Ethical Issues in Paediatric Research

Sharon Kling
Department of Paediatrics and Child Health, Tygerberg Children’s Hospital & Centre for Medical Ethics and Law Stellenbosch University

ARESA September 2015
Overview

• Historical perspective
• Why do research on children?
• Regulatory frameworks
• Research on newborns and children: What are the issues?
• Specific considerations
  – Emergency research on children and newborns
  – Research consent from young people in resource-poor settings
Paediatric experimentation: A Historical Perspective

• “Little medical heroes” – John Lentz, 1940
• “The history of pediatric experimentation is largely one of child abuse.”
• Orphans used for vaccine trials and diagnostic tests for infectious diseases
• Spinal punctures done on 423 African American newborns in 1925 to determine normal CSF composition
• Children termed “volunteers”; “experimental material”
Orphans as guinea pigs

- Scurvy induced by withholding orange juice
- Diet to induce rickets

My experience embraces a period of two and a half years, and a careful observation of about 150 cases. My opportunity for a clinical study has been exceptional, as the children were in a model institution and, where the diet was prepared in a central kitchen, and all the conditions were uniform and capable of control. Furthermore, I was sure that the infants received a diet adequate in calories and other food factors. It is only under similar conditions that studies on chronic nutritional disorders can be carried out. (Hess, 1921)
Smallpox

- First vaccination in 1721: prevention of smallpox: variolation - transfer of virulent material between subjects
- Jenner substituted cowpox for smallpox – fewer side-effects ("vaccine inoculation": *vacca* = cow in Latin)
- Pasteur modified virulence of infectious agent to produce an attenuated form of disease

Bazin Curr Opin Immunol 2001; 13: 505-510
Smallpox: The first ethical issues

- Initial tests in UK carried out on condemned prisoners and orphaned children – morality of this not questioned!
- In Boston, tested on doctor’s own 6-year-old son and two young Black slaves
- Jenner tested cowpox inoculation on 8-year-old James Phipps, son of a labourer
The Beecher Exposé

• Henry Knowles Beecher: anaesthetist
• 1966: Ethics and Clinical Research NEJM
• 22 examples of unethical research out of 50 published in leading medical journals
SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON
Willowbrook State School was one of New York’s largest institutions for mentally retarded children on Staten Island. In 1949, Hepatitis was first detected amongst the children. In 1954 Dr Krugman and Dr Giles started to study the natural history of Infectious Hepatitis, an endemic disease amongst institutionalised children. The doctors wanted to infect new admissions to the institution with hepatitis and observe the progress of the mild flu-like illness that would result. Their reasoning was that all children admitted to the institution would eventually contract the disease, they would be admitted to an isolation unit where they would be protected from other infectious diseases, they were likely to have a sub-clinical infection followed by immunity and only children whose parents gave informed consent would be included. While their initial aim was to determine the period of infectivity of infectious hepatitis, their eventual aim was to develop a hepatitis vaccine and this was accomplished.
Example 16. This study was directed toward determining the period of infectivity of infectious hepatitis. Artificial induction of hepatitis was carried out in an institution for mentally defective children in which a mild form of hepatitis was endemic. The parents gave consent for the intramuscular injection or oral administration of the virus, but nothing is said regarding what was told them concerning the appreciable hazards involved.

A resolution adopted by the World Medical Association states explicitly: “Under no circumstances is a doctor permitted to do anything which would weaken the physical or mental resistance of a human being except from strictly therapeutic or prophylactic indications imposed in the interest of the patient.” There is no right to risk an injury to 1 person for the benefit of others.
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.
Drug safety issues

- Grey baby syndrome in neonates after receiving chloramphenicol
- In utero exposure to thalidomide resulting in phocomelia
- Legislation in USA 1962 and UK 1968 to ensure safety and efficacy of new drugs in patients of all ages
The ethics of paediatric research: a delicate balance

(Book review)

Joal Hill

The Lancet 2005; Volume 365, Issue 9474, Pages 1841-1842
Paediatric research: What are the issues?

