Ethics of Clinical Trials in Children

European Commission
Research DG
F Hirsch, P Zilgalvis, M Fitzgerald, E Pauwels
Unit L 3, Governance and Ethics
I. EC Ethical Reviews in Context
Why set up Ethical Reviews?

Two Major Objectives:

- Assuring *citizens* and *decision-makers* that EU-funded research complies with the *highest ethical standards*

- Facilitating *Research Excellence* in FPs
Since the 1980s, the Framework Programmes have increasingly emphasized the importance of ethics as essential principles and best practices framing research activities.

This emphasis on ethics is particularly in line with the current European Commission objectives to promote a responsible governance of research and to bring science closer to society.
EC Ethics Reviews—Historical Overview

Sixth Framework Programme (FP6)

- FP6 shows a substantive increase of research proposals undergoing ethics reviews.

![Bar chart showing the number of research proposals undergoing ethics reviews from 2002 to 2006. The chart shows a significant increase from 49 in 2002 to 280 in 2006.]
Breakdown of projects having undergone ethics reviews, by research area

11% of all funded FP6 projects

- Bio-medicine and Genetics; 45%
- ICT; 8%
- Mobility (Marie Curie); 11%
- Food and green biotech; 11%
- Nano-tech; 9%
- Other; 18%
II. EC Ethics Reviews in practice
EC Ethics Reviews Panels – Optimal Composition (1)

- EC Ethics Reviews are performed by a panel of experts from different disciplines such as law, sociology, philosophy and ethics, psychology, information technology, medicine, molecular biology, and veterinary science.
- Representatives of civil society may also be invited, such as representatives of patient organisations.
- The experts in the Ethics Review panel have the same status as experts performing the scientific evaluation and are bound by the European Commission obligations concerning conflict of interest and confidentiality.
Balance in Fields of expertise - Ethical Reviews 2004 (FP6)

45% of female experts

- Bioethics: 31%
- Health and Medical Sciences: 24%
- Biology and Biotechnology: 6%
- Technological Sciences: 2%
- Animal Welfare: 9%
- Humanities and Social Sciences: 6%
- Law: 12%
- Other: 16%
Optimal Composition (3)

Geographical Balance in Ethics Reviews in 2006

Experts mainly from the EU Member States, but also from outside EU

First Nationality

AL  BE  BG  CZ  DE  DK  EE  ES  FI  FR  GR  HU  IE  IL  IT  LT  LV  MT  NL  NO  PL  PT  RO  RU  SE  SK  TR  UK

23  12  3  2  5  5  21  12  12  6  5  7  7  6  6  5  7  6  4  5  7  3  1  1  20
**Legal Basis for Ethical Reviews in FP7 – (1)**

- **Seventh Framework Programme (Decision N° 1982/2006/EC), Article 6 (1§):**
  
  « All the research activities carried out under the Seventh Framework Programme shall be carried out in compliance with fundamental ethical principles. »

- **Rules for Participation, Article 10:**
  
  « A proposal […] which contravenes fundamental ethical principles […] shall not be selected. Such a proposal may be excluded from the evaluation and selection procedures at any time. »
Legislation, regulations and conventions

European references on ethics and science

This section lists European legislative, regulating and advising documents related to ethics and science.

- Directive 95/46 on the protection of personal data
- Directive 2001/20/EC on good clinical practice
- Directive 2001/83/EC on medicinal products for human use
- COMMISSION REGULATION (EC) No 1084/2003 on the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State
- COMMISSION REGULATION (EC) No 1085/2003 the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93
- Directive 98/44/EC on the legal protection of biotechnological inventions
- Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes
- Protocol on Protection and welfare of animals (Protocol to the Amsterdam Treaty)
- Directive 90/219/EEC on the contained use of genetically
Ethical Reviews in Practice: The Project Evaluation Process

■ Scientific Evaluation

→ **Scientific evaluators identify** the proposals raising ethical issues and needing ethical reviews.

■ Ethical Review (if required)

*All proposals for funding involving a research intervention on humans, the use of hESC and/or foetal issues, and non-human primates will be automatically submitted to an ethical review panel.*
Ethical Review Methodology

**COMMON PROBLEMS:**

→ **Issues related to Children**: Minimum Risks, Fear, Pain and Distress? Real and Direct Benefit?

→ Research on Animals: Number; Humane End Points; Checked alternatives?

→ Developing Countries: Benefit sharing

→ Conflict of Interest: Treating Doctor; Research Interest
III. Typology of ethical issues
Sensitive ethical issues in FP6 proposals having undergone ethics reviews (2006)
Research involving children (1)

For which purpose?

- Research involving children mainly concerned biomedical research.
- A significant part of research on children applied to behavioural studies.

Criteria to be taken into account?

- Number of children involved
- Direct benefit from the study
- Burden of the study
- Informed consent from parent/tutors
- Assent of children (when possible)
Research involving children (2)

Case study 1: Preventing coeliac diseases – Research involving children (FP6 Proposal 2005)

This case study focuses on the influence of the dietary history in the prevention of coeliac disease.

- One of the ethical issues raised by this study is the involvement of infants (1 000) and children of school age (16 000) unable to give consent.
- The other issue was the biopsy performed on children with family history of coeliac disease.
Case study 1: Preventing coeliac diseases (ctd)

- Article 17 of the Council of Europe Convention on Human Rights and Biomedicine seeks the protection of persons not able to give consent (e.g. 4-6 month old babies).

  Research involving such persons is only allowed if:

  I) The results of the research have the potential to produce real and direct benefit to his/her health.

  (II) The research entails only minimal risk and minimal burden for the individual concerned.
Case study 1: Preventing coeliac diseases (ctd)

- Problems raised by ethics review panellists:
  - Children can only be enrolled in research projects if their participation has the potential to produce **real and direct benefits for them**, or if the intervention imposes **minimal burden/risk**.

  - An estimated 160 children will fall into neither category and **the intervention will impose more than a minimal burden/risk for no direct benefit**. In this current design, this population study therefore contravenes the Council of Europe Convention on Human Rights and Biomedicine.

As a consequence, the PI did modify the study design in order to get EU funding.
Research involving children (2)


This case aimed to extend an EC-funded survey in several European countries to non developing countries (Ethiopia, Gambia).

- The first ethical issues raised by this study is the lack of authorization by RECs from these two countries.
- The other issue was the involvement of children of school age unable to give consent. Teachers were supposed to select the children involved.
Case study 2: Survey on the family impact of contraception in African rural villages (ctd)

- Problems raised by ethics review panellists:
  - A clearance should be get from local RECs.
  - There is no clear benefit for local population.
  - There is a clear risk of stigmatisation of involved children.

The Commission decided to reject this project
Our address:
European Commission
DG RTD
Unit L3, Governance and Ethics