# Ethics in Research involving Children

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# What is research?

Any social science, biomedical, behavioural, or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new knowledge, in which human beings:

1. are exposed to manipulation, intervention, observation, or other interaction with investigators either directly or through alteration of their environment; or
2. become individually identifiable through investigator's collection, preparation, or use of biological material or medical or other records.

***Definition of research with human subjects: WHO – ERC***

# Ethics in Research

- Research ethics govern the standards of conduct for scientific researchers *(WHO)*
- It is a set of moral principles in conduct of research *(Derived from Oxford dictionary)*

The principles of right and wrong that are accepted by an individual or a social group

# Defining vulnerability in research

- Vulnerable persons are those who are relatively incapable of protecting their own interests.

- They may have insufficient power, competence, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

# Why children are considered as vulnerable in research ethics?

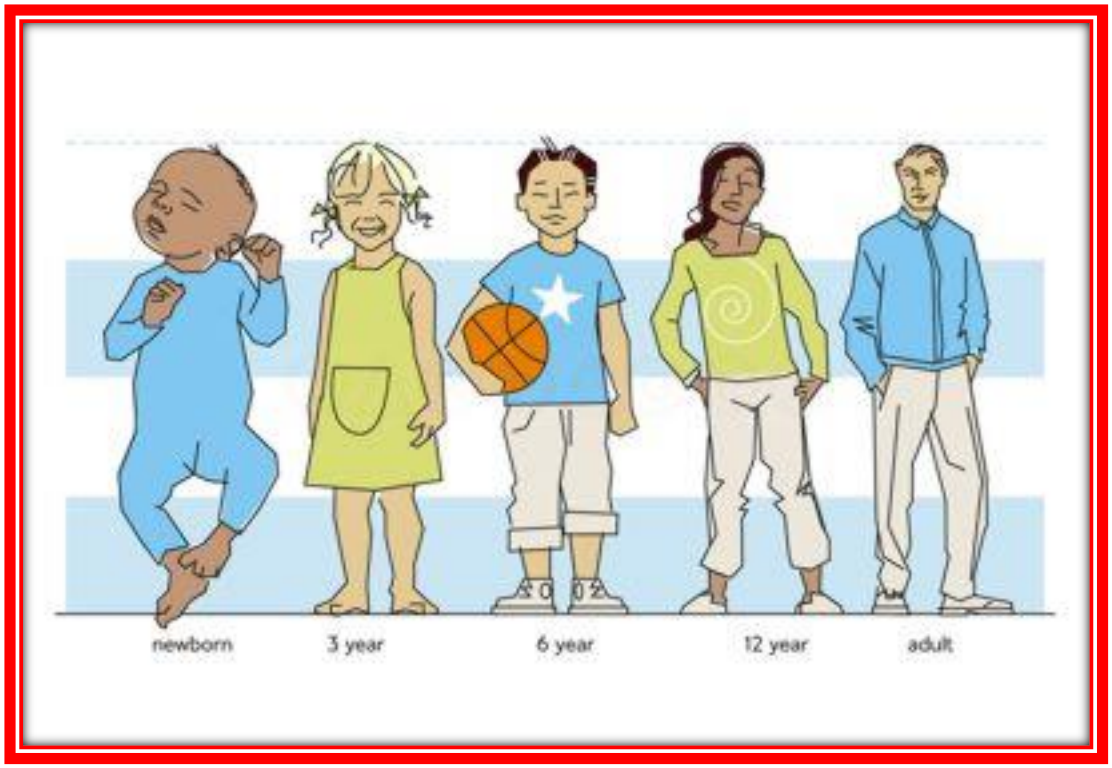
- Because they are incapable of protecting their own interests as they may have insufficient power, competence, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

# Research with children is worthwhile if each project……

1. has an identifiable prospect of benefit to children
2. is well designed and well conducted
3. does not simply duplicate earlier work
4. is not undertaken primarily for financial or professional advantage
5. involves a statistically appropriate number of subjects
6. Is eventually to be properly reported

