ETHICS IN PEDIATRIC CLINICAL RESEARCH

André Baruchel

Hôpital Robert Debré, Université Paris Diderot
Boldini Institute and UNICAMP
Limitations

• A clinician is speaking

• Himself an investigator:
  – e.g. 21 trials activated in Department
    • Phase I-II: 10
    • Phase III: 10
    • Epidemiology: 1
  – e.g. International collaborations

• A non exhaustive and systematic talk
Ethics, also known as moral philosophy

• Branch of philosophy that involves systematizing, defending, and recommending concepts of right and wrong behavior

• Applied ethics include bioethics i.e. the study of controversial ethics brought about by advances in biology and medicine.
Clinical research

• Branch of medical science that determines the safety and effectiveness of:
  – medications, devices, diagnostic products and treatment regimens intended for human use.

• In clinical practice, one used established treatments while *in clinical research evidence is collected to establish a treatment.*
Medical schools and university hospitals are increasingly dominated by investigators. Every young man knows that he will never be promoted to a tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator. If the ready availability of money for conducting research is added to this fact, one can see how great the pressures are on ambitious young physicians.
A visionary statement (II)

« One can therefore anticipate an increase in experimentation; and the newly developed concept of clinical research as a profession…

And this of course can lead to an unfortunate separation between the interests of science and the interests of the patient »

What is pediatrics? What subsets?

• European Directive: 0-18 years
• ICH E 11
  – Preterm newborn infants,
  – Term newborn infants (birth to 27 days)
  – Infants from 1 to 23 months
  – Child: 2 to 11 years
  – Adolescents from the age of 12 up to but not including 18 years above).

*these age groups poorly correlate with maturation especially from the developmental point of view and trials may be performed across age groups, with consequences for ethical aspects of their conduct.*
The Pediatric Dilemma (I)

• Millions of children: diseases and illnesses that do not have adequate treatment
• Many others: harmed by medicines intended to help them
• ~50% of prescribed drugs in Pediatrics: no regular pediatric indication/evaluation

In order to protect and help the children, society must conduct pediatric research to identify safer and more effective medical treatments.
The Pediatric Dilemma (II)

• This research requires exposing some children to risks for the benefit of others.

BUT

• « it is unethical to expose children to research risks for the benefit of others »
  – this practice seems to violate our obligation to protect children from harm and exploitation.
Clinical research with children thus appears to represent an irresolvable dilemma:
- either we can protect pediatric subjects from exploitation
- or we can protect pediatric patients from dangerous medicines
- but not both!
Why medicinal products and strategies need to be studied in children

- Children are not small adults.
- Differences in pharmacokinetics and pharmacodynamics compared to adults.
- Difference in adverse reactions.
- Growth and maturation processes.
- Certain specific diseases unique to children.
- Specific consequences of medical interventions may be seen in children and may only appear long after exposure.
Many Documents about Ethics (I)


A Brazilian forum in 2000: "Even though the Declaration of Helsinki is the responsibility of the World Medical Association, the document should be considered the property of all humanity"
Articles in
The declaration of Helsinki
with a potential implication
for the pediatric population
DoH: Article 5

• Medical progress is based on research that ultimately must include studies involving human subjects.

• Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
DoH: Article 9

• Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights.

• Some research populations are particularly vulnerable and need special protection.
  – These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
DoH: Article 17

• Medical research involving a disadvantaged or vulnerable population or community is only justified if:
  – the research is responsive to the health needs and priorities of this population or community AND
  – If there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
DoH: Article 26

• When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress.

• In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

Difficulties / hypocrisy?
DoH: Articles 27 and 28

• For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative.

• These individuals must not be included in a research study that has no likelihood of benefit for them unless:
  • it is intended to promote the health of the population represented by the potential subject
  • the research cannot instead be performed with competent persons
  • the research entails only minimal risk and minimal burden.

