Ethical Considerations for Clinical Trials Performed in Children

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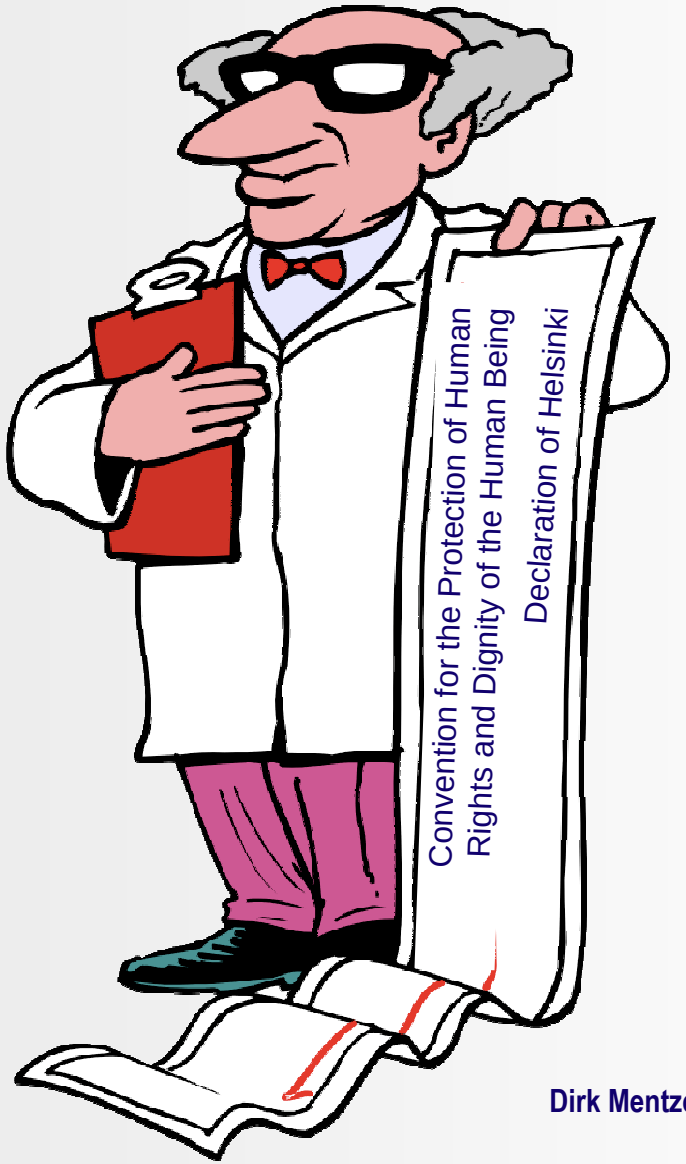
Ethical Considerations for Clinical Trials Performed in Children

Points to consider

- Ethical Consideration
- Legal basis and Guidelines
- Target population
- Consent and Assent
- Clinical Trial designs
- Risk and Benefit

Ethical Considerations for Clinical Trials Performed in Children

Ethical Considerations



Ethical Considerations for Clinical Trials Performed in Children

Ethical Considerations

- Children, due to their enormous developmental dynamic from their foetal and embryonic Phase throughout the birth and infancy up to their puberty and adolescence, are very vulnerable for adverse drug reactions.
- Up to date systematic drug development and conduction of clinical trial does rarely included children.
- Consequently, the Paediatric population is often granted a contraindication in the SmPC.
- Ethical aspects of clinical trial initiation needs to be held against treatment without any information
- Children should not be used on behalf of adults; research that can be done in less vulnerable subjects (adults and older children) should not be done in more vulnerable subjects.