*Guidelines for ethical conduct of medical research involving children: RCPCH, ADC: 2000: 82: 177-82*

# Children are not small adults



# Ethics in research

1. Autonomy
2. Respect for research participants
3. Confidentiality
4. Non-malfeasance (non maleficence), and benevolence (beneficence)
5. Justice
6. Fidelity and veracity:
   - Being faithful to these principles
   - Respect, competency, commitment to ethics, follow laws, honor whatever is agreed
   - Telling the truth and honesty

*Source: Principles of biomedical ethics by Tom Beauchamp*

# Ethics in research

1. Social Value
2. Scientific Validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for human subjects
8. Collaborative partnership

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# Ethics in research involving children **(RiC)**

1. **Social Value**
2. Scientific Validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for human subjects
8. Collaborative partnership

# Social Value

- Enhancements of health or knowledge must be derived from the research
- Should judge how the research will improve health of **Research participant** ? Community ? World ?
- Valueless research includes non-generalizable studies, “me too” studies, non-disseminated research, unsuitable study population, etc

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# RiC

1. Therapeutic: It is probable (or at least the aim should be) that the research will directly benefit the child (research participant)

2. Non-therapeutic: It will not benefit that particular child, although the results may be very useful in benefiting future children (Serves as a learning mechanism for future children)

*Morton N S: Ethical Issues in Research with Children in the UK. Paediatric and Perinatal Drug therapy 2001; 4 (4): 135-9*

# Therapeutic research

## Social value

- Most agree that it is justified ---------**BUT**
- ALL other ethical requirements should be fulfilled

*Morton N S: Ethical Issues in Research with Children in the UK. Paediatric and Perinatal Drug therapy 2001; 4 (4): 135-9*

# Non- therapeutic research

## Social value

- Extreme arguments are not acceptable
  - advocating no research at all OR
  - justifying it as a duty to society


- Middle of the road attitude should prevail
  - Balancing the risks to the child with the many advantages to society as a whole *(Researchers, ERC)*

*Morton N S: Ethical Issues in Research with Children in the UK. Paediatric and Perinatal Drug therapy 2001; 4 (4): 135-9*

# Non- therapeutic research

## Social value

- If the risks are significant, the research should not be allowed because this would clearly be acting against the best interests of the child

- It is unethical to submit a child to more than minimal risk when the procedure offers no benefit to them (RCPCH)

# Before undertaking research in children

Final 2008

**ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION**

**Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use**

The determination of the levels of risk and the associated potential benefits are the basis for ethical approvability. The following distinct risk levels are proposed as a means to decide on the ethical acceptability of trials.

- Minimal risk, which could be defined as probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests
- Minor increase over minimal risk
- Greater than minor increase over minimal risk

Final 2008

**ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION**

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## ANNEX 4: Examples for levels of risks

| No or minimal risk | Minor increase over minimal risk | Greater than minor increase over minimal risk |
|---|---|---|
| – History taking | – Urine collection via endo-luminal or suprapubic catheter | – Heart catheterisation |
| – Clinical examination | – Arterial puncture | – Endoscopy |
| – Auxological measurements | – Umbilical catheter | – Biopsy |
| – Tanner staging | – pH metry | – Surgery or modification of standard surgical procedure carried out as part of medical treatment |
| – Behavioural testing | – Nasogastric tube insertion and use | – Sedation |
| – Psychological testing* | – Transcutaneous oxygen or carbondioxide tension monitoring | – Anaesthesia |
| – Quality of Life assessment | | – Systemic analgesia |
| – Venipuncture* | | |
| – Heel prick* | | |
| – Finger prick* | | |

- Category 1: Research not involving greater than minimal risk (one parent permission required)
- Category 2: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child (one parent permission required)
- Category 3: Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition (two parent permission required)
- Category 4: Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (two parent permission required)

As per code of federal regulations, USA

# Assessing social value of Non- therapeutic RiC

- *"An experiment is ethical or not at its inception"*

- *……goals of research, not just the study methodology, have an ethical component……."*

