oncological and rheumatic diseases. It is well known that paediatric oncological diseases have so far been in nearly all cases treated within the framework of clinical studies or in accordance with nationally or internationally consented study protocols without these having to be classified as clinical drug trials.

Ethic committees consider in particular two essential requirements for the protection of patients and non-patient volunteers:

1. the benefit/risk assessment
2. informed consent

The experience of decision-making practice shows that the application of these criteria in the review of clinical trials on minors results in the following interpretation of the two protective requirements.

1. *Benefit/Risk Assessment*

The general benefit/risk assessment, i.e. the assessment of the justifiability of clinical trials (sect. 40 para. 1 p. 3 no. 2 AMG) is specified for clinical trials on minors by the provisions of sect. 40 para. 4 no. 4; clinical trials on minors with "direct group benefit" furthermore have to comply with the specific requirements of sect. 41 para. 2 p. 1 no. 2 AMG.[16]

The two requirements of sect. 40 para. 4 no. 4 AMG — "as little distress and other foreseeable risks as possible" and "degree of distress and risk threshold must be defined in the protocol and constantly monitored by the investigator" — reflect the general requirement of justifiability of clinical trials but also relate to specific criteria and procedures. The wording corresponds very closely to Art. 4 lit. g of

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[15] Revised regulation of clinical drug law through the 12th AMG Amendment of 30 July 2004, BGBl I, p. 2031 of 5.8.2004.

[16] See I 2 f. above.

the GCP directive. As to the requirements of "minimal" distress and "minimal" risks for trials offering no individual but only direct group benefit (sect. 41 para. 2 p. 2d AMG), the specific relevance of these requirements remains to be seen.

The provisions of sect. 40 para. 4 no. 4 AMG are aimed at the specific requirements of the protection of minor patients and non-patient volunteers; they reflect the intensity of and emphasis on benefit-risk assessment under the aspect of risk prevention in clinical trials on minors, they serve to establish clearly defined criteria for a permanent process of benefit/risk observation during clinical trials on minors, and they constantly remind investigators of this task.

What is specific about this requirement is not the benefit-risk assessment as such but its organisation as a process and a permanent criteria-oriented task of investigators. The protocol of clinical trials is to determine a maximum level of distress and a risk threshold, generating at least an attention signal or — going further — resulting in a negative benefit-risk balance and thus the suspension or the termination of the trial. The corresponding requirements may include the definition of unacceptable undesired effects, criteria for the termination of trials, assessment and decision-making criteria for the safety board or procedural requirements like "in the event of… an assessment conference has to be called" in the protocol.

In particular, such provisions will be required for placebo-controlled trials in the form of add-on trials (combined with standard therapy) and above all for exclusively placebo-controlled trials. According to a report of the Federal Government, 965 applications for placebo-controlled trials (of a total of 2957 applications) were filed with the Federal Superior Authorities from August 2004 to December 2006; 42 (= 4%) of these concerned clinical trials on minors.[17]

2. *Informed Consent*

The requirements relating to the information of clinical trial participants as a central prerequisite for valid consent have to be adequately differentiated in accordance with the minor's capacity of understanding (up to the age of 7, the age of 12 or 14, the age of 18). The ethic committee can only consider the general adequacy and comprehensibility of (written) information — however, first of all this is a matter of good practice of the investigators and their (psychological) competence. It has to be emphasized that the legal representative's consent must represent the minor's presumed will and that, if in doubt, the minor should be presumed to be capable of giving consent at an earlier rather than a later age. As a result, this sets an earlier date for the minor's capability of giving consent and his/her participation in the decision.

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[17] Report of the Federal Government on experiences with the participation of ethic committees in clinical trials (on the occasion of the 12th AMG Amendment), BT-Drs. 16/7703 of 20.12.2007.

III. Conclusion

There is a shortage of approved drugs for children and adolescents, resulting in a widely spread paediatric off-label use of drugs and higher risk of undesirable drug effects.

The GCP Directive and the EC Regulation no. 1901/2006 on medicinal products for paediatric use are intended to address this deficit by facilitating clinical drug trials on minors and providing incentives and requirements for the approval of drugs.

At present, the number of clinical trials on minors has not yet increased as a result of these endeavours, but it is likely to rise in the future.

The implementation of the Directive in Germany was timely and adequate. The interpretation of its standards by the ethic committees in particular will provide clear outlines for the protection of minors in clinical trials.