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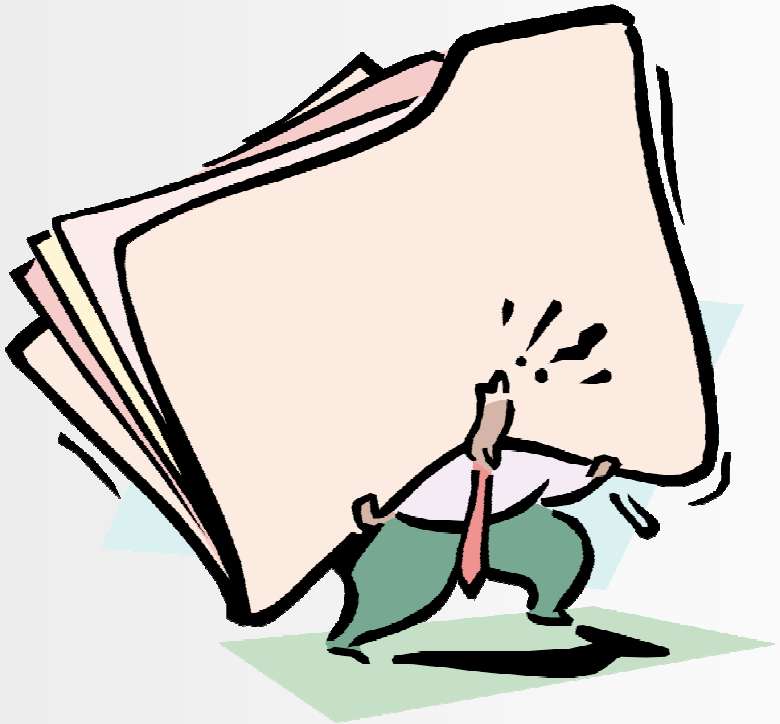
Legal basis and Guidelines



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Legal Basis

- Regulation on Medicinal Products for Paediatric Use (EC) 1901/2006 as amended by Regulation (EC) 1902/2006
- Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use
- Regulation No (EC) 141/2000 on orphan medicinal products
- Regulation (EC) No 726/2004 on Community procedures for the authorisation and supervision of medicinal products for human and veterinary use

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Guidelines (ICH, CHMP)

- ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population and ICH E6 guideline on Good Clinical Practice
- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population CHMP/EWP/147013/04
- Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population EMEA/CHMP/PhVWP/235910/2005- rev.1
- Guideline on Clinical Trials in small populations CHMP/EWP/83561/05
- Guideline on the need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications CHMP/SWP/169215/05
- Guideline on the investigation of Medicinal Products in the term and preterm neonate
- Reflection Paper on Formulations of Choice in Paediatric Population EMEA/196218/05
- Discussion Paper on the Impact of Renal Immaturity CHMP/PEG/35132/03
- Concept Paper on the Impact of Liver Immaturity CHMP/PEG/194605/05
- Concept Paper on the Impact of Lung and Heart Immaturity CHMP/PEG/114218/06
- Concept Paper on the Impact of Brain Immaturity CHMP/PEG/181377/06
- more to come Guideline
- more and more
- more

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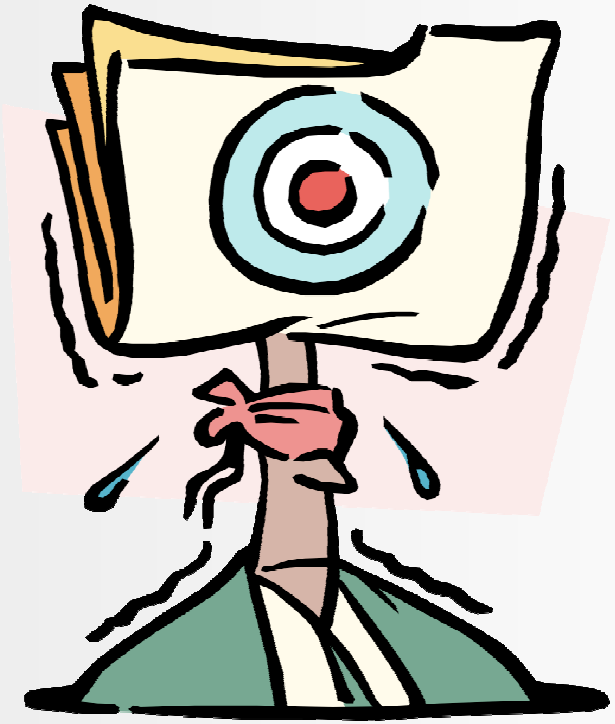
Target population