*Beecher, HK. Ethics and clinical research. N Engl J Med 1966;274:1354-60*

# Assessing social value of Non- therapeutic RiC

- Before selecting the research topic, social value of that research in children should be strongly considered *(Researchers)*

- Background, Justification, literature review, objectives and ethical considerations should provide evidence for social value *(Researchers)*

# Assessing social value of Non- therapeutic RiC

1. The research might not equally well be carried out with adults (Participation of children is indispensable because information available from research on other individuals cannot answer the question posed in relation to children) - *Can the answer be obtained by study of an adult?*
2. The purpose of the research / the research question posed is to obtain knowledge relevant to the health needs of children (*is the question worth asking?)*

# Assessing social value of Non- therapeutic RiC

3. Has this been done before? *(Is it me too?)*
4. All actual and potential “risks”, “burdens” to study children should be thought about and presented
5. Research procedure should be clearly explained
6. Claims supported by relevant recent literature
7. Risk should be classified as no or minimal risk, minor increase over minimal risk,……
8. Plan for dissemination of findings should be given

# Case scenarios for social value

- Objective – Study 1
  - To describe the changes in CRP during an acute febrile illness in children < 5 years
- Objective – Study 2
  - To describe the normal haemoglobin values for children studying at year 1 in an urban national school
- Objective – Study 3
  - To describe efficacy of drug X in the treatment of Rota virus induced acute gastroenteritis in children < 5 years
- Objective – Study 4
  - To determine immunogenicity of human papilloma virus vaccine in infants

# Ethics in RiC

1. Social Value
2. Scientific Validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. **Informed consent (autonomy)**
7. Respect for human subjects
8. Collaborative partnership

# Autonomy- RiC

- **Autonomous person** "An individual capable of deliberation about personal goals and of acting under the direction of such deliberation."

- *Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U.S. Department of Health and Human Services: Part B, section 1, "Respect for Persons" (http://ohsr.od.nih.gov/guidelines/belmont.html)*

# Autonomy- RiC

- **Diminished autonomy**: An individual with restricted capability of deliberation about personal goals and of limited ability to act under the direction of their deliberations.

- *Developed in contrast to the concept of the "autonomous person" in The Belmont Report. Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: Human Services: Part B, section 1, "Respect for Persons." (http://ohsr.od.nih.gov/guidelines/belmont.html)*

# Autonomy- RiC

- Children are considered as persons with diminished autonomy because they have limited cognitive capacity to:
  - give informed consent
  - understand his/her rights to refuse to participate
  - understand the risks or risk vs. benefits
- Autonomy in adults is ensured by informed consent, but IC is “invalid” and “unreliable” in children

# Autonomy- RiC

- The United Nations Convention on the Rights of the Child states that children should be informed about decisions that affect them and they should be assured that they have the right to express their views freely, these views 'being given weight in accordance with the age and maturity of the child'.

# Informed consent - RiC

- Consent requires five preconditions to make it legal:
  - The person is required to be of *"competent"* mind
  - They must be *fully informed regarding the* nature of the procedure, including the associated risks
  - They must *understand the information they* have been given
  - Their decision must be made *voluntarily*
  - Finally they must give *authorization*

*National Institutes of Health, Office of Human Subjects Research. The Belmont report: Ethical principles and guidelines for the protection of human subjects of research. <http://ohsr.od.nih.gov/guidelines/belmont.html>*


Informed consent!!!!

# “Informed consent” – RiC

- Child/children/minors: Under the age of 18 years old. Proxy consent from parent/ legal guardian
- In some circumstances minors can give consent for themselves: Mature minors, married, parent, pregnant
- Children > 6-7 years: Assent
- Dissent should be respected
- If the child becomes major during the research period.. formal consent process should replace assent and PC

# Assent

- A child's affirmative agreement to participate in research
- Generally children > 7 years
- Assent is the concept of providing agreement to participation in research where full consent is not possible by virtue of compromise in the 5 main elements of consent
- The assent should provide the child with an age-appropriate explanation of the proposed research procedures (7-12 years, one page document)

De Lourdes Levy M, Larcher V, Kurz R. Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Eur J Pediatr 2003;162:629-33.

