Paediatric research demands child-specific guidelines for ethics and good clinical practice

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The Concerns of children in Ethics Declarations

Adults	Children
1947 Nuremberg Code	
1949 Declaration of Geneva	
1964 Med.Res.Council, London	1980 British Paediatric Ass.
1964 Declaration of Helsinki (WMA)	1981 CIOMS
1975 Decl.Helsinki, Version Tokio	1990 Royal College Phys.,London
1977 National Comm. Washington	1991 OPRP of NIH
1983 Decl.Helsinki, Version Venice	1995 CPMP,EWP, London
1989 Decl.Helsinki,Vers. HongKong	1998 NIH
1996 Decl.Helsinki,Vers. Somerset	1999 Declaration of Ottawa
1996 EFGCP	2000 ICH,Topic 11
1999 Decl.Helsinki, Version Chile	2000 Royal Coll.Paed.Child Health
2000 Decl.Helsinki,Vers.Edinbourgh	2001 EU Directives GCP
2001 EC Directives GCP	2002 CESP

THE NECESSITY TO SPECIFY AN ETHICAL FRAMEWORK FOR RESEARCH ON MEDICINES IN CHILDREN

- a child is not a small adult
- a child has specific somatic, mental, emotional and social needs to provide an optimal development
- all medicinal measures have to respect the best interests and the rights of children

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THE BASIC ETHICAL PRINCIPLE IN PAEDIATRICS " IN THE BEST INTERESTS OF CHILDREN "

means

- protecting the personality of the child
- saving the potential of the development of the child
- respecting the age specific vulnerabilities and fears of the child
- considering the biological differences between different ages and between the child and the adult

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THE UNO-CONVENTION OF THE RIGHTS OF CHILDREN (General Assembly of the UNO in 1989)

- all human rights and full identity are granted to every child
- the child has the full right to the respect of his/her life and personality
- the child has the right to the highest possible level of health by providing optimal medical care in each phase of his/her development

NECESSITY
OF RESEARCH ON MEDICINES IN CHLDREN

- optimal medical care needs scientific evaluation of preventive, diagnostic and therapeutic measures
- there are significant deficits in the objective knowledge of quality and efficacy of current therapeutic measures in respect to the paediatric population
- more than 50% of medicaments used in paediatric hospitals are not officially registered
- Pathophysiolgy is sometimes better known in rats than in children. Children are “therapeutic orphans”
- there are evident differences in physiology, pathology, pharmacokinetics and pharmacodynamics between children and adults
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APPLICATION OF MEDICAMENTS "OFF LABEL" AND "UNLICENSED" IN PAEDIATRIC HOSPITALS

		"off label"	"unlicensed"
CONROY S. et al. 1998	General Paediatrics	39%	7%
TURNER S. et al. 1996	Paed. Intensive Care	23%	14%
CONROY S. et al. 1999	Neonatal Care	55%	10%

CONROY S. et al. 1999 Neonatal Care 55% 10%

AGE SPECIFIC DIFFERENCES ON BEHALF OF THE APPLICATION OF MEDICINAL PRODUCTS

- ***Pharmacokinetics***:
  metabolic pathway, organ functions, metabolic rates
- ***Pharmacodynamics***:
  receptor functions, effector systems, homeostatic mechanisms
- ***Growth and Development***:
  dependency of dosage on body weight or surface
- ***Specific Pathology***:
  different diseases, severity, natural courses and phenomenology

GENERAL ETHICAL PRINCIPLES IN MEDICINE
(WMA - Declaration of Helsinki)

- respect for life and personal dignity
- personal autonomy
- beneficence
- non-maleficence
- distributive justice
- common spirit and personal solidarity

Publication: P.P.Sauer
Research in children. A report of the Ethics Working Group of the CESP.
Eur J Pediatr (2002) 161: 1-5

SPECIFIC ETHICAL CONCERNS ON PAEDIATRIC CLINICAL TRIALS

- ***respect for life and personal dignity:***
  - **respecting the ”best interests of the child”**
  - **protecting the child from inadequate risks**
  - **understanding the necessity of a proper and child-specific research to provide an optimal medicine**
- ***personal autonomy:***
  - **considering the incapacity of the child**
  - **obtaining informed consent/assent**
  - **respecting the will of the child**
- ***beneficence / non-maleficence:***
  - **benefit to the individual or relevant group**
  - **specific measures to minimise risks, discomfort**
- ***distributive justice:***
  - **children have all human rights**
  - **no discrimination of the child**
- ***community spirit and solitarity:***
  - **accepting properly conducted trials**
  - **possibly without direct personal benefit**