• Why research on children?
• Why are children seen as vulnerable?
• Regulatory and legal frameworks
• Issues regarding consent / assent
• Risk-benefit / best interests
• Non-beneficial / non-therapeutic research
• Specific considerations, including emergency research and research in “resource-poor settings”
Why research on children?

• “The ethical challenges in paediatric research rest in part on our understanding that physiologically, developmentally, emotionally, and in myriad other ways children are not merely miniature adults.

• “If, in an attempt to protect them from potential risks of human research, we develop treatments for children by extrapolating results from adult studies, we may actually impose harm.”

Hill Lancet May 2005
Children and research

• Often it is not sufficient, scientific, or ethical to carry out research with adults and apply the findings to children. This may be because:

• The **disease processes** in children may **differ** from those in adults.

• The **physiology of children is different** from that of adults, and the pharmacokinetics of many drugs will vary with the age of the child.
Children and research 2

• Many disorders can only be understood in the context of a child's growth and development.
• **Children are not small adults.** For the therapy to be effective, its delivery must suit their needs.
Children: “Therapeutic orphans”

- Lack of evidence for many aspects of current paediatric therapeutics
- Few therapeutic indications unique to infants and children
- Absolute quantities of drugs required small
- Actuarially, humans spend 16 years as children and 60-80 years as adults!
- Thus little incentive to develop drugs and dosing guidelines for children

Blumer Pediatr 1999;104:598-602
Encouraging research in children

- The Pediatric Rule (1994, 1999)
- The Food and Drug Administration Modernization Act (FDAMA) (1997)

Drug development programs should usually include the pediatric patient population when a product is being developed for a disease or condition in adults and it is anticipated the product will be used in the pediatric population. Obtaining knowledge of the effects of medicinal products in pediatric patients is an important goal. However, this should be done without compromising the well-being of pediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.

Why are children regarded as vulnerable subjects?
Why are children regarded as vulnerable subjects?

- Lack of mature decision making capacity
- Subject to others’ authority
- They may be deferential in ways that can mask underlying dissent
- Rights and interests socially undervalued
- Serious underlying medical conditions
- Acute medical conditions requiring immediate decisions without time for deliberation
- Lack important socially distributed goods
Paediatric research

• Fundamental issue is whether others can give valid consent on behalf of someone who is unable to do so
• Particularly important in research that does not offer benefit to the child in a narrow medical sense, i.e. non-therapeutic research
• Is the stronger duty to protect child from actual or imputed harms or should the wider beneficial consequences of performing scientifically valid research prevail?
Additional “nested” protections for children to be enrolled into research

1. The principle of scientific necessity
2. Appropriate balance of risk and potential benefit
3. Design and conduct of paediatric research must be ethically appropriate
4. Parental permission and child assent

Roth-Cline MD in press
Regulation: historical

• Nuremberg Code 1947
  – “the voluntary consent of the human subject is absolutely essential.”
  – This means that the person involved should have legal capacity to give consent.
  – Hence prohibition on non-therapeutic paediatric research
Non-therapeutic research on minors is not permissible, except where parental consent (and the assent of the minor concerned) is obtained for:

i. observation research of a non-therapeutic and non-invasive nature, because there is no risk and no interference with the integrity of the minor, provided that the research entails no more than negligible distress or discomfort;

ii. observation research of a non-therapeutic and invasive nature, provided that normally no more than negligible risk is foreseeable or known from routine clinical practice, and that the distress or discomfort is negligible. (See also 9.12.4.1)
5.1 Research involving minors

Minors should participate in research only where their participation is indispensable to the research and where participation is not contrary to the individual minor’s best interests. The research should investigate a problem of relevance to children. Where research involving minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. Note that all types of clinical research on minors should be scrutinized carefully.
5.2 Research involving a child should be approved only if:

- The research, including observational research, places the child at no more than minimal risk (that is, the risk commensurate with daily life or routine medical or psychological examinations – referred to as ‘negligible risk’ in some guidelines); or
- The research involves more than minimal risk but provides possible benefit for the child participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research, involves greater than minimal risk, with no prospect of direct benefit to the child participant, but has a high probability of providing significantly generalisable knowledge; that is the risk should be justified by the risk-knowledge ratio. The risks must represent no more than a minor increase over minimal risk.

