Sri Lanka Medical Association

Ethical issues in Paediatric Health Research

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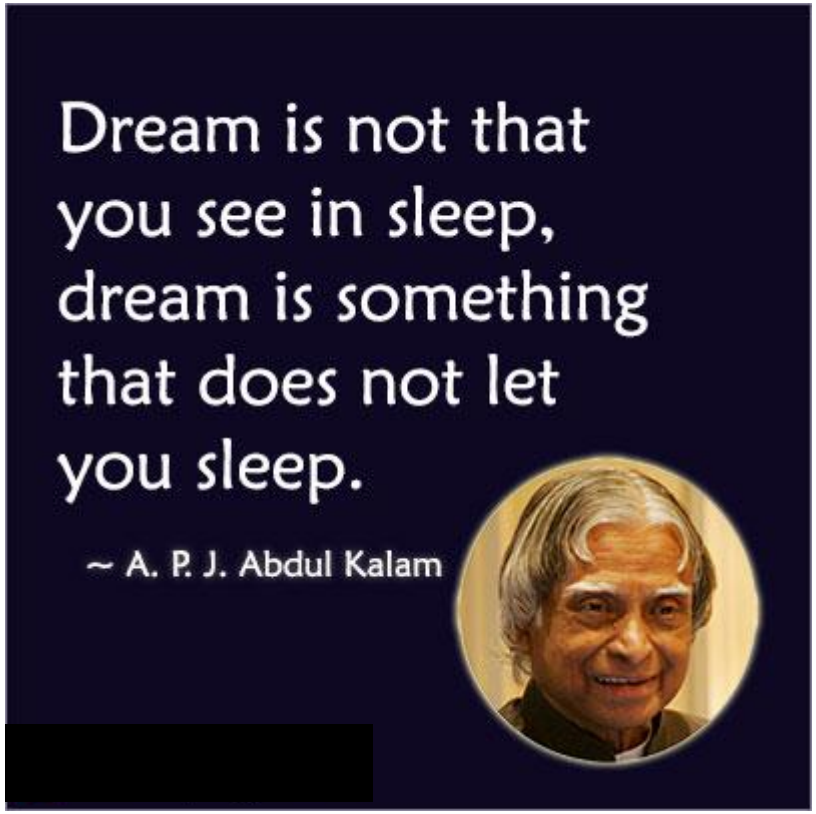
Birth of this topic



Eye opener

- 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

1. Lenzer J. Nigeria files criminal charges against Pfizer. BMJ. 2007;334(9 June):1181.
2. Loewenberg S. Drug company trials come under increasing scrutiny. Lancet. 2008 Jan 19;371(9608):191-2.
3. Willyard C. Pfizer lawsuit spotlights ethics of developing world clinical trials. Nat Med. 2007 Jul;13(7):763.
4. Jegede AS. Understanding informed consent for participation in international health research. Dev World Bioeth. 2009 Aug;9(2):81-7.

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.

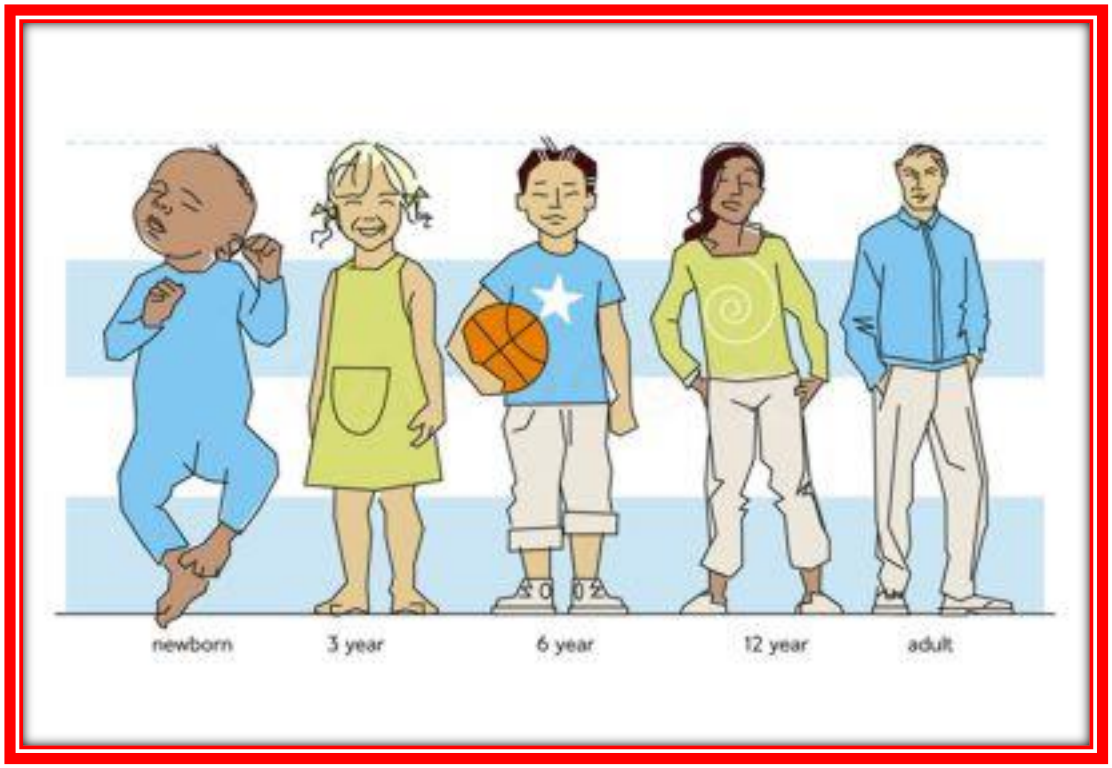
Definition of research with human subjects: WHO – ERC

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

Children are not small adults



Research in children – Moral duty

- Research in children is recognized as a moral duty based on several ethical principles
  1. Distributive justice: High-quality health care available to all populations, including vulnerable ones
  2. Beneficence in providing evidence-based care
  3. Nonmaleficence in avoiding harmful therapies, adopted either without evidence or extrapolated from experience with adults.