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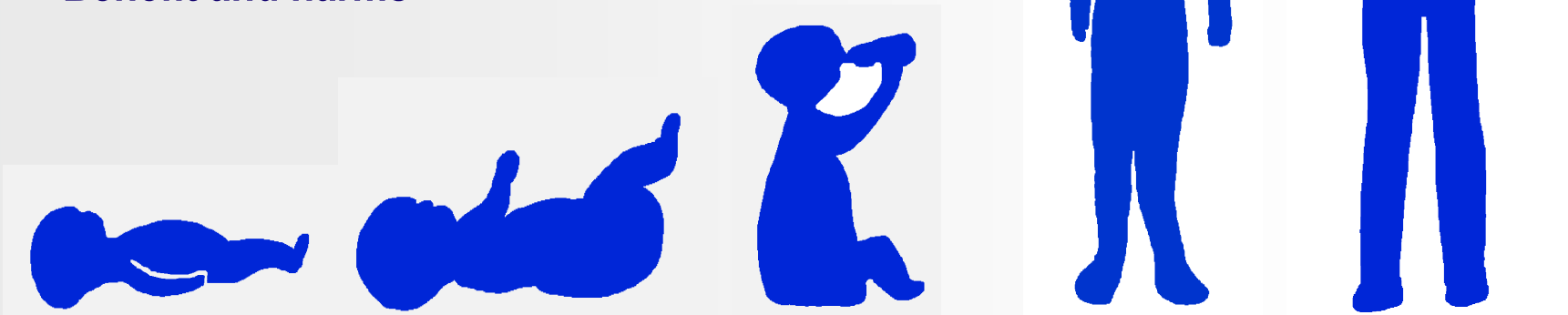
Target population

- Development and maturation during childhood
- observation methods and sampeling
- Special recruitment for trials
- broad geographic coverage
- Consent and Assent
- Benefit and harms



Preterm newborn

Term newborn
(0 to 28 days)

Infants and toddlers
(29 days to 23 months)

Children
(2 to 11 years)

Adolescents
(12 to (16) 18 years)

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Consent and assent

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Consent

- Consent begins when the initial contact is made and continues throughout the study and observation period
- Consent language must convey the information in words that suits the parent's and child's level of understanding
- The investigator must ensure that the parent and child has adequately understood the information
- The documentation of informed consent should be in written form
- For paediatric studies consent should be taken by a person with paediatric experience

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Consent and Assent

- Appropriate decision time
- Surrogate consent in emergency trials
- Country laws and Ethics Committee recommendation apply
- The child should provide assent (from age 3 - 4 years)
- Assent is voluntary and the wish to refuse participation or withdraw must be 'considered' at any time
- The parent/child should retain a copy of all forms and the records will be kept confidential
- Duration of participation and contact person should be named
- Providing information at a level of understanding

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Assent

- Requirements and age for assent vary by Country and Ethics Committee
- The central role of Parental consent should be recognised before involving children in discussions and decision-making process, the assent is in addition to informed consent
- The child's assent is not sufficient to allow participating
- Separate information and forms should be used to provide age appropriate information and extensive information on purpose of the trial and benefits and harms should be included.
- Information should be given in language and wording appropriate to age, psychological and intellectual maturity.
- Assent like consent is a continuous process during the trials
- Objections raised by a child at any time during a trial must be considered as the child's will should be respected

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Clinical trial design

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Clinical trial design - general aspects

- Trials enrolling several hundred patients may not be practical or possible in most cases and even common adverse reaction may not be detectable

- In particular, if there is a latent period before onset or a trigger such as a change in growth, maturation or development

- Conducting, analysis, and interpretation of trials within the paediatric population may at times be constrained by the prevalence of the disease and varying degrees (e.g. neurometabolic disease)

- Pathophysiological knowledge of organ function supported by juvenile animal toxicology studies, mutagenicity and carcinogenicity data my be supportive

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Clinical trial design - concept

