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ETHICS IN PEDIATRIC TRIALS

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Summary

Ethics help professionals to be familiar with the central concepts of medical ethics, professionalism and medical jurisprudence. It should be expected that physicians, will be more aware of, and sensitive to, the ethical dimensions of modern medicine. Ethics contributes to high quality patient care and professional behaviour. It should also be followed in every sound scientific research. Ethics in paediatrics is a bit different from adults. Parents and physicians should not exclude children and adolescents from decision-making without persuasive reasons The American Academy of Pediatrics (AAP) believes that in most cases, physicians have an ethical (and legal) obligation to obtain parental permission to undertake recommended medical interventions. In many circumstances, physicians should also solicit a patient assent in emancipated minors. The statement on informed consent, parental permission, and patient assent has a long and extraordinary historical background. The first draft of this document, prepared by William G. Bartholomew was presented to AAP Committee on Bioethics in 1985. Since then the concept has evolved much and become more formal. In paediatrics most of the studies is compared with historical control. Besides, intervention in healthy child should take considerations of both social stigmata and altuism. In fine, boundary of research work should be guarded by institutional review board.

Introduction

Ethics in research is very critical. Today every one is required to address ethics and comply with, and do research in ethically proper way. Ethics is about what is morally right (Ethics>ethicos>moral custom) and proper in research. They are vital because they ultimately require involvement of human subjects. So researchers should follow the code of conduct and specific guidelines[1,2]. All healthy research must be scientifically sound. Unsound research on human subjects may expose research subjects to risks or inconvenience. Everyone is aware of past atrocities in research work as in experiments conducted by the Nazi doctors on Jews, the Tuskegee experiments in the United States etc.[3].The fundamental document to guide research involving human subjects is Declaration of Helsinki known as "Helsinki I" [4].

Ethical issues encompass life in womb to the dying of human being. In cases of children studies should be done only aiming to improvement of Paediatric population with proper consent [5].

Definition of biomedical ethics

Ethics is a philosophical consideration of morals-right or wrong. It is a process of thinking, of morals, of behaviour and intentions. It evolves out of a collective responsibility to humanity. The term "bio-medical ethics" was coined in the early 1970s to refer to the application of moral reasoning to vexing questions at the frontiers of biology and medicine

Ethical principles

There are three Basic Ethical Principles [6,7,8,9]

1. Autonomy- Respect for persons, community etc

2. Beneficence or Malficence- ensuring that no harm is done

3. Distributive justice- equality of individuals and that the benefits and risks should be distributed fairly.

Autonomy [10,11,12]

Informed consent of individuals participating will be obtained orally, through tapes, or in written form (international funding bodies require Written Consent). It provides description of entry into homes of respondents and how informed consent will be obtained. Confidentiality of data should be assured even in case of under-aged. It should also share outcomes with targeted individuals etc.

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Beneficence [13,14,15,16,17]

The theme is "DO NO HARM". There should be description how harm to respondents or targeted community will be avoided at all cost. It should ensure full disclosure of the nature of the research with particular reference to harm/ risks and benefits.

Distributive justice

It means giving every person or community equal chance of participating in the work. Distributing benefits fairly is also hidden moto.

These three principles approach may not be easily applied (if at all) to children. This is because both respect for autonomy and beneficence depend on the child being sufficiently mature to be competent. Also this approach leads to the risk that respect for parental autonomy may overwhelm the child's interests.

Ethical principles in pediatric clinical trials

Safe & effective pharmacotherapy in children requires clinical studies in children . The ethical imperative to obtain needed information in clinical studies must be balanced against the ethical imperative to protect each child in such studies. Initial role is played by Institutional Research Board (IRB).

Roles of IRB

A) Clinical role to protect children in studies.

B) Assurance of scientific validity of studies.

C) In reviewing pediatric protocols.

The IRB must have members and/or bring in consultants knowledgeable in pediatric ethical, clinical and psychosocial issues

Recruitment of participants

Information that can be obtained in a less vulnerable population should not be forecasted in a more vulnerable population. Studies in handicapped or institutionalized children should be limited to diseases or conditions found principally or exclusively in these populations or where the underlying conditions of the patients would be expected to alter the disposition or pharmacodynamic effects of a medication. Recruitment and retention of patients in studies must be noncoercive. Reimbursement and subsistence costs may be covered. Coercive inducements (financial or other) either to parents or the child are not appropriate. An attempt must be made to recruit patients representing the demographics of the community, unless there is a valid reason not to.

Consent [18]

Consent for a minor (age defined by local law) to participate in a study is typically obtained from the minor's parent or legal guardian. It should be informed written consent. "Permission" for the minor to participate in the study from the parent/guardian is typically obtained prior to discussing the study with the minor. "Emancipated minors" (defined by local law) may sign their own consent form which is called assent.

Informing the child and assent

i) Information about the study must be provided to children in language appropriate for their age.

ii) Active written "assent "should be obtained from children of appropriate intellectual age (often 7 years of age but defined by the local IRB)

iii) Such "assent" includes the child's right to refuse to participate or withdraw from the study at any time[19]. It may be over-ridden by parental consent in therapeutic trials only where the child's welfare is endangered by 'not participating' [20] .