• When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.
The physician may combine medical research with medical care only to the extent:

– that the research is justified by its potential preventive, diagnostic or therapeutic value

– and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
Many Documents about Ethics (II)

- Convention on the Rights of the Child
- Charter of Fundamental Rights of the EU (2000)
- Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)
- Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997)
- International Declaration on Human Genetic Data (UNESCO, 2003)
- Universal Declaration of Human Rights of 1948
- Council of Europe’s Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine
- ICH E6 guidelines on Good Clinical Practice.
Some concepts

Vulnerability
Scientific necessity
Extrapolation
Vulnerability of children

- Lack of mature decision making capacity (age limit?)
- Subject to the authority of others
- Can mask underlying dissent
- Rights and interests may be socially undervalued.
- May have acute medical conditions requiring immediate decisions without time for education and deliberation
- May have serious medical conditions that cannot be effectively treated

Parental permission and child assent procedures alone cannot mitigate these vulnerabilities.

Studies in the pediatric population to be designed to minimize risk and maximize the possibility of therapeutic benefit

Kipnis K Theor Med Bioeth 2003
Vulnerability of children

• Because of the special protection they deserve, children should not be the subject of clinical trials when the research can be done in legally competent subjects (i.e. adults capable of informed consent) (Directive 2001/20/EC of the European Parliament)

• If research with children proves necessary, the least vulnerable among them should usually be included (i.e. older children).

• If there is a necessity to subject children to a clinical trial, the choice of subsets of the paediatric population to be included should be made on the basis of:
  – the likely target population for the medicine being tested
  – the possibility of extrapolation
  – the scientific validity of such an approach.
Scientific Necessity: an ethical principle (I)

• Fundamental pillar of pediatric research

• Children not be enrolled in a clinical investigation unless necessary to achieve an important scientific and/or public health objective concerning the health and welfare of children.
  – “important scientific question”: generates information that is necessary and timely for establishing the appropriate pediatric use of investigational therapeutics.

• Corollary: children not be enrolled in studies that are duplicative or unlikely to yield important knowledge applicable to children about the product or condition under investigation.

• Principles grounded in regulations and/or guidelines governing human subject protections worldwide.
Scientific Necessity (II)

• « Equitable selection » : subjects who are capable of informed consent (i.e., competent adults) to be enrolled prior to subjects who cannot consent (e.g., children) (Dpt of Health Education and Welfare 1978b, USA)

• Broad international agreement
  – vulnerable populations such as children not to be enrolled in a clinical investigation unless involvement essential to answer a scientific objective relevant to the health and welfare of that vulnerable population.
The ethical principle of “scientific necessity” has been operationalized in the scientific principle of “extrapolation.”
USA (2007): Pediatric Research Equity Act: “if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies”.

Principle also found in the International Conference on Harmonization guidance on pediatric research (2000).

- The need for pediatric studies is assessed by asking a series of questions about the similarity of the adult and pediatric disease, response to treatment, drug exposure-response, and PK and PD measurements that could be used to predict efficacy.
Problem

• What is the real similarity?
  – How deep is the knowledge?
Specific regulations and guidelines (I)

• Consequence of the vulnerability
Regulations and guidelines: USA (II)

- 1973: first proposals to develop regulations providing additional protections for **vulnerable populations** that had “limited capacities to consent”.
- 1979: US FDA proposed establishing regulations for the protection of human subjects, including protections pertaining to clinical investigations involving **children**.
- 1983: regulations were promulgated that governed research on **children** conducted or funded by the Department of Health and Human Services.
- 2001, similar protections were extended to research regulated by FDA (2001).
• 2001: **Specific guidelines on pediatric research** within the European Union. Directive 2001/20/EC required Member States to develop laws, regulations, and administrative provisions for the implementation of good clinical practice in the conduct of clinical trials (2001). Specific protections were to be implemented to ensure adequate protections for minors, including parental permission and assent of able children, assurance of direct benefit for the child or for the group of patients with the particular condition, minimization of risk, and scientific necessity of the research.

• An ad hoc group responsible for guidelines development made **further recommendations** for implementation of this Directive (2008).
2008 Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC

LEGAL CONTEXT

- Directive 2005/28/EC of the European Commission of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
- Regulation (EC) No 1901/2006 of the European Parliament and the Council, as amended, on medicinal products for paediatric use (herein the ‘Paediatric Regulation’).