Consent for minors to participate in research must be obtained from:

- The parents or legal guardian in all but exceptional circumstances (such as emergencies); and
- The minor where s/he is competent to make the decision; and
- Any organization or person required by law, eg the National Health Act 61 of 2003.

Where the minor is not competent, assent from the child (where appropriate) and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of a child in providing consent to participate.

- A minor’s refusal to participate in research must be respected, ie such refusal settles the matter.
- In all cases, the protocol must provide sufficient information to justify clearly why children should be included as participants.

5.2.1 Child assent:

The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the child’s assent when, in the judgement of the research ethics committee, the child is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.
Research involving minors should be approved only if:

- The research interventions, including those in observational research, presents the participant with no greater than minimal risk (that is, the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine medical or psychological examinations or tests – referred to as 'negligible risk' in some guidelines); or
- The research interventions present more than minimal risk but hold out the prospect of direct benefit for the participant. The risks must be justified by the anticipated benefit; or
- The research interventions, including those in observational research, present more than minimal risk and do not hold out the prospect of direct benefit to the participant, but have a high probability of yielding generalizable knowledge. That is the risk should be justified by the risk-knowledge ratio. The risk should represent a minor increase over minimal risk. The intervention or procedure should present experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or education settings.
- In all cases, the protocol must provide sufficient information to justify clearly why minors should be included as participants.
2.3.1.1 Consent Requirements: For research with minors, the following should be obtained:

- Consent from a parent or legal guardian in all but exceptional circumstances (e.g. emergencies). A caregiver (e.g. custodian, person providing long-term day-to-day care for the child) can act on behalf of a minor;
- Assent from the minor where s/he is capable of understanding;
- Any organization or person required by law, e.g. National Health Act, Act No 61 of 2003.
- A child's refusal to participate in research must be respected, i.e. such refusal settles the matter.

2.3.1.2 Assent Requirements: Assent means a minor's affirmative agreement to participate in research. Mere failure to object should not be construed as assent. The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the minor's assent when, in the judgement of the research ethics committee, the minor is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.
71 Research on or experimentation with human subjects

(2) Where research or experimentation is to be conducted on a minor for a therapeutic purpose, the research or experimentation may only be conducted-

(a) if it is in the best interests of the minor;
(b) in such manner and on such conditions as may be prescribed;
(c) with the consent of the parent or guardian of the child; and
(d) if the minor is capable of understanding, with the consent of the minor.

(3) (a) Where research or experimentation is to be conducted on a minor for a non-therapeutic purpose, the research or experimentation may only be conducted-

(i) in such manner and on such conditions as may be prescribed;
(ii) with the consent of the Minister;
(iii) with the consent of the parent or guardian of the minor; and
(iv) if the minor is capable of understanding, the consent of the minor.

(b) The Minister may not give consent in circumstances where-
(i) the objects of the research or experimentation can also be achieved if it is conducted on an adult;
(ii) the research or experimentation is not likely to significantly improve scientific understanding of the minor’s condition, disease or disorder to such an extent that it will result in significant benefit to the minor or other minors;
(iii) the reasons for the consent to the research or experimentation by the parent or guardian and, if applicable, the minor are contrary to public policy;
(iv) the research or experimentation poses a significant risk to the health of the minor; or
(v) there is some risk to the health or wellbeing of the minor and the potential benefit of the research or experimentation does not significantly outweigh that risk.
STATEMENT FROM THE COUNCIL ON PROCLAMATION OF S71 OF NATIONAL HEALTH ACT

1. The NHREC wishes to inform stakeholders that s71 of the National Health Act (NHA) (2003) was proclaimed with effect from 01 March 2012.

2. S71 introduces a number of new requirements for health research, including (1) written consent (2) consent from a parent or guardian for research with children (3) ‘therapeutic research’ should be in a child’s best interests and (4) consent from the Minister must be obtained for ‘non-therapeutic research with children.

