



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ethical considerations for clinical trials on medicinal products conducted with the paediatric population

Revision 2016

Enpr-EMA 2016 annual work shop

Presented by Ralf Herold and Agnès Saint-Raymond on 2 June 2016
Paediatric medicines office / Programme design board

An agency of the European Union





Revision – Objectives

- To include:
 - experience with paediatric trials,
 - experience from discussing and agreeing paediatric developments (PIPs),
 - suggestions coming from research into ethics of paediatric trials,
 - provisions concerning ethics from the clinical trial Regulation
- Drafting group: led by Ministry of Health, Welfare and Sports, The Netherlands; on behalf of the Ad-hoc group for the development of implementing guidelines for Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
- Public consultation: June to August 2016

Public consultation opened 1 June 2016

- Open until 31 August 2016

Specifically feedback sought:

- Q1: Proposed categorisation (table annex 3) of procedures adequate?
- Q2: Which insights may lead to changes in categorisations?
- F1: Clinical trials in minors in emergency situations?
- F2: Other relevant references?

http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm

http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_1_consult.pdf





Guideline improvements on paediatric trial ethics

- Protocol to be designed with, and reviewed by patients - “exceptions should be justified” – empowerment of children and their families
- Assent strengthened (first time mentioned in EU law), dissent to be respected
- Guide on paediatric emergency situations (where lack of prior consent)
- Removal of age staggering for development (not shown to protect younger pts., delays study)
- Methods: novel trial designs encouraged, with regulatory advice; use of micro-assays becomes the rule rather than exception
- Assessing benefits, harms, risks and burden from subjects’ perspective
- Transparency and learning from other trials



Clinical Trials Regulation (EU) No. 536/2014 on Assent

Article 29(8): *"This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial."*

Article 32 (Clinical trials in minors):

1. (c) *"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;"*
2. *"The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity".*



The more difficult discussions

- **Differences between trials with the prospect of direct benefit to the minor, and those without prospect of direct benefit**



Clinical Trials Regulation (EU) No. 536/2014

Article 32 (Clinical trials on minors)

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

- (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or*
- (ii) 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."*



The more difficult discussions

- **Evaluating risks between trials with the prospect of direct benefit to the minor, and those without prospect of direct benefit**
- Direct benefit: assessed at level of trial, or per component (e.g. purpose of a particular investigation), or per arm?
- No prospect of direct benefit: what are the acceptable risks and burdens?
- NB International perspective: differences in wording ("*minor increase over minimal risk*" from the US), will this make the ethical approval of international trials more difficult?



Clinical Trials Regulation (EU) No. 536/2014

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Paediatric trials with prospect of direct benefit

- Balancing exercise of benefits with risks and burden for participants: expected benefits for participants should always outweigh risks and burdens
- Does certain level of benefit justifies certain level of risk and burden?
- Different balancing exercise for the placebo and the active arms?
- Realistic possibility to improve health or well-being by participating in the trial, including through more thorough safety monitoring
- Direct benefit may not materialise – investigational medicinal product may be less effective than standard or come with more adverse reactions



Clinical Trials regulation (EU) No. 536/2014 (cont.)

Article 32 Clinical trials on minors (cont.)

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

- (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or*
- (ii) 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."*



Paediatric trials without prospect of direct benefit

- No benefit for participants → is there a balancing exercise for risks and burden?
- New concept: risks and burden should be minimal "*in comparison*" with standard treatment of the condition
- Procedures limited to those experiences in line with standard treatment?
- What are the risks and burden associated with interventions?
- What are the acceptable risks and burdens in such trials if the condition requires invasive procedures as standard (muscle biopsy, MRI under general anaesthesia, bone marrow biopsy, etc.)?



Next steps

- Public consultation: information on launch will be shared via Enpr-EMA
- **Please comment! Your practical experience will be highly appreciated.**
- EMA/PDCO involved in review of comments of “Ethical considerations ...”
- Further research and discussions needed to protect children while ensuring they are given proper access to research
- Keep topic on agenda!



Infants', Children's and Young People's Child Health Research Charter

Remember it's about me; involve and support me at every stage and keep me safe from harm.

Empower me, my family, and the people caring for me; help us to understand and feel more confident about research.

Support me, my family, and the people caring for me; give us time to understand research processes, how to assess risks and benefits, and what it will mean to be involved.

Engage with me and my family; listen to our questions and ideas, so we can help you to help us benefit from research.

Actively gain my consent or assent and explain my right to change my mind and withdraw at any time.

Rights are important to me; my right to understand research, be involved in decisions, be respected, and to help others benefit from research.

Communicate with me directly and clearly; make it easy for me to talk to someone about the research when I have questions or ideas.

Help others by sharing our stories; the things that worked and the things that didn't.









Thank you for your attention

Further information

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International perspective – U.S. Code of Federal Regulations

- 21 CFR 56.111(a)(2): Risks are reasonable in relation to anticipated benefits, if any, to subjects and to importance of the knowledge that may be expected to result
- 21 CFR 50.52: Research involving children must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives
- 21 CFR 50.53: Research involving children must be restricted to minor increase over minimal risk absent a potential for direct benefit to the child but yielding generalizable knowledge and experiences in line with actual or expected health situation
- 21 CFR 50.51: Research involving children must be restricted to minimal risk absent a potential for direct benefit to the child
- 21 CFR 50.54: Not otherwise approvable: Opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children