Specific issues that Research Ethics Committees (RECs) face with paediatric trials

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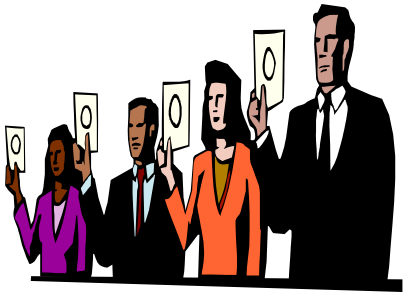
Directive 2001/20/EC

Responsibility of RECs



… to protect the rights, safety and wellbeing of human subjects involved in a trial

- advocate of each individual participant

Scope of evaluation

RECs must examine and evaluate whether a research project is justifiable and reasonable

- medically
- scientifically
- legally

} ethically

Evaluation ...

… must be in accordance with

- national laws
- European directives
- international guidelines

- Ethical principles are (meanwhile) included.

Benefit

- patient
  - ➢ individual benefit
  - ➢ foreign benefit
  - ~~*does not apply to the healthy volunteer*~~ → „group benefit“

Directive 2001/20/EC

- Adults able to give informed consent
- Minors (art. 4)
  – not able to give *legal* consent
- Incapacitated adults (art. 5)
  – not able to give *legal* consent

- ➢ Research with **or** without personal benefit
- ➢ Research with personal benefit **or** with direct benefit for the group
- ➢ Research with personal benefit only.

Directive 2001/20/EC

Article 4e

In addition to any other relevant restriction, a clinical trial on minors may be undertaken …

- only if some direct benefit for the group of patients is obtained from the clinical trials and

  patients

- only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or (obtained) by other research methods

  subsidiarity

- additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers
  or
  be of such a nature that it can only be carried out on minors.

  indicated

Directive 2001/20/EC

Article 4g

… only if …

- the clinical trial has been designed to minimise
  - pain,
  - discomfort,
  - fear and
  - any other foreseeable risk

  in relation to the disease and developmental stage;
- both the risk threshold and the degree of distress have to be specially defined and constantly monitored

Directive 2001/20/EC

Article 4i

… only if …

- The interests of the patient always prevail over those of science and society.

individual benefit ⇔ foreign benefit
„group benefit“

“Survey” among RECs

- Few clinical trials on minors, numbers did not increase
- Difficulties for approval:
  - number and amount of blood samples
  - number of other painful / burdensome investigations (MRT…)
  - “minimal risk, minimal burden” for investigations often not fulfilled
  - mixed populations, i.e. adults and minors in the same trial
  - lacking data of adults with the same clinical condition
  - no necessity to include minors to answer trial objectives
- Hardly any disapprovals, sometimes restrictions
  - subsidiarity: first adults, then minors
  - subsidiarity and stratification: first elder minors, then younger ones

More “Survey” among RECs

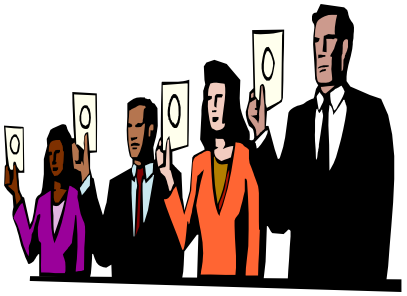
What could be reasons for the small number of trials on minors?

- Directive has made trials more expensive.
- Researchers, particularly those who do small projects, have been discouraged by the enormous effort that is needed to meet all the requirements and regulations.
- PIP produces unrealistic promises which cannot be fulfilled by sponsor.
- The effort overweighs the potential economic benefit.

Further reasons

- Health care market and clinical trials move East (India, China).
- Increasing populations. Many children. No access to good and affordable care. Lower costs for clinical trials.
- 09/11, Indian newspaper *Economic Times*
  India and Russia are set to sign a deal in December 2011 that will speed up drug registration of Indian manufactured drugs in the Russian market. This Pharma Collaboration Agreement may be extended to include clinical trial co-operation.
- 11/11, ZEIT, Germany
  In India increasing number of cases of death after clinical drug trials.
- 06/11 WHO - Ethics ignored in clinical trials in India
  … most of the organisations … take advantage of the poverty in rural areas and recruit economically disadvantaged people.
  Objecting strongly to the practice of recruiting volunteers for clinical trials from among the poor, the WHO has noted that fewer than 40 ethics committees in India are properly constituted and functioning.

Evaluation in Detail



- Must the questions be answered by trials on children?
- Trial design: Control group? Standard or placebo?
- Individual benefit to each child or *direct* benefit to the group?
- Are risk, distress, burden of additional measurements justifiable to the verum group? And also to the placebo group?
- Are the thresholds of risk and burden defined in the protocol? Minimal – or at least minimalised?
- Is continuous safety monitoring by the investigator described in the protocol?
- Is the written information adequate to all age groups and participants, to the legal representatives?
- Are investigators, study teams qualified?

Minimal – what is that?

„..at most very slight and temporary“
- absolute criterion -

- weigh, measure, interview
- laboratory tests of urine, stool
- ECG, EEG
- blood drawing through indwelling canula
- capillary blood
- venous blood sampling - repeated?