3. Regulations are yet to be issued providing greater detail and operational guidance to RECs, particularly for the latter requirement.

4. The NHREC is in the process of obtaining clarity on how RECs can meet the new requirements, particularly the latter requirement.

5. The NHREC is aware that there is conflict between the legal requirements and current national ethical guidelines.
<table>
<thead>
<tr>
<th>No.</th>
<th>Page No.</th>
<th>Gazette No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. 719</td>
<td>National Health Act (61/2003): Regulations relating to research with human participants</td>
<td>4</td>
</tr>
</tbody>
</table>
Ministerial consent for non-therapeutic research with minors

7. Protocols for human participants’ research that propose non-therapeutic research with minors must have ministerial consent in terms of Section 71(3)(a)(ii) of the Act or, where appropriate, consent from a delegated authority in terms of Section 92(a) of the Act.

(a) Applications for ministerial consent must be made on Form A;

(b) the application should be considered by the Minister or the delegated authority after the protocol is reviewed by a registered health research ethics committee to assess whether it meets the required norms and standards of the health research ethics committee;
Ethics in Health Research

Principles, Processes and Structures

Second Edition

Department of Health
Republic of South Africa

2015
Anyone <18 years may not choose independently whether to participate in research

Parent or guardian gives permission for minor to choose

Minors should participate in research only where their participation is indispensable to the research
• Best interests principle difficult in research context
• Participation in research should not be contrary to the individual minor’s best interest
• Research should investigate a problem of relevance to minors
• REC should require all relevant information to be provided by the researchers
• Children should participate in research when their participation is scientifically indispensable to the research. Equipoise required in interventional clinical research
• Children should participate in research only where such research poses acceptable risks of harm
• Minimal risk of harm – “everyday risks standard”
• Greater than minimal risk of harm: provides direct benefit for the minor. Degree of risk of harm should be justified by the potential benefit
• Or: High probability of providing significant generalizable knowledge
Consent / assent for paediatric research
Who makes decisions for children?

- If children are autonomous and competent, they are able to make their own decisions related to health care.
- Current legislation in SA places age of consent for medical treatment at > 12 years.
- This does not apply to research on children.
- If children are unable to make decisions for themselves, the parents/guardian make that decision: they are in the best position both legally and ethically.
Essential elements for autonomous choice

- **Information** – the patient must have access to the information to be able to make a choice
- **Comprehension** – able to assess the information within the framework of the patient’s own values and interests
- **Voluntariness** – the patient must feel free to make the decisions reached after discussion
Elements of Informed consent

1. **Threshold elements**
   I. Competence (to understand and decide)
   II. Voluntariness (in deciding)

2. **Information elements**
   I. Disclosure of material information
   II. Recommendation (of a treatment plan)
   III. Understanding (of I and II)

3. **Consent elements**
   I. Decision (in favour of or against a plan)
   II. Authorisation (of the chosen plan)
Consent/Assent/Permission

• Parental Permission
  – Not the same as consent
  – More limited scope and authority than consent

• Adolescent Consent
  – In addition to parental permission
  – In place of parental permission in some contexts

• Child Assent (=“positive agreement”)
  – Not necessary in all research
  – Not “mini-consent”
  – Obtaining assent vs respecting “dissent”
  – Limited disclosure and voluntariness
Assessing the child’s capacity for informed consent
Assessing capacity

• Reasoning
  – Age
  – IQ
  – Cognitive functioning
  – Emotional functioning
Assessing capacity 2

• Understanding
  – Experiential factors
  – Knowledge of the problem

King Pediatrics 1989;115:10-16
Assessing capacity 3

- Voluntariness
  - Uncoerced patient decision
  - Valid consent = free choice

King Pediatrics
1989;115:10-16
Assessing capacity 4

• The nature of the decision to be made
  – Gravity
  – Immediacy
  – Risk-benefit balance

King Pediatrics 1989;115:10-16
Age thresholds

• Provide assent at the age at which they have the capacity to understand the nature of the research study in question - variable

• Rule of 7’s?