# Dissent

- Dissent (the voicing of a desire not to take part in research) should be respected.

- Fully developed articulation of the reasons for dissent should not be required to end a child's participation in research.

# Assessing autonomy in RiC

1. Process of proxy consent, assent and dissent

2. Investigator responsible for the process

3. All the documents (information sheet, consent form, assent form): language, clarity, accuracy, non-technical, sincerity, honest, reflects what is given in the proposal, etc

# Issues – Personal experience

- Information sheet to parents *(carelessness)*
  - "we will obtain 5 ml of blood from you every day"
- Assent form to child of 7 years *(technical)*
  - "genetically you are at more risk to develop this autosomal recessive disorder, hence to avoid you get a child with this disorder……"
- Information sheet – Clinical trial in children *(inaccurate)*
  - 'the IP has clearly shown benefit to cure your child's condition
- Tamil translation of IS to parents *(inaccurate translation*)
  - "if you refuse to participate, you have no rights to access any government services in the future"

# Case scenarios for “informed consent”

1. Questionnaire will be administered in year 8 students after obtaining informed consent

2. When children are brought for routine immunization at the age of 18 months, 2 ml of blood will be taken to measure rubella antibodies

3. If a child continue to refuse, a play item will be given to stop the cry and measurements will be done in an hour or so

# Ethics in RiC

1. Social Value
2. **Scientific Validity**
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent (autonomy)
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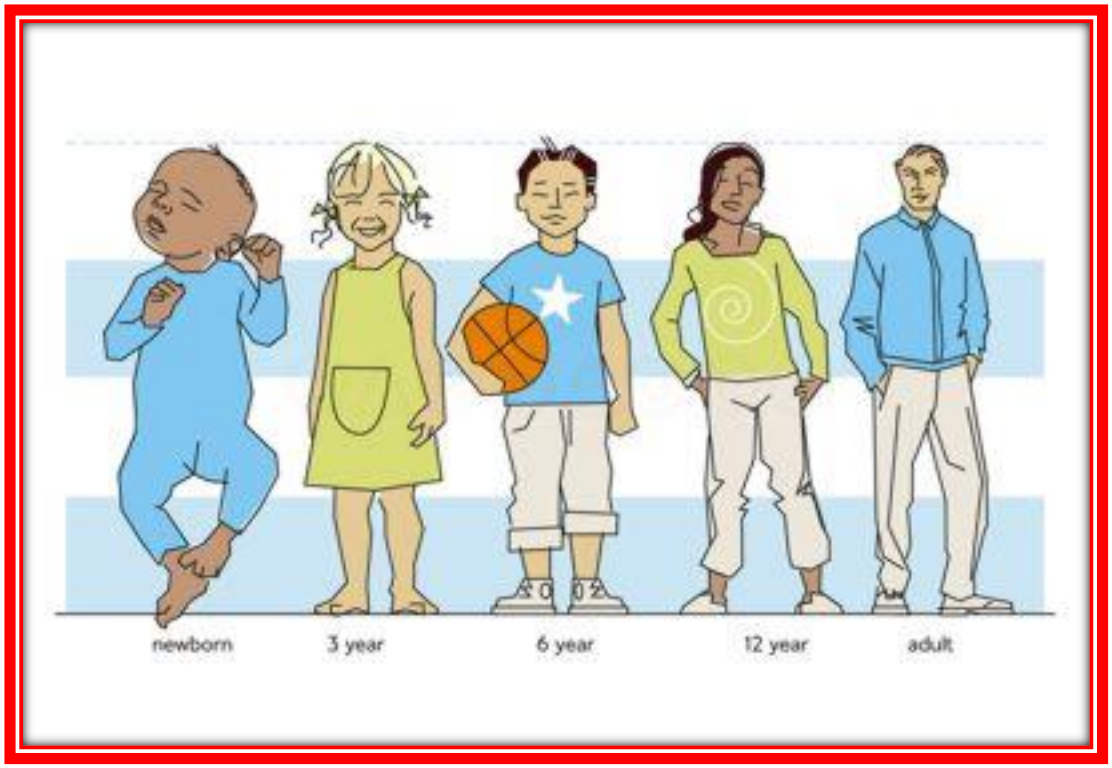
# Scientific Validity