RELEVANT GUIDELINES

- Clinical Investigation of Medicinal Products in the Paediatric Population (E 11), CPMP/ICH/2711/99
- Guideline for Good Clinical Practice (E 6), CPMP/ICH/135/95
- Choice of Control Group in Clin. Trials (E 10), CPMP/ICH/364/96
- CHMP Guideline on clinical trials in small populations, CHMP/EWP/83561/2005
- CHMP Guideline on conduct of Pharmacovigilance for medicines used by the paediatric population (June 2006), EMEA/CHMP/PhVWP/235910/2005- rev.1
- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2) as required by Article 18 of Directive 2001/20/EC.
- Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) (revision 1) as required by Article 11, Article 17 and Article 18 of Directive 2001/20/EC.
- Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1) as required by Article 8 of Directive 2001/20/EC.Page 7/34
- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revision 2), as required by Article 9 (8) of Directive 2001/20/EC.
- Detailed guidance on the European clinical trials database (EUDRACT Database) as required by Article 11 and Article 17 of Directive 2001/20/EC, CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset.
- Revised Questions and Answers on Clinical Trials Vol10, April 06
- WHO, Operational Guidelines for Ethics Committees (Geneva, 2000)
- Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO. International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002).
- Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI.
- Confederation of European Specialists in Paediatrics (CESP) guidelines.
Recommendations of the ad hoc group for the implementation of guidelines for Directive 2001/20/EC

• The protection against the risks of research in such a vulnerable population is paramount whilst this should not lead to denying them the benefits of research.
• Children are not small adults (specific trials).
• Children (minors) are unable to consent (in the legal sense) but their assent should be sought
• Ethics Committees need paediatric expertise to balance the benefits and risks of research in children.
• The lack of legal ability to consent has implications on the design, analysis and the choice of comparators used in trials, (trained investigators with paediatric experience).
• Pain, fear, distress and parental separation to be prevented.
• The neonate represents the most vulnerable of all paediatric age groups.
• Finally, performance of trials in children are discussed.
The Child

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The perfect investigator

The investigator’s competence and ethical conduct are the most important safeguards for the protection of the child as a research subject.

The investigator must:

- have the qualifications and expertise to carry out the study to completion;
- understand the developmental and ethical issues involved in research with children;
- have scientific uncertainty with regard to the research question being asked;
- understand the pathophysiologic features of pediatric illnesses and how they evolve with age;
- understand the adverse effects of drugs, drug interactions, and pediatric drug formulations;
- strive to prevent bias from affecting the design, conduct, or reporting of the results of the research study;
- ensure adequate disclosure of all conflicts of interest (COI) related to the research to the subjects and their families;
- be an effective communicator and present a balanced view of the risks and benefits of the research when seeking participation in the study;
- vigorously guard against scientific misconduct; and
- maintain complete records and comply with all regulatory, legal, and ethical standards for research in children.

If the investigator is a junior investigator, there should be evidence of appropriate mentorship and oversight by a more senior investigator or oversight committee.

Shadde RE and Denne SC Pediatrics 2010
Informed consent

• “A decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented:
  – by any person capable of giving consent or,
  – where the person is not capable of giving consent, by his or her legal representative

• if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.”

Article 2 of the Clinical Trials Directive
Assent

• The notion of assent is recognised in the Declaration of Helsinki:
  – “When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.”

Obviously, the capacity of a child to make voluntary, informed decisions, i.e. to assent, evolves with age, maturity and previous experience of life and illness.
Assent from children

- Whenever appropriate, the child should participate in the (informed) consent process together with the parents. This process should be conducted with enough time.
- The evaluation of whether or not a child can give assent should not solely be based on chronological age, but should also depend on other factors such as developmental stage, intellectual capacities (especially in children with special needs and/or learning difficulties), life/disease experience, etc. Role of parents +++.
- The minor’s assent is not sufficient to allow participation in research unless supplemented by informed consent of the legal representative.
- Separate information sheets for adults and children, and separate consent and assent forms should be used in order to provide age-appropriate information, in language and wording appropriate to age, psychological and intellectual maturity. The assent information sheets and assent forms should be age-appropriate and should include provision of information on the purpose of the trial, and potential benefits and harms.
- Assent, like consent, is a continuous process and should be sought during the trial as well, e.g. during repeat trial visits.
- The processes for informing the child and seeking assent should be clearly defined in advance of the research and documented for each child. While assent may not be possible in all age groups (e.g., neonates) or in all research conditions (e.g., research in emergency situations), the information process provided to the child and the child’s response should be documented.
### INFUSION OF XXX AND SAMPLING PROCEDURES