• Tailor to ability of individual child? Resources

• Children achieve ability to understand altruistic nature of non-beneficial research at between 10-14 years of age

Wendler Ch 60 in Oxford textbook
Assent for a blood draw?

• Can the parent tell his child she should do it?
• What if the child does not understand what the blood will be used for?
• What if the child does not know she has a disease?
• What if the child says she doesn’t want it?
• What if the researcher pays R20?
• What if the parent gives his child R20?
Can children who don’t know they have HIV truly provide assent to participate in HIV treatment trials?
Proxy Consent

**SUBSTITUTED JUDGMENT**
- Subjective
- Respects autonomy

**BEST INTERESTS**
- Objective
- Promotes beneficence
Best Interests

• When making decisions for children, we cannot estimate what their preferences would have been; no “substituted judgment” is possible

• Therefore use the “best interests” standard

• The “best interests of the child” refers to both those interests that are in the present and those that are in the future
The Concept of Best Interests

• “The highest net benefit among the available options that apply to any situation in which a decision has to be made regarding the health of the child.”

• “The best interests standard protects another’s well-being by assessing risks and benefits of various treatments and alternatives to treatment, by considering pain and suffering, and by evaluating restoration or loss of functioning.”

• It is therefore a quality-of-life criterion
Risk & Benefit in Paediatric Research
Non-beneficial research

• Is it acceptable to expose children to research risks for the benefit of others?

• For children to decide on participation in non-beneficial research they must understand and appreciate the potential to be altruistic, i.e. take on risks and burdens to help others

• Most guidelines suggest non-beneficial research should not be done on children
Study on Growth Hormone in Children

• Children with short stature may lack human growth hormone (hGH)
• Not all short children are deficient in hGH
• Short stature may be a problem even in the absence of disease (social, cruel taunts)
• Use of hGH in children who are not hGH deficient prompted NIH to seek approval for research project to study effect of hGH injections in such children

Murray TH in Steinbock 2003
hGH Study

- 80 children, 9-15 years, normal hGH levels, well below average height for age
- Three injections per week for up to 7 years
- Control group receive saline injections (600-1100 over the study duration)
- Special panel concluded the study to be ethically acceptable based on regulations

Murray TH in Steinbock 2003
hGH Study: Two questions

• Do parents who enrol their children in this study exceed the limits of parental discretion?
  – Risks of placebo injections more harm than benefit

• Is it good, morally sound, public policy to encourage such an experiment?
  – Harms to > 50% of children in study
  – Social justice consequences of hGH use for short but not hGH deficient children

Murray TH in Steinbock 2003
Risk assessment for research involving children (45CFR)

1. No more than minimal risk
2. More than minimal risk but with direct benefit
3. More than minimal risk with no direct benefit, but benefit/generalisable knowledge for the class of patients
4. All other research
Limiting pediatric research based on risks and benefits (45 CFR 46.404-407)

<table>
<thead>
<tr>
<th>Prospect of direct benefit</th>
<th>Minimal risk</th>
<th>Minor increase over minimal risk</th>
<th>Greater than minor increase over minimal risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO PROSPECT OF DIRECT BENEFIT</td>
<td>404</td>
<td>405</td>
<td>407</td>
</tr>
<tr>
<td>PROSPECT OF DIRECT BENEFIT</td>
<td>404</td>
<td>405</td>
<td>407</td>
</tr>
</tbody>
</table>

- **Minimal risk**
  - Risk is justified by the benefits
  - Risk/benefit is as favorable as alternatives
  - Commensurate experience
  - Vital knowledge about subject's disorder

- **Minor increase over minimal risk**
  - Risk is justified by the benefits
  - Risk/benefit is as favorable as alternatives