Minimalize – what is that?

… as „minimal“ as possible
in *relation* to disease & developmental stage & **benefit**

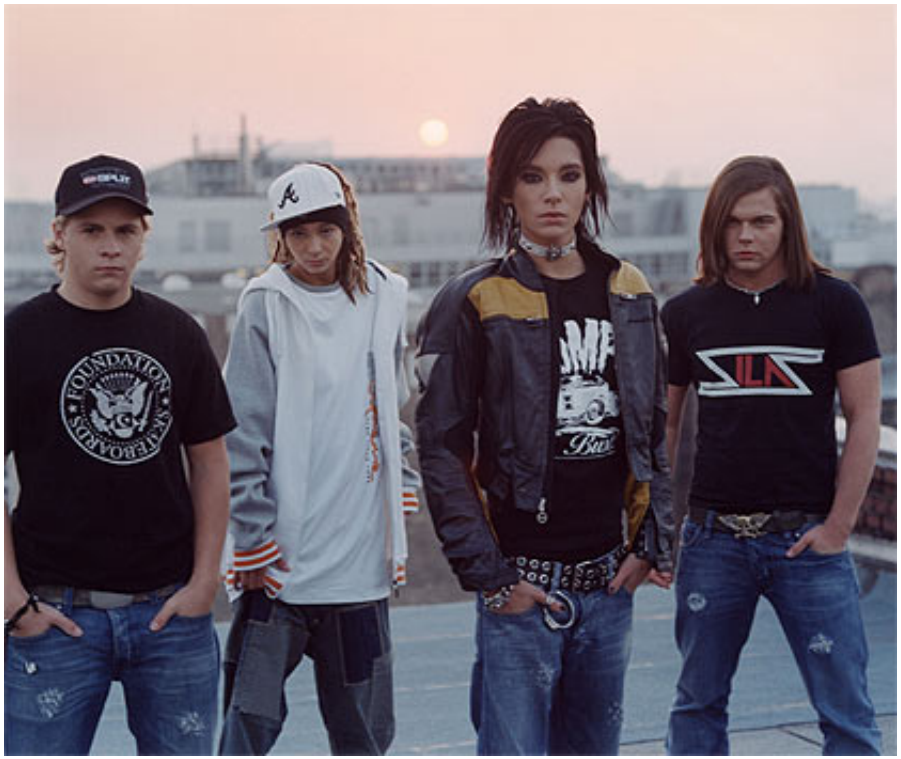
- Reduction of procedures to the absolutely necessary
- Reduction of invasive examinations to the absolutely necessary
- Reduction of pain by local anaesthetic strip
- Analytics with micromethods
- Data monitoring safety board (DMSB)

Age

Burden, such as risk, depends on age:

- premature babies
- newborns/toddlers
- school kids
- adolescents

Subsidiarity and stratification



Struggle for adequate evaluation

- Rare metabolic disorder in toddlers, no therapy available, placebo-controlled trial, placebo-infusion **once a week for 6 month**.
  Yes, but
  - placebo group must receive study therapy for free for next 4 years
  - investigator must assess impact of burden in each individual child
- Malignant skin tumour, stage III-IV, life expectancy 6 months, no adequate therapy, in early phase II trial in adults improved survival rate
  - Yes, also inclusion of minors (≥ 12 years).
- Phase IIa dose-finding trial, new anticoagulant therapy, children 2-12 and 0-2 years; inclusion **at end of hospitalization** after successful completion of standard anticoagulant therapy for VTE (due to CVL).
  - clear benefit for the group, no indication, no benefit for participating child, risk and burden cannot be considered minimal.

Struggle for adequate evaluation cont.

- New coagulation factor for hemophilia, first-in-human
  - *part 1a/b:* pharmacokinetics, dose finding
  - *part 2:* safety & efficacy in adults **+ children**
  - *substudy:* **adults + children with surgery.**
    - ➢ yes to part 1 & 2 without children
    - ➢ when results are known, trial for surgery patients and trial for children
- Antiepileptic drug, marketed for adults, efficacy and safety trial.
  - placebo-controlled, add-on, randomised, double-blind
  - 4 age groups: new-born, toddlers, school children, adolescents
  - **several MRTs, many blood samples** for pharmacokinetics & dose
    - ➢ Yes, but only if
      - elder age groups first, plus interim analysis,
      - reduction of blood samples in younger groups,
      - no additional MRT with general anaesthesia (except routine)

Conclusions! Solutions?

- No increase in clinical trials on minors in Europe.
- Expectations by PIPs, which cannot be fulfilled.
- More children in countries with growing populations.
- In Europe, good and affordable care, high costs of clinical trials.
- High ethical and legal standards to protect each individual participant.

← Not negotiable!

- No exchange between PDCO and RECs, little knowledge of daily work, of aspects which must be considered

← Communication, exchange!

- ***Unclear:***
  How many waivers?
  How many sponsors go East?
  When Europe – then why?

← Statistics?
Survey?

Thank You