



Implications of the Clinical Trial Regulation on clinical research with minors

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Preliminary note

- **There are no conflict of interests to declare.**
- **The views expressed here do not necessarily represent exactly those of the Association of Medical Ethics Committees in Germany (AkEk e.V.).**

Tasks and responsibilities of ECs

To assess

- the scientific quality of the clinical trial (CT)
- the lawfulness
- the ethical tenability
- the medical tenability

Legal and ethical framework for clinical trials with minors

- Clinical trials with minors are regulated in detail in the CTR 536/2014. The margin of discretion for Ethics Committees is limited.
- The ethical standards get more and more ambitious. The *Ethical considerations for clinical trials on medicinal products conducted with minors, published* in Eudralex in 2017 comprise 48 pages! (Version 2008: 27 pages)

Legal framework for clinical trials with minors: CTR

Article 32: Requirements

- the informed consent of their legally designated representative has been obtained;
- the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;

Legal framework for clinical trials with minors: CTR

Article 32: Requirements

- the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is ***respected*** by the investigator;
- no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;

Legal framework for clinical trials with minors: CTR

Article 32: Requirements

- the clinical trial is intended to investigate treatments for a medical condition that ***only*** occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
- the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;

Legal framework for clinical trials with minors: CTR

Article 32: Requirements

- there are scientific grounds for expecting that participation in the clinical trial will produce:
 - a **direct** benefit for the minor concerned outweighing the risks and burdens involved;
or
 - **some benefit for the population** represented by the minor concerned and such a clinical trial will *pose only minimal risk to, and will impose minimal burden on*, the minor concerned in comparison with the standard treatment of the minor's condition. (group benefit)

Legal framework for clinical trials with minors: CTR

Article 32: Requirements

- The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
- If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained ***before*** that subject can continue to participate in the clinical trial.

Legal framework for clinical trials: CTR Article 28:

General Requirements

- the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;
- the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects and both the ***risk threshold and the degree of distress*** are specifically defined in the protocol and constantly monitored;

Ethical considerations for clinical trials on medicinal products conducted with minors (2017)

- **Revision of the European Commission Expert Group on Clinical Trials guidance of 2008 (27 p.), needed due to the new CTR 536/2014.**
- **48 p., made public in Eudralex in 2017.**
- **Key aspects: Informed Consent, trial designs, risk and burden vs chance of benefit-weighting, required qualifications, monitoring of risks and burdens.**

Intention

These recommendations should serve as a starting point, and stimulate reflection on the best interests of the children involved in trials. Some situations may ask for deviation from these recommendations; deviations should be justified in the protocol to allow review by assessors and ethics committees. (2.)

Basis

The four principles of ethics in biomedical research:

- **Respect for Autonomy**
- **Nonmaleficence**
- **Beneficence**
- **Justice**

Age and Informed Consent

- Preschoolers 2 - 5 years
- Pupils 6 – 9 yrs
- Youngsters 10 – 18 years

Depending to their maturity minors, *starting at age 2*, have to get involved in the Informed Consent procedure → age-adjusted IC materials, e.g. cartoons, comics, videos.

Both parents/custodians have to be encouraged to participate in the IC procedure too.

Informed Consent

- **The attending physician should not be the one who provides the information for the consent.**
- **The physician providing the information for consent has to have professional experience with minors.**
- **Assent and consent are understood as a dynamic process that should be reinforced ideally at each visit.**
- **If needed, a competent translator has to be involved.**

Pediatric Expertise in Ethics Committees

- **Specialisation in pediatrics, professional experience with minors and knowledge in pediatric clinical pharmacology → more than one member with pediatric expertise thus might be needed in an EC.**
- **Expertise with pediatric trial designs and methodology.**

Points to consider when planning a trial with minors

- No repetition of research* → **syst. Review**
- Description how the trial-related procedures are explained to the minor and how potential distress is avoided or attenuated.
- Equipoise-assumption at the start of the trial: no minor should receive a treatment worse than the current standard of care.
- The trial protocol and the IC material should be prepared with parents and patients whenever possible. If not: Obligation to provide reasons!
(9.2)

* s. auch 18.

Points to consider when planning a trial with minors

- Age-based preparation of the IMP.
- Age-based outcomes/endpoints.
- DSMB/DMC with pediatric expertise.
- Securing the risk and burden/expected benefit-balance during the whole trial.
- Obligation to minimise risks and burdens for the minor *and* the parents/family.
- Choice of trial designs suitable for minors only, use of extrapolations/simulations when appropriate → obtain Scientific Advice (NCA and EC)

Burden - Definition (11.)

Burden is defined as the (mostly) subjective load that affects a participant, parents and family, due to elements of the trial that cause pain, discomfort, fear, disturbances of their lives and personal activities, or otherwise unpleasant experiences. It is by definition mostly determined by the person bearing the burden. For minors, burden may include missing out on social activities, sports and even normal schooldays and for parents finding the time to fill out questionnaires, missing work days, driving their child to appointments, collecting samples, or recording diary entries.

Burden - Definition (11.)

The trial burden is an important decision factor for children and parents on whether to enrol or withdraw, in particular for trials without a prospect of direct benefit for the child, and it also impacts their compliance. Both risks and burden may be physical, psychological, or social, may be immediate or delayed, and may vary according to age, duration, previous experience, repetition or accumulation. → **As far as I know there are no established instruments to measure burden for minors and their parents.**

Burden

- The whole setting of the trial centre has to be age-based, e.g. furniture, toys, etc.
- All burdens have to be continuously monitored and to be minimised whenever possible.

,Minimal' means: comparable with common day-to-day risks and burdens.

Risk and Burden / Benefit-Weighting

**Trials with chance for direct benefit: Benefit
> R+B**

**Trials with chance for group benefit only: just
minimal risk and burden permitted.**

Cave: Trials with both options are common.

Trial designs und statistical planning

- **Cooperation with experienced biometricians is essential.**
- **New, innovative age-based trial designs have to be developed, evaluated and used.**
- **The monitoring of risks and burdens has to be improved. All participants have to be encouraged to report AEs/ADRs and trial-related burdens.**

Staggered Approach

= strategy to start CTs with older minors and progressing only then to younger minors.

EMA has abandoned that approach as it may prolong the time it needs to make new treatments available for younger or very young minors.

Data Protection

- **Strict compliance with the EU GDPR.**
- **Age-/maturity-based involvement of the minor in the procedure for informed assent/consent. Reaching legal age Informed Consent according to EU and local regulations needs to be provided.**

Annexes

- I List of issues for a clinical trial involving minors.**
- II Information for informed consent and assent/agreement.**
- III Examples for levels of risks and burden of study procedures.**

Missing issues

- **Clinical trials with embryos / fetuses.**
- **Clinical trials with institutionalised minors or minors looked after by professional custodians.**

Conclusions

- ✓ **Drug research with minors is strictly regulated in the EU. It is not easy to fulfil the legal and ethical standards. The level of protection for minors in clinical trials is very high.**
- ✓ **The CTR 536/2014 strengthens the level of protection.**
- ✓ **Placebo controls are permitted.**
- ✓ **Research is definitely needed in the area of measures for burdens and informed assent with minors.**

Conclusions

- **The Ethical Considerations comprehensively elucidate ethical issues and standards for pediatric CTs. By intention they are not meant as explicit and binding recommendations.**
- **As a rule, deviations should be justified in the trial protocol however.**
- **If applied too strict there is a non-negligible risk that pediatric CTs are not done. (→ my opinion)**