<table>
<thead>
<tr>
<th>Avant</th>
<th>Cure n°1</th>
<th>14 à 28 jours sans perfusion</th>
<th>Cure n°2</th>
<th>Après</th>
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<tbody>
<tr>
<td>Jour n°1</td>
<td>Jour n°2</td>
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**M** : prélèvement de moelle osseuse (myélogramme)

**PL** : ponction lombaire
Parental comprehension and satisfaction in informed consent in paediatric clinical trials: a prospective study on childhood leukaemia

H Chappuy,¹,² A Baruchel,³ G Leverger,⁴ C Oudot,³ B Brethon,³ S Haouy,⁴ A Auvrignon,⁴ D Davous,⁵ F Doz,⁶ J M Tréluyer⁷,⁸

Arch Dis Child published online June 15, 2010
• How well informed is a consent obtained in the framework of a life-threatening disease?
Objectives

• Main objective
  – To evaluate the extent to which parents are satisfied with and understand the information they are given when their consent is sought for their child to participate in a phase III randomised clinical trial (FRALLE 2000 A) and the reasons for their decision.

• Secondary objective
  – To identify predictive factors for understanding
Fralle 2000 A protocol

- Children (1 y < age <10 y) with standard-risk B lineage acute lymphoblastic leukemia
- Randomized phase III multicenter study
- Main objective
  - Event-Free Survival with or w/o anthracyclins during induction therapy
- 2 arms : anthracycline+ / anthracycline -
- Information sheet describing disease, adverse events, randomization
- Signed informed consent of the two parents
- Duration of the treatment ~ 3 years
- Inclusion period: 5 years
- Follow-up period: 10 years
Methodology

- Prospective study
  - 2 pediatric departments (Paris)
- Parents questioned twice by a qualified psychologist using a semidirected interview
- 1 and 6 months after consent was sought.
### Questions asked during the interview addressing the level of understanding

<table>
<thead>
<tr>
<th>Concept</th>
<th>Question</th>
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<tbody>
<tr>
<td>Participation in a research protocol</td>
<td>Is your child being treated as part of a research protocol?</td>
</tr>
<tr>
<td>Aim of the protocol</td>
<td>What is the aim of this protocol?</td>
</tr>
<tr>
<td>Course of the protocol</td>
<td>What is planned for your child in the framework of this protocol?</td>
</tr>
<tr>
<td>Principle of randomisation</td>
<td>If you gave consent for a protocol in which two different treatments might be given, do you know how the treatment given to your child was chosen? If yes, how?</td>
</tr>
<tr>
<td>Individual benefit</td>
<td>What benefits to you expect your child to gain from participation in this protocol?</td>
</tr>
<tr>
<td>Collective benefit</td>
<td>Could you describe the possible benefits to other children of participation of your child in this protocol?</td>
</tr>
<tr>
<td>Risks</td>
<td>What are the possible risks to your child of participating in this protocol?</td>
</tr>
<tr>
<td>Alternatives</td>
<td>If you had not consented to the participation of your child in this protocol, what care would your child have received?</td>
</tr>
<tr>
<td>Voluntary nature of participation</td>
<td>Was the participation of your child in this protocol voluntary?</td>
</tr>
<tr>
<td>Duration of participation</td>
<td>How long were you told that the participation of your child in this protocol would last?</td>
</tr>
<tr>
<td>Freedom to withdraw from the project at any time</td>
<td>Could you change your mind once the study had begun?</td>
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Results

- **75 interviews:**
  - first interview: 43
  - second interview: 32 (6 refusal + 5 « LFU »)
- **Children**
  - 26 boys, 17 girls
  - Mean age: 3.68 years (SD=2.26; range 1.61-9.8 years)
- **Parents:**
  - French as non first language: 18%
  - high socio-professional standing (senior management, company director, etc): 43%
  - intermediate status (employees, agriculture): 38%
  - w/o profession: 19%
Results

• consent for FRALLE 2000A inclusion sought from both parents seen together: 38 (88%).

• only one parent (geographical separation or single-parent families) : 5 (12%)

• mean time to give a response : 4.56 days (1-21 days; SD 4.37).