- **Greater than minor increase over minimal risk**
  - Address serious problem affecting children
## Survey of IRB Chairs (N=188)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minimal Risk</th>
<th>Minor increase</th>
<th>More than a Minor increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood draw</td>
<td>82%</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td>Sexual activity survey</td>
<td>45%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Allergy skin testing</td>
<td>23%</td>
<td>43%</td>
<td>27%</td>
</tr>
<tr>
<td>PK Study</td>
<td>8%</td>
<td>30%</td>
<td>59%</td>
</tr>
<tr>
<td>1/100,000 chance of death</td>
<td>8%</td>
<td>30%</td>
<td>59%</td>
</tr>
<tr>
<td>LP</td>
<td>6%</td>
<td>24%</td>
<td>70%</td>
</tr>
<tr>
<td>Drug tested safe in 500 adults</td>
<td>5%</td>
<td>23%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Specific considerations in research
Placebos
Placebos

• Placebo arms are not acceptable particularly when there is an effective intervention to avoid significant morbidity or mortality
  – i.e. ALL, meningitis, status epilepticus, severe asthma

• Placebo may be acceptable if:
  – No commonly accepted therapy
  – Commonly used therapy is of questionable efficacy
  – Commonly used therapy has significant side effects
  – Disease has spontaneous exacerbations and remissions
  – Placebo is an add-on to established therapy

(AAP Committee on Drugs, 1995)
Risks and benefits of placebos

• Need to clarify what would happen without the trial.
  – For purpose of assessing relatives benefits and risks

• Does the placebo arm offer “prospect of direct benefit” compared to the standard alternative? (405)

• Does the placebo arm pose more than minimal (406) or more than minor increase over minimal risk?

Benjamin S. Wilfond, Seattle Children’s Hospital & University of Washington
NHLBI asthma guideline adherence in clinical asthma trials including children (n = 70)

Were all subjects with more than mild asthma on anti-inflammatory medications prior to the study?

Yes 18(4)  No 52(14)

Were all subjects kept on anti-inflammatory medications throughout the study?

Yes 12(1)  No 6(3)

Were all subjects begun on anti-inflammatory medications upon enrollment?

Yes 10(1)  No 42(13)

Total number of trials (number of trials including only children)

Are placebos and controls ever justified in paediatric research?

“New treatments should always be tested against old and there is no case for withholding established treatments from children even if the evidence for efficacy is thin. Furthermore, placebos mean deception and controls signify uncertainty of a kind to which children should not be exposed.”

Deception of children in research

- Parents ask researchers not to reveal something about the research to the child (not planned deception)
- Children may be distressed or harmed by being given information regarding the research
- Limiting information may be ethically acceptable if promoting understanding is the reason, ie not deception
- Generally not ethically acceptable in research setting

Spriggs, Gillam JME doi:10.1136/medethics-2013-101618
Deception of children in research 2

- Usually children aged 7-14 years
- Researchers should be asked what they plan to do if limiting disclosure is requested or necessary
- Child should rather not be included in research if no alternative to deception
Emergency research
Emergency research

• Definition: research in circumstances when intervention must take place within 24 hours

• Examples:
  – Surgical / trauma emergencies
  – Resuscitation medicine
  – Critical care
  – Unconscious patients

• Consent either by surrogate decision-makers or waiver of consent until subject can be informed
Guidelines for waiver of consent: FDA

• Life-threatening illness precludes subjects’ ability to give consent
• Determination of the safety and efficacy of a new intervention is necessary
• Appropriate animal and preclinical studies available
• Risks reasonable given severity of illness and known risks of standard treatment
• Community and public involvement

Manning DJ JME 2000
Research involving newborns

- Neonates – Therapeutic orphans
- Neonatal research - inherent conflict
  - Obligation to evaluate efficacy and safety of new treatments
  - Justice in recruitment of subjects
  - Respect for autonomy in protecting subjects
- Requirement to evaluate drugs used vs trial of RDS treatments without consent of parents
Emergency research in neonates

• Examples in neonatal medicine
  – resuscitation
  – surfactant treatment
  – investigating modes of respiratory support
  – cerebral protection in hypoxic ischaemia encephalopathy (HIE)
  – treatment of neonatal seizures
• Frequently even less time available than in adult emergency research
Parental rights to decide in emergency research

