ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN
IN DER BUNDESREPUBLIK DEUTSCHLAND E.V.

Clinical Trial Regulation 536/2014: Additional Protection for specific Study Populations

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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.).

Content

- Incapacitated persons
- Minors
- Pregnant and breastfeeding women
- Emergency situations

Clinical trials with incapacitated subjects Art. 31

A clinical trial may be conducted only where **all** of the following conditions are met: .....

(d) no incentives or financial inducements are given....., except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;

(e) the clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods;

(f) the clinical trial relates directly to a medical condition from which the subject suffers;

Clinical trials with incapacitated subjects Art. 31

A clinical trial may be conducted only where **all** of the following conditions are met:

(g) there are scientific grounds for expecting that participation in the clinical trial will produce:

- (i) a direct benefit to the incapacitated subject outweighing the risks and burdens involved; **or**
- (ii) some benefit for the population represented by the incapacitated subject concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only **minimal risk** to, and will impose **minimal burden** on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition.

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…..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 outweighting 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.……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***;

Risk and Burden / Benefit-Weighting

Trials with chance for direct benefit: Benefit > Risk+Burden

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

Cave: Trials with both options are common.

How to measure burden?

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.

Missing issues

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

Clinical trials on pregnant or breastfeeding women CTR Art.33

A clinical trial on pregnant or breastfeeding women may be conducted only where... the following conditions are met:

(a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; **or**

(b) if such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, it can be conducted only if:

Clinical Trials on pregnant or breastfeeding women
CTR Art.33

- (i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breast feeding;
- (ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and
- (iii) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;

Clinical Trials on pregnant or breastfeeding women
CTR Art.33

(c) where research is undertaken on breastfee-ding women, particular care is taken to avoid any adverse impact on the health of the child; **and**

(d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.

Clinical trials in emergency situations Art. 35

The following conditions have to be fulfilled:

- (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
- (b) there are scientific grounds to expect that **participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement** alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
- (c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;

Clinical trials in emergency situations Art. 35

The following conditions have to be fulfilled:

(d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject,

(e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;

Clinical trials in emergency situations Art. 35

The following conditions have to be fulfilled:

(f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

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 enrole 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 neither for adults nor minors.**

Conclusions

- ✓ Drug research with special (vulnerable) populations is strictly regulated in the EU. It is not easy to fulfil the legal and ethical standards. The level of protection in clinical trials is very high.
- ✓ Research is definitely needed in the area of measures for burdens.
- ✓ When applying the CTR the right to be treated in medically challenging situations with evidence-based medicinal products shall not be neglected.