• reading of all or part of the information provided: 31 (72%)
Question 1

• «Is your child being treated as part of a research protocol?»

→ 8 parents (19%) did not know about that participation.....
Why this protocol?
None
Partial
Complete

Course of this protocol?
How is chosen the treatment to be received by your child?

*Information sheet explaining the randomisation process.*
Can you describe to me the benefit(s) expected for your child within this protocol?
Do you see a potential interest of the results of this study for other children?
What are the possible risks for your child within this treatment protocol?
If you would have disagreed with the inclusion of your child in this study, what type of treatment would have been administered?
Does the participation of your child in this protocol rely on your will, free of any pressure?
What is the approximative duration of your child’s participation in the protocol?
Could you change your mind after the beginning of the treatment?
Complete understanding of all the 10 elements

None of the parents!
Misunderstandings…

• « Therapeutic misunderstanding »
  Identical proportion vs a previous study
  (15-20% principle of research; 40% about randomization)

• Misunderstanding on relevant informations
  Relevance for parents vs relevance for doctors/investigators/legislation.

## Predictive factors

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<table>
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<tbody>
<tr>
<td>Reading of the information sheet</td>
<td>NS for all items</td>
</tr>
<tr>
<td>Personal seeking for information</td>
<td>NS for all items</td>
</tr>
<tr>
<td>Professional activity of the parents</td>
<td>NS for all items</td>
</tr>
<tr>
<td>Language spoken at home</td>
<td>p&lt;0.001 for randomization</td>
</tr>
</tbody>
</table>

Were also studied: age, sex, country of origin, marital status…,
Main determinants of decision

- Trust of the medical team (67%)
- Potential benefit for other children (37%)
- Access to the best treatment possible for their child (30%)
Conclusion

• Parents sign an informed consent without a precise understanding of the specificities of the experimental protocol.

• The decision is not based on a complete understanding of the informations considered as necessary by the investigators and IRBs but on TRUST, even (more?) in the setting of a life-threatening disease.
Propositions

• Better distinguish what is the subject of research from care even if intricated

• To insist on the continuity of the consent process
  – Confirmation ? Questionnaire ?

• Reformulation of the information:
  – Training of doctors and other care providers
  – Role of the parents association
  – New methods (videos, internet etc)

• Reinforce the process of consent if the maternal language is different from the one of the country where the child is treated
Many other fields for ethics/science

- e.g. to include less children in a defined protocol
  - Bayesian statistics or cluster randomization, should be studied and promulgated to reduce the patient-recruitment burden by minimizing sample sizes, to permit earlier detection of inadequate benefit in exploratory trials
One area of amazing recent medical advances has been childhood cancers, for which survival rates have quadrupled over the past four decades and now exceed 80%. This progress has been driven not only by the introduction of novel therapies but also by the remarkable level of patient and physician participation in the clinical research process. The robust clinical trial enterprise for this patient population may offer a model for improving outcomes in other age groups, populations, and conditions. The success stems largely from the Children’s Oncology Group, a cooperative clinical research group that includes more than 5000 U.S. pediatric cancer specialists. Ninety percent of U.S. children with cancer receive care in centers affiliated with this network, and more than 60% of children with cancer are enrolled in clinical trials. This engagement permits rapid evaluation of new therapies, including delineation of appropriate subpopulations, which
Conclusion

• Very complicated field
• To be based on:
  – a honest and compassionate relationship with the child and parents
  – the preeminence of patient interest over science interest or any other form of interest
• Many research to do about ethics!
BACK-UP SLIDES
DoH: 5 ethical principles

1. Research must conform to moral and scientific boundaries and should be based on laboratory or animal experiments or established facts. *In other words, it is unethical to test a new theory that has no background research immediately on humans, with no idea what the results are likely to be.*

2. Research should only be conducted by fully trained and qualified staff. *This stops the risks of misuse of equipment and subsequent injury, to either the participant or the researcher.*

3. Research may only be carried out when the potential benefits gained from conducting the research outweigh the potential negative impact on the health of the subject. *So in layman’s terms, the research must do more good if it works, than bad if it fails.*

4. All experiments should have initial research done beforehand, to minimize the risk to the participating subject or subjects.