- Medicines used in the Paediatric population have not been properly investigated, assessed and authorised.
- Active-control trials may be more difficult to interpret than placebo controlled ones but may provide useful information on comparative benefit/risk balance.
- The choice of active control products should be discussed thoroughly, as they may not be authorised in the Paediatric population.
- Unauthorised products may be considered as controls if they represent evidence-based standard of care.
- All measures to avoid bias should be included in trials performed in children like in adults.
- In principle uncontrolled trials should be avoided for demonstration of efficacy in trails conducted in children

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Clinical trial design - placebo

- Placebo use in children is more restricted than in adults but the use in Paediatric trials may often be needed for scientific reasons
- Placebo use is not equivalent to absence of treatment.
- Placebo may be warranted in children like in adults when evidence for efficacy or safety is lacking, but when the level of evidence increases, the ethical need for placebo in Paediatric trials decreases.
- Placebo must not be used when it means withholding effective treatment
- Placebo should be used on top of standard of care additionally rescue treatment and escape procedures should be set up.
- Exclusion as well as inclusion of placebo in paediatric clinical trials needs to be discuss with the best evidence available.

Dirk Mentzer, DGRA Annual Conference, June 2007

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Clinical trial design - conducting

- Monitoring ADRs with laboratory values may be very difficult due to lack of normal ranges information
- The observation and monitoring of the patient should contribute as much information as possible to support the Pharmacovigilance assessment at any time.
- Non-clinical pharmacology studies may are of special importance for planning study design.
- Fear should be prevented and separation of the child from parents or familiar persons should be avoided whenever possible.
- Tolerance of pain increases with age and maturation when medical procedures are not considered any more as punishment.

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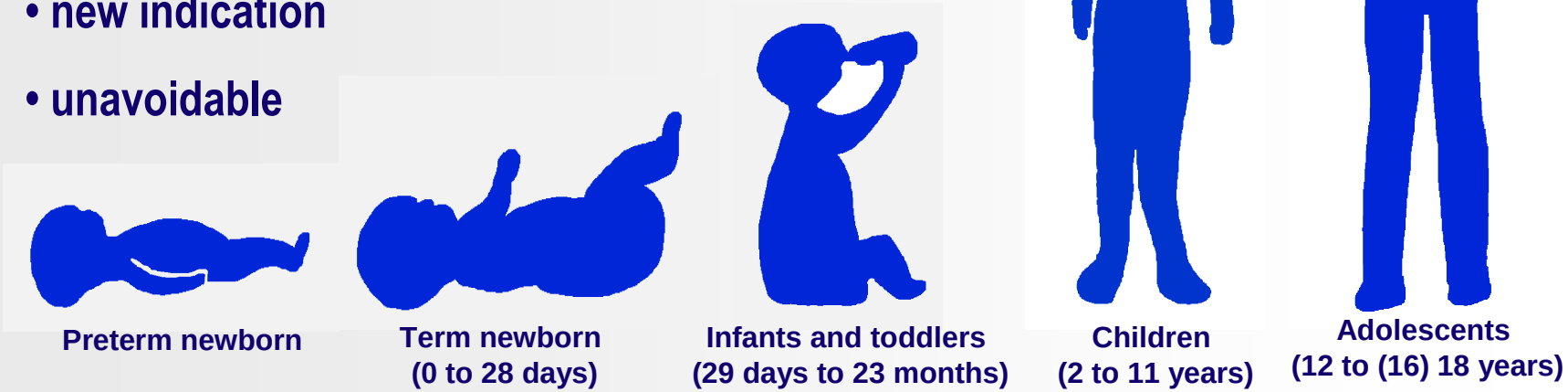
Clinical trial design

Significant therapeutic effect in Paediatric population

- new clinical relevant and therapeutic evidence
- proposed positive effect on efficacy
- substantial increase of safety
- Optimal application or dosing
- age appropriate formulation
- new indication
- unavoidable



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Clinical trial design

Monitoring and measurements

- Pain should be prevented and effectively treated when unavoidable
- Sampling and monitoring needs to be appropriate for age
- Maximum of 2 ml/ kg bw blood per eight week period
- Collection of material - especially urine or saliva
- Acceptable time differences between sampling
- Assessment of pain and distress intensity
- Growth, height and eight charts
- Maturation/ puberty