Risk, distress, benefit

Critical to the ethical conduct of any clinical studies in children is the need to:

1. Minimize risk

2. Minimize distress

3. Maximize direct and indirect benefit

4. Optimize the risk, distress with benefit ratio

Minimizing risk

i) Understanding and utilizing all pre-clinical data and clinical safety data from adults.

ii) Utilizing adult pharmacokinetics (PK) and safety data to plan single dose and multi dose PK studies in children.

iii) Designing studies to minimize the number of participants and of procedures, consistent with good study design.

iv) Performing studies at pediatric centers experienced in clinical investigations and management of pediatric patients

Minimizing distress

i) Design protocols specifically taking into account the needs of children.

ii) Design clinical investigative centers to be staffed

by personnel knowledgeable in dealing with the medical and psychosocial needs of children.

iii) Provide a comfortable, familiar setting with age appropriate furniture, food and play equipment

iv) Minimize discomfort of procedures

vv) Provision of skillful staff

Common examples are

1. Topical anesthesia to place IV catheters

2. Indwelling catheters rather then repeated venipunctures.

3. Collection of some research samples at same time as routine clinical samples.

Maximizing benefits

Research Studies are ethically permissible

1. When potential benefits out weigh potential risks

2. Potential benefit to a individual child

3. Provide generalizable knowledge in case of research with healthy child.

Components of Benefits

1. Potential direct benefit to the patient in study

2. Advancing knowledge of a disease or treatment

3. Understanding by the child that He or She has contributed to the welfare of other Children

Benefit and risk categories

1. Research not involving greater than minimal risk.

2. Greater than minimal risk but presenting the prospect of direct benefit to the individual patient.

3. Greater than minimal risk with no direct benefit but generalizable knowledge about the patient's condition or disorder ("Non therapeutic research")

Non-therapeutic research

1. Single dose PK studies to establish dose/safety, and guide subsequent clinical trials.

2. Critical to subsequent safe effective therapy.

3. Most often performed in patients with the disease for which the drug was intended (as in cancer)

4. Different from many adult phase 1 studies.

5. Increases potential benefit to the individual as well as other children.

Examples of non-therapeutic research

1. A single needle stick.

2. Bone marrow aspirate in cancer children for evaluation of a new therapeutic agent.

Conclusion

So, in children we should follow at least the following minimum guidelines such as, supporting existing guidelines, assuring standards detailed in these guidelines in all studies involving children, keeping studies to a minimum consistent with obtaining critically needed data. However further studies of clinically well and healthy subjects can be done, but require an additional level of protection.

Disclosure

All the authors declared no competing interestes.

References

1. Percival, Thomas . Medical ethics. John Henry Parker.3rd ed.Oxford.1849; 49-57
2. Walter JK, Klein EP, eds. Georgetown University press. The Story of Bioethics: From seminal works to contemporary explorations. Georgetown University press, Washington, 2003
3. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law. No10, Vol 2, pp181-182. (The Nuremberg Code.).US Government Printing Office, Washington, DC
4. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.www.wma.net/e/policy/b3.htm Last accessed: 2009
5. Royal College of Paediatrics and child health: Ethics Advisory Committee (2000) Guidelines for the ethical conduct of medical research involving children. Archives of Disease in Childhood. 2000; 82, 2 :177-182
6. P. Bains. J Med Ethics 2008; 34; 41-145
7. Beauchamp TL and Childress JF. Principles of Biomedical ethics. 5th edn. New York, Oxford: Oxford University Press, 2001
8. Gardiner P. A virtue ethics approach to moral dilemmas in medicine. Journal of Medical Ethics 2003; 29: 298
9. Gillon R. Four Scenarios. Journal of Medical Ethics 2003; 29: 267-268
10. Gillon R. Ethics needs principles - four can encompass the rest and respect for autonomy should be first among equals. Journal of Medical Ethics 2003;29: 307-312

11. Dworkin G. The Theory and Practice of Autonomy. New York: Cambridge University Press, 1988

12. Bains P. Medical ethics for children: applying the four principles to paediatrics. J Med Ethics 2008;34:141-145

13. Wheeler R. Gillick or Fraser? A plea for consistency over competence in children. Gillick and Fraser are not interchangeable. BMJ. 2006; 332: 807

14. De Grazia D. Value theory and the best interests standard. Bioethics 1995; 9: 50-61

15. Rowell M, Zlotkin S.The Ethical Boundaries Of Drug Research Inpedriatrics.Pediatric Clinics of North America, 1997; 44 : 27-40

16. Seyberth HW, Demotes-Mainard, Wrobel P. Developing a European framework for research on Children's medicine.Paediatr Nephrol 2005;20:1537-1540

17. Aligne CA, Stoddard JJ.Tobacco and children: an economic evaluation of the medical effects of parental smoking. Arch Pediatr Adolesc Med 1997; 151: 648

18. Committee on Bioethics. Informed Consent, Parental Permission, and Assent in Pediatric Practice. PEDIATRICS, 1995; 95: 314-317

19. King NMP, Cross AW. Children as decision makers: guidelines for pediatricians. J Pediatr. 1989; 115: 10-16

20. Vol P.Assent in paediatric research: theoretical and practical considerations. J. Med. Ethics, 2006; 324: 229-234