- Methodologically rigorous that is practically feasible
- To be ethical the research must produce reliable and valid data that can be interpreted
- Invalid research includes underpowered studies, studies with biased endpoints, instruments, or statistical tests, and studies that cannot enroll sufficient subjects

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# Children are not small adults



# Children are not small adults

1. Pharmacokinetic differences
2. Pharmacodynamic differences
3. Age specific dosing regimens
4. Paediatric formulations
5. Different spectrum of ADRs
6. Young children cannot explain: SEs, Response

# Children are not small adults

7. Medicines may not have been tested in children – Lack of evidence
8. Difficulties in giving medicines to children
9. Children continue to grow and develop
10. Different diseases, different treatment guidelines

# Scientific validity – RiC

1. Children are not small adults
2. Study designs should be appropriate for the age
3. Age groups appropriate for the research question
4. Outcomes – “Paediatric specific”
5. Tools: Need to be validated in children
6. Adequate sample size
7. Blood samples – suitable alternatives
8. Dose, dosage form, administration of medicines, etc

# Scientific validity – RiC

9. “Child friendly” physical environment
10. Monitoring and follow up different from adults
11. Compliance with the research procedures

*Scientific validity of clinical trials in children*

*?? Another workshop*

# Assessing scientific validity in RiC

1. Paediatric expertise in ERC

2. Researchers should provide all the details regarding methods

3. To use a check list

# Case Scenarios for scientific validity

1. Proposal for a clinical trial in children < 5 years: Efficacy will be measured by a pain questionnaire
2. Proposal for a PK study in infants: Tablet X will be dissolved in formula milk and administered
3. Proposal for a comparative study: Children in arm A will be given half the adult dose of drug X and……
4. Proposal for a descriptive study in children < 5 years: Side-effects of dizziness, blurring of vision will be enquired from them and entered in a check list

# Ethics in RiC

1. Social Value
2. Scientific Validity
3. Fair subject selection
4. **Favorable risk-benefit ratio: Beneficence, Non maleficence**
5. Independent review
6. Informed consent (autonomy)
7. Respect for human subjects
8. Collaborative partnership

# Favorable risk-benefit ratio

Risks must include:

- Physical —death, disability, infection
- Psychological —depression and anxiety
- Social —discrimination
- Economic —job loss

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# Favorable risk-benefit ratio

- Four Step Evaluation

1. Risks identified, assessed and minimized.
   - Evaluate the
     - Likelihood of harm
     - Magnitude of harm

     1. No risk
     2. Minimal risk
     3. Minor increase over minimal risk
     4. Greater than minor increase over minimal risk
   - Identify mechanisms to minimize risks:
     - Additional diagnostic tests
     - Hospitalizations

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# Favorable risk-benefit ratio

- Four Step Evaluation

2. Potential benefits (physical, psychological, social, and economic) to individual participants enhanced

*Consider <u>only benefits from research interventions</u> not benefit from added health services or payment that are not necessary to the research goals*

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# Favorable risk-benefit ratio

- Four Step Evaluation

3. If potential benefits to the individual outweigh risks to the individual then proceed

4. If risks outweigh benefits to the individual, then evaluate risks against social benefit of knowledge gained

Source: Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711

# Assessing favorable risk-benefit ratio in RiC

- Four steps is the corner stone, but
  1. Risk– Quantitatively and qualitatively different
  2. Burdens – More in children (fasting, waiting in a queue, blood drawing, depriving sleep, depriving school, etc)
  3. Benefits – In paediatric context
  4. Adult data cannot be extrapolated

- Investigators and ERC – Should be “child friendly”