Key Principles

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 on children if comparable research on adults could not answer the same question

Key Principles

4. A research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal
5. All proposals involving medical research on children should be submitted to a research ethics committee
6. 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.

The level of trust that has characterized science and its relationship with society has contributed to a period of unparalleled scientific productivity. But this trust will endure only if the scientific community devotes itself to exemplifying and transmitting the values associated with ethical scientific conduct.

Research in children – A dilemma

- We want children to benefit from the dramatic and accelerating rate of progress in medical care that is fueled by scientific research.
- At the same time, we do not want to place any children at risk of being harmed by participating in such research, even though their very involvement may be essential to improving the overall medical care of children.
- We also want to discourage research that is of minimal value.

To resolve this dilemma

1. Infants, children, and adolescents need **additional protections** beyond what is provided to competent adults when they participate in research.

    1. *Assessment of vulnerability*
    2. *Informed consent, proxy consent, assent, dissent*
    3. *Risk vs. Benefits assessment*

To resolve this dilemma

2. **Design** of the research required to improve the health and well-being of infants, children, and adolescents must consider their physical, cognitive, emotional, and social development. Similarly, when children of any age become participants in such research, the protections provided must be appropriate to their stages of development.
    1. *Assessment of vulnerability*
    2. *Informed consent, proxy consent, assent, dissent*
    3. *Risk vs. Benefits assessment*
    4. *Scientific validity – Observational studies, Clinical trials*

To resolve this dilemma

3. Special emphasis on **protecting them from harm** caused by standard medical procedures and treatments based on research with adults when the **benefits and risks** for children of different ages have not been established through scientific research involving these populations
    - *Risk vs. benefits assessment*

To resolve this dilemma

4. **System f**or protecting infants, children, and adolescents involved in research, while ensuring such protection, should not unreasonably impede research that may benefit them

– *Role of ERCs*

To resolve this dilemma

- Finally, all of those responsible for research involving infants, children, and adolescents need to understand the **special ethical issues** that are relevant to the conduct of such research and the additional protection that must be provided. In certain cases, ethical standards will preclude some otherwise desirable research.

Ethical conduct of paediatric health researches – Who is responsible?

1. Investigators and the research team
2. Ethics Review Committees
3. Research participants, public, etc

BOX S.3
Key Responsibilities of Investigators for the Ethical Conduct of Clinical Research Involving Infants, Children, and Adolescents

- Achieve and maintain appropriate training, credentials, and skills to perform or supervise all clinical and research procedures required for a study that includes children.
- Achieve and maintain appropriate training and knowledge to meet the ethical and regulatory requirements for conducting research that includes children.
- Ensure that research protocols involving children conform to ethical and scientific standards for such research.
- Submit proposals and proposal amendments for scientific and ethical review and approval before beginning or modifying research and, as required, during the course of research.
- Conduct the study in accord with the approved protocol.
- Disclose potential conflicts of interest to appropriate parties.
- Ensure that the processes for securing parents' permission and children's assent to research participation meet ethical and regulatory standards and are effective and active through the duration of the study. Provide the rationale and propose appropriate protections consistent with federal and state laws if a waiver of parental permission is sought.
- Communicate with children participating in research in developmentally appropriate ways—and with guidance from their parents—about what will happen to them throughout the course of the research.
- Support appropriate safety monitoring and reporting of adverse events.
- Report protocol violations, errors, and problems as required to research sponsors, regulators, or IRBs.
- Disclose research results to the scientific community and the public.
- Communicate research results, as appropriate, to research participants or participant communities.

SOURCE: Adapted from IOM, *Responsible Research: A Systems Approach to Protecting Research Participants*. Washington, D.C.: The National Academies Press, 2003a.

BOX S.4
Key Ethical and Legal Responsibilities of IRBs and Research Institutions Involved with Clinical Research That Includes Infants, Children, and Adolescents

- Educate IRB members and, as needed, IRB pediatric consultants about the ethical, legal, and scientific standards for approving research involving children and their appropriate interpretation.
- Educate investigators who conduct research that includes infants, children, or adolescents about their special ethical, legal, and scientific responsibilities.
- Apply ethical and regulatory standards for the initial and continuing review and approval of research protocols involving children, including careful evaluation and categorization of research risks.
- Provide for adequate expertise in child health and research in the review of protocols that include children, including assessment of whether those conducting the studies have adequate pediatric expertise.
- Make available reference materials and resources on research involving children, including information on research ethics, as part of IRB or research administration web sites and educational programs.
- Conduct ongoing assessments to guide improvements in IRB performance in reviewing and monitoring research involving children.
- Develop explicit policies or guidelines on important topics for which additional guidance to IRB members or investigators is needed (see Box 8.3).

Value of ethical research with children

1. Medical research involving children is an important means of promoting child health and wellbeing.
2. Such research includes systematic investigation into normal childhood development and the aetiology of disease, as well as careful scrutiny of the means of promoting health and of diagnosing, assessing, and treating disease.
3. It is also important to validate in children the beneficial results of research conducted in adults

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


Knowing is not enough
we must apply
Willing is not enough;
we must do
Johann Wolfgang von Goethe
Love