• Compromised in emergency research
  – Parental distress
  – Inadequate time for explanation of the clinical intervention
  – Voluntariness compromised
  – Adequate understanding of trial and randomisation procedures

Manning DJ JME 2000
Emergency neonatal research requirements

- Good ethics review
  - Careful benefit versus risk assessment of intervention
  - Ethics review – include neonatal and other special expertise as appropriate
- Good recruitment strategies
  - Information and recruitment at antenatal care clinics
  - Presumed consent to cover several trials of emergency treatments in circumstances which preclude conventional consent
- Presumed consent
- Opt out
- Continuing consent

Manning JME 2000
Presumed consent

• Autonomy overridden as consent to specific intervention is bypassed
• However, may be preferable as acknowledge parental distress in neonatal emergencies
• Better recruitment
• Less selection bias
• More equitable

Manning JME 2000
Opt out as an option

- An opt out system for parents’ consent
- Recruitment in antenatal care clinic (ANC)
- Parents could opt out during ANC visit or after baby’s inclusion in trial; baby then receives conventional treatment
- Criticism: autonomy is overridden
Continuing consent

- Deferred consent until parents are able to satisfy the ethical and legal conditions for voluntary informed consent
- The concept of “continuing consent” where parents given sufficient information to make a free choice about entering the study
- As early as possible
- Throughout treatment/intervention
- Once situational incapacity resolved – actual consent

Brierley JME 2011
Parental perspectives

• Parents not aware baby was in a trial
• 83% of parents would be unhappy for baby to be included in a trial without their permission even if REC approval given
• 12% parents thought babies on trial would get better care
• Higher educational level – pressurised to make decision
• 24% parents felt more anxious

Stenson Arch Dis Child 2004
Parental perspectives

- Hypothetical consent procedures in neonatal resuscitation research
- 34% / 318 parents, Canada
- Preference for prospective consent in prenatal classes or visits, but unhappy with prospective consent once labour had begun
- Uncomfortable with waived consent, deferred consent and opting out

Culbert JME 2005
Specific problems in paediatric research from the literature
African perspective: Zimbabwe

- Antiretroviral Research for Watoto (ARROW) Phase III multicentre clinical trial in 1200 HIV-infected children in Uganda & Zimbabwe
- Legislation requires parental / legal guardian consent for minors for treatment, not specific for research
- 30% potential research participants (120/400) in Zimbabwe were orphans whose relatives wanted them to participate in the study but not legally permitted to give consent
ARROW Trial

• Zimbabwe patrilineal society but most orphans cared for by mother’s relatives
• Ethics Committee decided to provide a “waiver” of legal guardianship requirement
• Care-givers signed affidavit stating their understanding of high level of commitment required of them. Custodians recognised by family provided consent for participation. Maternal & paternal sides of family involved in information & consent process
Childhood Cancer Research

• Life-threatening illness – increases vulnerability, limits choice
• Children have experience of chemotherapy and illness
• Prospect of direct clinical benefit to the child – “ethics of hope”
• Separate care of the patient and procedures that are purely for research purposes (“therapeutic misconception”)
• Equity of access?

Kodish Account Res 2003
Rare diseases

- Early phase gene transfer trials:
  - Significant risk, even death
  - Novel approaches & surgical procedures
  - Children as research subjects
    - E.g. late infantile neuronal ceroid lipofuscinosis (LINCL)
    - Progressive degenerative neurological condition
- Promise with transfer of gene to brains of children using an adeno-associated virus through burr holes in skulls

de Melo-Martin Hum Gene Ther Sept 2011
Problems with LINCL trial design

- Placebo controls
- Small numbers of affected children
- Sham surgery
- More than minimal risk or minor increase over minimal risk
- Randomisation
**Trial design**

**ETHICAL CONSTRAINTS IN PEDIATRIC TRIALS**

**Subjects with LINCL**

- Screening protocol (5 genotypes, mild to moderate LINCL)
- Decision by 4 faculty, representing 3 departments, independent of PI
- Eligible
- Not eligible