# Case scenario of favorable R/B ratio

1. Descriptive cross-sectional study in children aged 10-15 years regarding methods of studying
2. Descriptive cross-sectional study in children aged 10-15 years regarding knowledge about HIV
3. Descriptive cross-sectional study in children aged 10-15 years on intimate partner violence at home
4. RCT in asthmatic children aged 10-15 years on efficacy and safety of a novel inhaler apparatus
5. Qualitative study in children aged 10-15 years on psychological impact of losing parents during war

# Ethics in RiC

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5. **Independent review**
6. Informed consent (autonomy)
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# Ethics in RiC – Other issues

1. Minimal / No pain
2. Circumstances in which the research is conducted provide for the physical, emotional, psychological safety of the children
3. Parental permission
   - Level of parental duress
   - Research incentives
   - Parental perception of physician-parent relationships
   - Child's thoughts and considerations

# Ethics in RiC – Other issues

4. Information may be given to parents/ guardians - ? Confidentiality
5. IRC, Research Team – Require paediatric expertise
6. Recognize, and accommodate children's emotional and social vulnerabilities
7. Consider a child's physical safety
8. Respect not only the child, but also the child's parents
9. Should not consider as "part of routine care"
10. Untrained data collectors

# Ethics in RiC – Other issues

11. Long questionnaires, Questions which lead to emotional distress, embarrassment, etc
12. Medicines irrelevant to children
13. Diseases irrelevant to children
14. Convenient groups should not be selected (CWC!)
15. Groups cannot be excluded without scientific reasons
16. Some more please??

# Ethical and research standards for Clinical trials in children – RLS

GCP workshop

# To conclude

- Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner
- Research should only be done on children if comparable research on adults could not answer the same question
- A research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal

# To conclude

- Exploitation of children in the name of research for financial, academic or personal interests of researchers/ organizations should never be allowed
- Children are not small adults; they have an additional, unique set of interests
- Research in children poses important challenges with regard to informed consent, assent, vulnerability, risk benefit ratio, social value and scientific validity

# To conclude

- Children reserve the right to be “informed” about their role in the proposed research
- Legally valid consent should be obtained from the 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
- If children are included, the means of protecting their rights and welfare must be strictly applied by the researchers

# To conclude

- The interests of the patient (person) always prevail over those of science and the society
- ERC plays a significant role in ensuring that RiC is conducted in an ethical manner
- Responsibility lies with the paediatric health researchers
- “Champions” of RiC should advocate for research participation by children, while being attentive to mitigating the risks and protecting children from unethical research conduct

# References used in the presentation


1. Principles of biomedical ethics by Tom Beauchamp
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4. Emanuel EJ, et al. What makes a clinical research ethical? JAMA. 2000; 283 (20): 2701-2711
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7. Handbook for good clinical research practice (GCP). World Health Organization. 2002

# An example

- Drug company X, Clinical trial of one of its oral antimicrobial agent in an outbreak of meningococcal meningitis in Nigeria
- A Team was flown in
- The Company paid a local investigator US$ 20 000 (a huge sum for the country) to undertake the study.
- ERC approval obtained
- 99 children = experimental drug
- Control group of 101 children = Ceftriaxone
- 11 children died and many suffered debilitating injuries.

# Subsequent Lawsuit

1. The investigator who was paid 20,000 USD by the company appointed himself chairman of the ERC, and backdated its approval for the trial
2. Meningitis require parenteral medicines, “oral” non-trustable (Scientific Validity, Social value)
3. Allege that Ceftriaxone was given in a dangerously low dose (Scientific Validity)
4. Company is accused of hiding or destroying data of the trial.
5. Parents claimed that they did not know if it was a research (? Informed consent, respect for persons)
6. Side-effect, that include severe liver damage have caused EMA and FDA to severely restrict its use (Favourable Risk vs. benefit ratio, scientific validity)

# References


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3. Willyard C. Pfizer lawsuit spotlights ethics of developing world clinical trials. Nat Med. 2007 Jul;13(7):763.
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Thank
You!