5. Particular caution: when a participant’s personality could be altered, either by drug or therapy, which could cause endangerment to the participant or the research team.
The Child

PI and co-investigators

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Ethical principles: generalities

• For the purpose of research, 3 ethical principles should be adhered to:
  – respect for persons
  – beneficence: ethical obligation to do good and avoid harm
  – justice: a fair distribution of burden and benefits of research

Fully applicable to clinical trials in children.
The perfect investigator

The investigator’s competence and ethical conduct are the most important safeguards for the protection of the child as a research subject.

The investigator must:

- have the qualifications and expertise to carry out the study to completion;
- understand the developmental and ethical issues involved in research with children;
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- ensure adequate disclosure of all conflicts of interest (COI) related to the research to the subjects and their families;
- be an effective communicator and present a balanced view of the risks and benefits of the research when seeking participation in the study;
- vigorously guard against scientific misconduct; and
- maintain complete records and comply with all regulatory, legal, and ethical standards for research in children.

If the investigator is a junior investigator, there should be evidence of appropriate mentorship and oversight by a more senior investigator or oversight committee.
A clinical trial on minors may be undertaken only if benefit for this group of patients is envisaged

- Still an opened question: whether or not it is acceptable to expose children to some research risks for the benefit of others.
  - Results of survey (Wendler and Jenkins) support the acceptability of such an exposure.
  - The absolute limit of minimal risks and minimal burdens stipulated by the EU recommendations may prohibit important appropriate research (Westra et al.).
  - The involvement of children in research that will not directly benefit from them clearly poses an ethical dilemma.
  - To get a fair informed assent/consent, the minor and his/her representative should have also had a clear idea of the possible direct effects in accordance with the following ethical principle that “patients’ interest should always prevail over science/society”.
  - The clinical physician should consider the patients and the trial NOT in a holistic way but on a careful case-by-case assessment.
tor's. The question rises, then, about valuable data that have been improperly obtained.* It is my view that such material should not be published.† There is a practical aspect to the matter: failure to obtain publication would discourage unethical experimentation. How many would carry out such experimentation if they knew its results would never be published? Even though suppression of such data (by not publishing it) would constitute a loss to medicine, in a specific localized sense, this loss, it seems, would be less important than the far reaching moral loss to medicine if the data thus obtained were to be published. Admittedly, there is room for debate. Others believe that such data, because of their intrinsic value, obtained at a cost of great risk or damage to the subjects, should not be wasted but should be published with stern editorial comment. This would have to be done with exceptional skill, to avoid an odor of hypocrisy.

**SUMMARY AND CONCLUSIONS**

The ethical approach to experimentation in man has several components; two are more important than the others, the first being informed consent. The difficulty of obtaining this is discussed in detail. But it is absolutely essential to strive for it for moral, sociologic and legal reasons. The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and unless all

*As far as principle goes, a parallel can be seen in the recent Mapp decision by the United States Supreme Court. It was stated there that evidence unconstitutionally obtained cannot be used in any judicial decision, no matter how important the evidence is to the ends of justice.

hazards are made clear. If these are not known this, too, should be stated. In such a situation the subject at least knows that he is to be a participant in an experiment. Secondly, there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.

Ordinary patients will not knowingly risk their health or their life for the sake of "science." Every experienced clinician investigator knows this. When such risks are taken and a considerable number of patients are involved, it may be assumed that informed consent has not been obtained in all cases.

The gain anticipated from an experiment must be commensurate with the risk involved.

An experiment is ethical or not at its inception; it does not become ethical post hoc — ends do not justify means. There is no ethical distinction between ends and means.

In the publication of experimental results it must be made unmistakably clear that the proprieties have been observed. It is debatable whether data obtained unethically should be published even with stern editorial comment.