CONSIDERING THE ETHICAL DILEMMA OF RESEARCH IN INCAPACITATED CHILDREN

The ethical imperative to obtain knowledge of biomedical data and the effects of medicinal products in paediatric patients

has to be balanced against

the ethical imperative to protect the individual child in clinical studies and respect his or her integrity and personal dignity

ICH 2000, Topic E 11

THE DIRECTIVE 2001/20/EC
of the European Parliament and the Council
of 4 April 2001

respects the ethical principles in medicine
for clinical trials in children

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection

……

There is a need for clinical trials involving children

……

Criteria for the protection of children in clinical trials therefore need to be laid down

DIRECTIVE 2001/20/EC

ARTICLE 4 : *CLINICAL TRIALS ON MINORS* (Summary)

- informed consent of the legal representative
- informed assent of the child according to his/her capacity
- explicit wish to refuse participation
- no incentives except compensation
- direct benefit for the group of patients
- research relates to minor´s clinical condition
- special definition of the threshold and degree of distress
- minimising foreseeable risks, pain, discomfort and fear, special definition of the threshold and degree of distress
- ethics committee with paediatric expertise
- priority of the interests of children

RECOMMENDATIONS
OF THE ETHICS WORKING GROUP
OF THE CONFEDERATION OF EUROPEAN SPECIALISTS IN PAEDIATRICS (CESP)*

ETHICAL PRINCIPLES AND OPERATIONAL GUIDELINES FOR GOOD CLINICAL PRACTICE IN PAEDIATRIC RESEARCH

Approved by the CESP on May 5th 2002

•**Members**: Timothy L.Chambers (UK), Francis P.Crawley (Belgium), Denis Gill (Ireland), Milena LoGiudice (Italy), Stefan Grosek (Slovenia), Marit Hellebostadt (Norway), Ronald Kurz (Austria) [Chairman], Maria de Lourdes-Levy (Portugal), Staffan Mjönes (Sweden), Armido Rubino (Italy), Pieter J.J. Sauer (Netherlands), Martti Siimes (Finland), Michael Weindling U.K.), Maximilian Zach (Austria).

• **Publication:** Eur J Pediatr 163: 53-57,2003

GCP – GUIDELINES OF CESP

AIM OF CLINICAL STUDIES

- focus only on the knowledge, the epidemiology, pathogenesis, prevention, diagnosis, cure or alleviation of child related diseases or conditions
- no involvement in research only for scientific interests
- no involvement for research objects on behalf of adults

GCP – GUIDELINES OF CESP

FORMS OF RESEARCH

- observational research (epidemiology, clinical data)
- interventional research
  - pharmacokinetic/pharmacodynamic research
  - controlled clinical studies
    (controls, placebo without withholding a proven effective treatment)
  - uncontrolled clinical studies
    (rare diseases)
  - post-marketing studies
    (long term effects)

GCP – GUIDELINES OF CESP

TIMING OF THE INVOLVEMENT OF CHILDREN

- Diseases affecting children exclusively — phase 1
  (following pre-clinical safety data)
- diseases mainly affecting children
  or with particular gravity in children
  or with different natural history (adults) — phase 2
  (following evidence of efficacy in adults)
- diseases occurring in children and adults
  with no or limited treatment — phase 2
  (following evidence of efficacy in adults)
- diseases occurring in children and adults
  with known treatment — phase 3
  (following completion of adult phase 3 trials)

GCP – GUIDELINES OF CESP

HOMOGENOUS AGE SPECIFIC GROUPS

- premature newborn infants (< 36th g.w.)
- term newborn infants (0-27 days)
- infants and toddlers (28 days- 23 months)
- small children (2-5 years)
- school children (6-11 years)
- adolescents (12-18 years)

GCP – GUIDELINES OF CESP

BENEFIT VERSUS RISK

- defining and monitoring the risk threshold
- considering all means to protect the integrity of the child
- observing preconditions to provide benefits and prevent inadequate risks
- specifying different categories of justifiable research depending on the degree of risk (National Institute of Health 1998)