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Clinical trial design

Minimal risk <=> minimal burden

Minimal risk is described as probability of harm or discomfort not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

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Term newborn (0 to 28 days)

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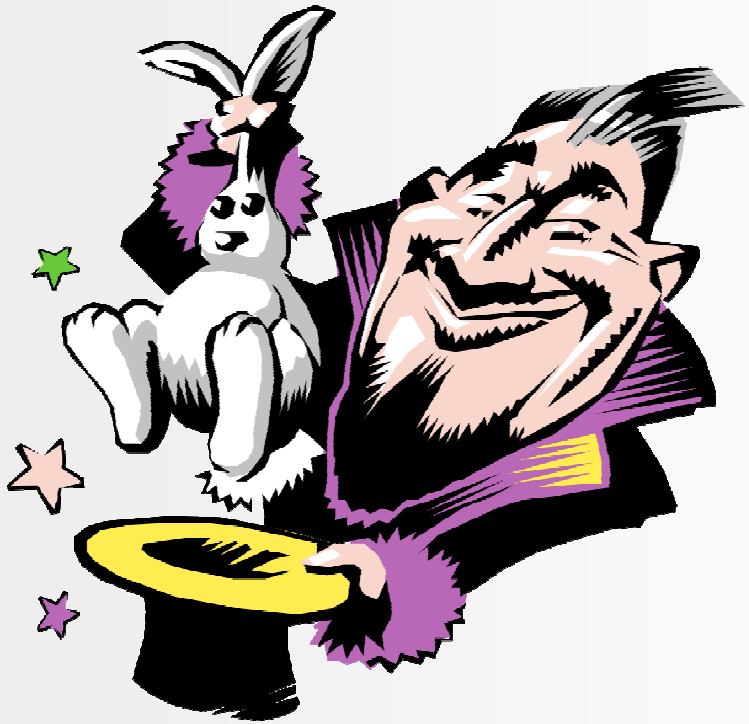
Benefit and Risk



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Benefit and Risk

- Risk assessment (physical, psychological, or social) is crucial in clinical trials aiming to define potential harm or potential consequence of an action to be assessed in terms of probability, magnitude and duration.
- If probability is unknown, elements influencing the risks should be taken into account.
- For identified risk and potential risks measures to prevent, minimise and how to monitor such risks should be proposed.
- Evaluation of the risk needs to include the medicinal product tested as well as the control or the risk of withholding active treatment.
- Potential harms would include
  - severity as well as seriousness of potential harms
  - reversibility of adverse effects and reactions

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Benefit and Risk

Examples of risk assessment as proposed in the United Staats

- No more than minimal risk
- More than minimal but potential for direct benefit
- Minor increase over minimal risk without direct benefit, but research is likely to yield generalisable knowledge about subject's disorder or condition
- Not otherwise approvable, but presents an opportunity to understand, prevent or alleviate a serious problem affecting health or welfare of children.
- Risks should be minimised and reasonable in relation to the expected benefit. Analysis should take into consideration risks of short term as well as long term risks including delayed occurrence of such risks.

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Benefit and Risk

- Benefit evaluation should include whether there is progress in treatment, diagnosis or prevention of disease in the group of children affected.

- Benefit evaluation may be obtained through assessment of
  - increased efficacy or safety resulting in better risk-benefit balance
  - provision of an alternative to existing treatment with at least similar expected benefit or risk
  - contribution to patient care (for example, better route of administration, decreased frequency of dosing)

- Evaluation whether or not there will be direct benefit for the children included in the trial or for the group of children affected by the same disease or shares similar features for which the medicinal product could be of benefit.

- Measures of such benefit would include the importance of knowledge gained, the likelihood of obtaining useful results concerning the better diagnosis, treatment or prevention.

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Conclusion

- Ethical aspects of clinical trial initiation needs to be held against treatment without any information
- The map concerning ethical consideration for clinical trials performed in children is not white!
- Strong proposal for joint effort performing clinical trials in children
  - Clinicial trial network
  - Academia / Paediatrician
  - Pharmaceutical Industrie
  - Authorities
- Ethical aspects of clinical trial for developing vaccines

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Thank you for your attention