**REFERENCES**

3. Pappworth, M. H. Personal communication.
Percentage of parents who understood the 11 items in M1 and M6.

Chappuy H et al, Arch Dis Childhood 2010
<table>
<thead>
<tr>
<th>Goal</th>
<th>Area of Change</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving effectiveness</td>
<td>Distinction between types of risk</td>
<td>For most studies in which risks are primarily informational, research could commence immediately after the study is registered through submittal of a one-page form, accompanied by a commitment to observe data-security protections.</td>
</tr>
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<td></td>
<td>Annual reviews</td>
<td>For research posing more than a minimal level of risk, an annual review would be conducted except when the activities performed involve only standard clinical follow-up data collection or data analysis.</td>
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<tr>
<td></td>
<td>Research activities posing minimal risk</td>
<td>For research posing minimal risk, no annual review would be required unless a reviewer explicitly justified the request for such a review.</td>
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<td></td>
<td>Review of multisite studies</td>
<td>The list of research activities qualifying for expedited review would be regularly updated as empirical data are accumulated.</td>
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<tr>
<td>Guidance</td>
<td>Guidance</td>
<td>Only a single IRB of record would be allowed for the oversight of all domestic sites.</td>
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<tr>
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<td>Federal oversight</td>
<td>The need for a mechanism intended to harmonize guidance across federal agencies would be evaluated.</td>
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<tr>
<td>Enhancing protections</td>
<td>Data concerning adverse events</td>
<td>If a U.S. institution receives some Common Rule agency funding for human-subjects research, all research conducted at the institution would be subject to federal oversight.</td>
</tr>
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<td></td>
<td>Informed consent</td>
<td>The goals of change in the treatment of informed consent would be to specify more explicitly the content of consent documents, limit the length of documents, simplify and streamline institutional boilerplate, promulgate the use of standardized consent documents, and permit the use of oral consent for surveys, focus groups, and interviews conducted with competent adults, even if identifiers are retained.</td>
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<td></td>
<td>Use of biospecimens</td>
<td>Written consent would be required (even if no information identifying the source was retained) but could be obtained with the use of a standardized form allowing open-ended use in future research. This change would be applied only prospectively — that is, to specimens collected after the revised regulations become effective.</td>
</tr>
<tr>
<td></td>
<td>Confidentiality protections</td>
<td>Institutions would be required to implement confidentiality and data-security protections modeled on those used in HIPAA (e.g., the use of encryption and audit trails).</td>
</tr>
</tbody>
</table>
Synthèse

Compréhension variable des parents

But
Bénéfice individuel
Liberté d’arrêter

Risques
Protocole
Alternative

Randomisation

Volontariat
Bénéfice collectif
Durée de participation

Langue parlée
Pediatric Oncology as a model?

Looking beyond Translation — Integrating Clinical Research with Medical Practice

Annette C. Gelijns, Ph.D., and Sherine E. Gabriel, M.D.

One area of amazing recent medical advances has been childhood cancers, for which survival rates have quadrupled over the past four decades and now exceed 80%. This progress has been driven not only by the introduction of novel therapies but also by the remarkable level of patient and physician participation in the clinical research process. The robust clinical trial enterprise for this patient population may offer a model for improving outcomes in other age groups, populations, and conditions. The success stems largely from the Children’s Oncology Group, a cooperative clinical research group that includes more than 5000 U.S. pediatric cancer specialists. Ninety percent of U.S. children with cancer receive care in centers affiliated with this network, and more than 60% of children with cancer are enrolled in clinical trials. This engagement permits rapid evaluation of new therapies, including delineation of appropriate subpopulations, which
A clinical trial on minors may be undertaken only if benefit for this group of patients is envisaged

- Still an opened question: whether or not it is acceptable to expose children to some research risks for the benefit of others.
  - Results of survey (Wendler and Jenkins) support the acceptability of such an exposure.
  - The absolute limit of minimal risks and minimal burdens stipulated by the EU recommendations may prohibit important appropriate research (Westra et al).
  - The involvement of children in research that will not directly benefit from them clearly poses an ethical dilemma.
  - To get a fair informed assent/consent, the minor and his/her representative should have also had a clear idea of the possible direct effects in accordance with the following ethical principle that “patients’ interest should always prevail over science/society”.
  - The clinical physician should consider the patients and the trial NOT in a holistic way but on a careful case-by-case assessment.
Activité clinique induite par les essais / études de Recherche Clinique

- 10 essais de phase I-II activés
  - 14 pts inclus
- 10 essais de phase III-IV
  - 45 pts inclus
- 1 étude épidémiologique (LAL)
  - 50 pts inclus
DoH: 5 ethical principles

• 1. Beneficence and nonmaleficence
• 2. Fidelity and responsibility
• 3. Integrity
• 4. Justice
• 5. Respect for people’s rights and dignity