GCP – GUIDELINES OF CESP

PRECONDITIONS TO PREVENT INADEQUATE RISKS

- Clinical study devoted to reducing suffering and improving the prognosis of diseases
- severe foreseeable risks should not be taken
- expected benefits must exceed recognisable risks (positive benefit / risk (chance) ratio)
- minimising risks by all possible means avoiding potential harm according to individual evaluation
- Considering different degrees of risk: minimal risk – greater than minimal risk

GCP – GUIDELINES OF CESP

PLANNING AND CONDUCTING CLINICAL TRIALS IN CHILDREN

ADDITIONAL CHILD-SPECIFIC CONSIDERATIONS TO BASIC GCP- GUIDELINES

- clarifying the target and necessity of the study for children
- clarifying the method of recruitment (no gifts, but compensation)
- elaborating a child-specific study design by experts
- clarifying foreseeable study-relevant risks and burdens and measures to minimise them
- focusing special attention on informed consent and assent
- describing biometric planning and statistical evaluation adapted to the age group
- performing the study by competent experts
- conducting the study in adequate institutions

GCP – GUIDELINES OF CESP

MINIMISING RISKS

- observing the Operational Guidelines for Ethics Committees of the WHO 2000
- safety data from pre-clinical and adults studies unless in child-exclusive diseases
- low number of subjects but high enough for adequate statistics
- limiting stressing and invasive interventions to the minimum necessary
- small blood sample volumes (e.g. micro-methods)
- conduct and supervision of the study by experienced personnel
- careful study protocols evaluated by ethics committee members experienced in paediatric research and special needs of children

GCP – GUIDELINES OF CESP

MINIMISING DISCOMFORT

- Experienced personnel with adequate knowledge and skills capable of empathic and trustworthy communication with children and parents
- child – suitable infrastructure of the institution (familiar environment, rooming-in etc.)
- measures to minimise inconvenience of interventions (e.g. local anaesthetics)
- blood samples in connection with routine blood sampling

GCP – GUIDELINES OF CESP

INFORMED CONSENT / ASSENT

Definitions

- **INFORMED CONSENT**
  approval of the legal representative
- **INFORMED ASSENT**
  acquiescence of the child to participate in the clinical trial

Publications

Guidelines for informed consent in biomedical research involving paediatric populations as research participants
Eur J Pediatr (2003) 162:455-458

Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specalists in Paediatrics (CESP)
Eur J Pediatr (2003) 162: 629-633

GCP- GUIDELINES OF CESP

INFORMED CONSENT / ASSENT

Main topics of guidelines

- respecting the child as a person
- no kind of pressure or improper influence
- obtaining informed consent of legal representatives including confirmation of the written sheets
- obtaining informed assent of the child capable to understand the aim, the possible chance and the risks of the study
- adapting content, language and mode of communicating the information to the child´s capacity
- accepting the refusal of the competent child
- observing different cultural backgrounds (mediator)
- written information sheets must be approved by the ethics committee

GCP – GUIDELINES OF CESP

THE ROLE OF ETHICS COMMITTEES
(INSTITUTIONAL REVIEW BOARDS)

- **observing the Operational Guidelines for Ethics Committees of the WHO 2000**
- **evaluating the competence of the responsible study investigator and the suitability of the institution for paediatric research**
- **evaluating the applied study protocol**
- **observing the child-specific GCP-aspects of the paediatric study (study design, minimising risks and discomfort, information sheets etc.)**
- **experts in paediatric research and special needs of children**

COMPATIBILITY
OF THE ETHICS PRINCIPLES AND GCP-GUIDELINES

with

- the CPMP/EWP Note for Guidance on Clinical Investigation of Medicinal Products in Children
- the UN Convention on the Rights of Children (1989)
- the Declaration of Helsinki (2000)
- the WHO Good Clinical Practice Guidelines (2000)
- the CIOMS International Guidelines for Biomedical Research Involving Human Subjects
- the EFGCP Guidelines
- the WHO Operational Guidelines for Ethics Committees that Review Biomedical Research
- the ICH-GCP-Guidelines, Topic E 11
- the EU-Directive