- Family given choice to continue in screening protocol or enter treatment protocol
- Consent process independent of PI, includes CTSC patient advocate

**Untreated**

- n=16
- Assess efficacy parameters at 18 months

**Treatment with AAVrh.10hCLN2**

- n=16

- 1st dose cohort
  - n=8
  - $7.5 \times 10^{10}$ gc/site
  - 12 sites
  - Total dose $9.0 \times 10^{11}$ gc
  - Assess efficacy parameters at 6, 12, 18 months

- 2nd dose cohort
  - n=8
  - $1.5 \times 10^{11}$ gc/site
  - 12 sites
  - Total dose $1.8 \times 10^{12}$ gc
  - Assess efficacy parameters at 6, 12, 18 months
Justification for paediatric research without potential clinical benefit

• Acceptable risks: risk allowance (low risks) vs risk ceiling (high risks)
• No serious harm / negligible harm
• Risks of daily life
• Parental authority
• Future benefit / educational benefit
• Children contributing to valuable causes – choosing lives for our children
• *Contra bonos mores* = against good morals or public policy
• RECs should consider nature of the study, how it will be carried out, assessment of whether consent would be appropriate in broad circumstances
• Research should not violate basic constitutional and human rights of child participants
• Consistent with prevailing legal norms governing research with children, eg best interests, risk level, children must be scientifically indispensable to the study
• Approach to children’s health rights in SA legislation is divergent (NHA and Children’s Act)
• Public opinion or community morals: potential reasons for consenting
Research consent from young people in resource-poor settings
Children in low-income settings

- Constitute significant proportion of population, but under-represented in research
- Children may be “emancipated minors”, but legal status not recognised for purposes of consenting to research
- Children therefore excluded or consent sought from “guardian” who may not be a suitable surrogate decision maker
Should children be permitted to consent to research in LIC?

- If prospect of direct benefit and research approved by relevant REC
- If competent to understand and retain information, weigh relative merits of options and make and communicate a decision
- Voluntariness: research participation may act as inducement as it provides access to health care that may not be otherwise available

Phaik Yeong Cheah Arch Dis Child 2015;100:438-40
Should children be permitted to consent to research in LIC? 2

• Maturity: can the child make a decision with long-term implications?
  – Nature of study important
• Fixed-age threshold: is 18 years really appropriate? What of excluded teenagers?
• Additional protections:
  – Minor should be relatively independent
  – Contextual appropriateness – cf clinical care decisions
Should children be permitted to consent to research in LIC? 3

- Trained consent taker
- Accessible information e.g. videos, comics
- Delay non-urgent decisions until competence can be maximised
- Lower age limit – proposal between 12-14 years for most experimental research
Summary
Research involving children

• The investigator must ensure that:
  – Child’s assent obtained to extent of capabilities
  – Child’s refusal to participate or continue always respected, unless...
    • child needs treatment not available outside research
    • investigational intervention shows promise of therapeutic benefit, and
    • there is no acceptable alternative therapy

CIOMS Guideline 14 (2002)
System of Protection

• Independent scientific & ethical review
  – Additional safeguards for vulnerable persons
• Voluntary and informed consent
  – Parental permission and child assent
• Responsible and Competent Investigators
Principles to guide research involving children

- Research involving children is important for the benefit of all children.
- Research should only be done on children if comparable research in adults could not answer the same question.
- All proposals should be submitted to a research ethics committee.
- Legally valid consent should be obtained from the child, parent or guardian as appropriate.
- If parents give consent, the agreement of school age children who take part should be requested.
Honouring the worth of a child in research

• Protect them from needless harm
  – Require researchers to demonstrate that the research is important and the risks minimal
  – Respecting parents’ authority to protect and guide their children

• Give moral weight to young child’s consent

• Participation in non-therapeutic research is one of a class of activities to contribute to community’s well-being

Murray TH in Steinbock 2003
Conclusion

• RECs must be first line of defence against risky research studies

• Regulation of research aims to achieve a balance between

  Protection of research participants

  AND

  Unnecessary bureaucracy that might stifle responsible research.
Thank you!