

Research in newborn infants. Ethical aspects, recruitment and informed consent.

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It is unnecessary to convince this audience that
- drug - research in humans is needed. Not all
relevant information can be obtained from
studies in animals or cell cultures.



It is - probably - unnecessary to convince this audience that - drug - research in newborn infants is needed. Not all relevant information can be obtained from studies in adults, animals and cell cultures.

So, why this meeting?



A child can not give consent to participate in a study

- so, no studies?
- only studies when the newborn-might-benefit from it ?
- are non therapeutic studies acceptable with extra safeguards ?



Why do adults consent to take part in studies?

- Community spirit and solidarity
- Distributive justice
- Money

Essential is autonomy: the right to make own decisions regarding one's own body and health.



Arguments pro and con research in newborns.

Pro:

- Essential to find
 - safe drugs for newborns
 - safe dosages for newborns
 - safe formulations for newborn
- Studies only can be done in newborn;
- example safe doses of gentamicin

Con:

- Newborns cannot give consent



Other arguments pro/con

- Community spirit and solidarity
 - will help improving cure and care
- Distributive justice
 - Benefits and burden distributed as fairly as possible throughout society
- Money.
 - Money cannot be involved.
- Autonomy.
 - Can a parent give consent for their child?



Can parents give consent? I.

- No formal legal basis
- Parents are supposed to act in the best interest of their child
- Parents should evaluate: “If my child would be an adult, would he/she have given consent?”



Can parents give consent? II.

Helsinki Declaration:

“For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with the applicable law.”



Safeguard for all studies in humans, medical ethics - institutional review - committees

For each protocol, the committee must evaluate:

- Does the study have a real question or questions?
- Is the study designed in the best possible way to answer the question?
- Can the study be done (number of patients, time frame)?
- What are the risks and burdens for the children involved?
- Are the results of the study to be published?



Additional requirements ethical committees

- Rights of the investigator to freely publish the results, sponsors can never block a publication, insight into the publication is allowed, however without upholding the publication
- The sponsor does not have the right to stop a trial without proper reasons



Additional requirements ethical committees especially for newborn or infants

- have studies been done in adults, what are the results
- are there data from studies in animals
- will the drug been used in newborns
- is the drug a real improvement above existing drugs



Problem with multinational studies

More and more studies sponsored by industry are designed and written by industry.

Next they have to be accepted by national ethics committees.

Industries are not willing to make adaptations just for one country.



Conclusion I.

- To conduct - drug related - studies in the newborn is ethically acceptable
- Parents can give consent
- Extra safeguards are needed



Kinds of studies

- Therapeutic:
 - Infant might have direct benefit
- Non-therapeutic:
 - Infant will not have direct benefit
 - Interventional (administration drug, phase I studies)
 - Non-interventional (normal levels, descriptive)



Legal frame work. I.

Helsinki Declaration:

“Research in children is not allowed, unless the research is necessary to promote the health of the population represented and this research cannot instead be performed in legally competent persons.”

Covenant on Civil and Political Rights:

“No one should be subjected to torture or to cruel, inhumane or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.”



- Legal - frame work. II. E.U. Directive

In 2000 the European Parliament proposed to prohibit all non therapeutic research in children

After heavy pressure from pediatricians it was accepted that:

Clinical trials in minors may be undertaken only if “some benefits for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods. 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.”



Conclusion II.

Studies in newborns are not acceptable unless the following conditions are met :

- either the infant itself or the group of infants should benefit
- studies can not be done in adults
- consent of parents
- approval ethical committee

IN ADDITION

Therapeutic:

- Burden must be acceptable in view of the potential benefit for the patient itself and the group of patients with the disease.

Non-therapeutic:

- requirement of: minimal risk

minimal harm/burden

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How to define minimal risk/burden.

CESP

- Observation
- Urine collection
- Blood sampling is not invasive

Royal College

- bloodsampling is invasive
- what to do with an extra x-ray, how much blood is acceptable



Phase I studies in children

Necessary when:

- Specific diseases for children
- Pharmacokinetics/dynamics different from adults

Are they acceptable:

- Minimal risk/burden



Randomized controlled trials

- Need to involve group without treatment. Acceptable when including this group will give proper answers, that cannot be obtained without including them.



Example I.

Respiratory disorders are frequently seen in very low birthweight infants. Different studies have shown that the administration of a surface tension reducing agent, surfactant, reduces the severity of the disease. A company designs a new surfactant, there are minimal differences with registered products. A study proposal is submitted. The study involves frequent suction of the endotracheal tube and blood sampling.

- Is this a therapeutic trial?
- Are the interventions acceptable?



Example II.

It is known from adult intensive care that gastric ulcers occur frequently in severely ill patients. Occasionally gastric bleeding is observed in newborn i.c. patients. In adult i.c. patients - routinely - H₂ blockers (or proton pump inhibitors) are given. A proposal is submitted to study the effectiveness of this medication in severely ill newborns. In order to evaluate the effect of medication, twice a gastroscopy is needed.

- Is this a therapeutic trial?
- Ratio burden/benefit?



Phase I/II studies.

- Can we give drugs to infants who do not have an indication to receive the drug?
- Should these studies only be done in infants with a disease who ultimately might benefit from the drug?



Example III.

A company would like to register a new antibiotic for use in newborns. In order to get sufficient data, a study is designed where one dose of the drugs is given. Thereafter 12 blood samples will be taken. It is clear that, when this is done in a healthy newborn, it is not therapeutic.

- Is this minimal risk/burden?
- If the drug is given to an infant with an infection, is that therapeutic? What is the balance then between benefit and burden?



Example IV

- One of the least mature organs in the newborn is the brain. Drugs therefore might have persistent effects on the brain. A new drug is developed, based on animal data there are worries about penetration of the drug in the brain. A study is designed involving fMRI. Is it acceptable to do a fMRI just for research purposes ?



Final conclusions - 1.

1. Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner.
2. Children are not small adults; they have an additional, unique set of interests.
3. Research should only be done in children if comparable research in adults could not answer the same question.
4. A research procedure which is not intended directly to benefit the individual child is not necessarily either unethical or illegal, if it is likely to yield generalised knowledge of vital importance.



Final conclusions - 2

5. All proposals involving medical research in children should be submitted to a research ethics committee involving experts in paediatric research.
6. Legally valid consent should be obtained from a child, parent or guardian as appropriate. When parental consent is obtained, the agreement of school-age children who take part in research should also be requested by researchers.



Not conducting research in newborn infants is detrimental for this group of children and therefore unethical.

However, not all studies in newborn are ethical. Strict safeguards are needed.

