ETHICAL CONCERNS IN PAEDIATRIC CLINICAL TRIALS

Peter Cooper

Prof Emeritus

Department of Paediatrics and Child Health, Wits

GUIDING PRINCIPLES

- Beneficence and Non-Maleficence
- Respect for Persons (Dignity and Autonomy)
- Distributive Justice

HISTORY OF GUIDELINES FOR RESEARCH

- Up until the 2nd World War there were no general guidelines for clinical research. Consent was often not obtained and subjects were often not aware that they were part of a clinical study or trial.
- Horrific experiments done during the 2nd World War by Nazi doctors resulted in the Nuremberg trials from which the first guidelines arose
- Subsequently resulted in international collaboration in developing guidelines
- Many organizations have developed guidelines but perhaps the best known is the Declaration of Helsinki as a result of the Nuremberg recommendations which has been updated on a number of occasions

SOUTH AFRICAN GUIDELINES

- National Health Act of 2003
- Department of National Health: Ethics in Health Research
- Department of National Health: Good Clinical Practice Guideline

HOWEVER...

- Many notorious examples of unethical research since then

- USA – Tuskagee – Male prisoners with diagnosed syphilis were followed up from the 1930s to detail the clinical progression of the disease. This carried on until the 1970s in spite of the availability of penicillin as a cure.

- A study published in the Lancet in the 1990s linking MMR vaccine to autism found to have been partially sponsored by an autism organization probably looking for compensation. Serious flaws in the study resulted in the withdrawal of the paper but…

IN SOUTH AFRICA

- Wits Oncology Professor published remarkably good results for the treatment of advanced breast cancer. International researchers came to SA to gain more insight and found unethical practices and unreliable results.

- Virodene, an industrial solvent, touted as a cure for HIV under a previous national minister of health

- Wits HREC came in for criticism in international journals for approving drug company sponsored anti-retroviral studies without the guarantee of ongoing availability of the drugs. People with AIDS approached the HREC and insisted on the studies ongoing.

MEDICATIONS USED IN INFANTS &CHILDREN

- Many drugs that we use were not tested in infants and children
- Most trials were originally done on adults and extrapolated to infants and children
- Package inserts often state that this medication should not be used in children under…
- This is especially so in neonates where the majority of drugs that we use state that they should not be used in neonates
- However, we use these drugs “off label”

REGULATORY BODIES – SAHPRA, FDA

- Trials on all new drugs must include women (pregnant when possible) and children of all ages

- However, for older drugs that are in general use and where the patent has expired it is not in the interest of the drug company to do new clinical trials so we are stuck with many of them. Studies are usually self initiated or initiated by non-profit organizations to attempt to optimize dosage etc.

GENERAL ISSUES WITH CLINICAL TRIALS

- Scientifically sound

- Subjects fully informed about the study overall, risks and benefits, side effects if drug trials etc

- Consent must be voluntary – usually require a written information sheet and page for signed consent. Language issues need to be addressed when indicated – simplified and multiple languages

GENERAL ISSUES CONTINUED

- No inducements to participate and reassurance that standard care will continue if declines participation
- Fair compensation for trial related expenses e.g. travel costs
- May withdraw from the trial at any time without any consequences
- Ensure confidentiality – delink identifiable details from data collection

MINORS IN RESEARCH

- Issues must be relevant to minors
- Risk should be minimal or low and benefit to risk ration generally should be higher than in adults. Exceptions to this may be in severely ill minors, e.g. life-threatening illness
- Best interests of the child should always be kept in mind

CONSENT IN THE CASE OF MINORS

- Legally a minor is anyone under the age of 18
- Consent needs to be given by a parent or legal guardian
- A caregiver who often brings the child to hospital and may be the de facto parent (e.g. granny, aunt) is not a legal guardian but there may be flexibility, especially if there is minimal risk
- All of the requirements for consent in adults must be met

ASSENT

- Minors cannot legally give consent but must assent to participation in a trial if capable of doing so
- Adolescent for the purposes of research studies is defined as one 12-17 years of age.
- A child is <12 years of age
- Adolescents and children above a certain age need to give assent to participation. The age of the child is usually 7 or above but some flexibility is given to the researcher to assess whether the child is capable of giving assent

ASSENT

- Assent forms should be available separately for adolescents and children 7-11 years

- The form for adolescents would be in language not very different from the one for parents but that for children should be much simpler and is usually enhanced by illustrations.

- The procedures for providing information about the study and the documentation of assent should be just as rigorous as for the parent information and consent

ASSENT

- If the child cannot sign assent some other form of documentation is required as to how assent was obtained

- Adolescents who turn 18 during the study need to be re-consented as adults

ASSENT

Even if the parent/guardian gives consent, if the adolescent or child refuses to assent to participation, they cannot be enrolled into the study

ENROLMENT OF MINORS WITHOUT PARENTAL CONSENT

- Adolescents are legally capable of giving consent for treatment, medical and surgical “with the assistance of the parent/guardian” if available but cannot give consent for research

- Some exceptions can be made, especially in relation to reproductive issues and non-interventional.

- For example, adolescents can consent to termination of pregnancy without parental consent and research around attitudes or psychological effects may be approved without parental consent but not an interventional study. However, HIV prevention study with minimal risk may be approved.

PARENTS WHO ARE MINORS

- Parents of neonates and infants may still be under the age of 18 years
- For example, a 17-year-old mother may be asked to consent for her newborn infant
- Legally she is unable to do so and she will have to give assent and her parent will have to give consent

CONTRACEPTION DURING DRUG TRIALS

- Studies on new drugs should not be done on pregnant women, but pregnancy may happen during a drug trial
- Adolescents of child-bearing age are required to use some form of effective contraception
- Should a girl of 12 years become pregnant during a drug trial it must be regarded as statutory rape
- Reporting channels will have to be followed. Details of this should have been included in the original consent and assent information sheets

NEONATAL STUDIES

- Some neonatal studies my require intervention very soon after birth e.g. trial of a resuscitation intervention immediately after birth, early intervention with surfactant

- Some papers from the UK recently have looked at various ways of getting consent from parents prior to birth but have highlighted the complexities

- In SA it is accepted that this is generally not feasible

NEONATAL STUDIES

- Ethics committees will generally give approval for such studies to go ahead
- A senior doctor not involved in the study may approve enrolment pending parental consent
- Parental consent must be obtained as soon as possible after birth with an explanation that consent prior to the intervention was not possible
- Should parental consent be refused, data from that infant cannot be used for the study

PAEDIATRIC ICU STUDIES

- Emergency admissions to paediatric ICU and sometimes ward admissions may be eligible for trials with early interventions before parental consent can be obtained
- If possible, a close relative may be available to give provisional consent
- Failing that a senior doctor not involved in the study may approve enrolment pending parental consent
- Parental consent should still be obtained as early as possible

BLOOD VOLUMES

- Clinical trials usually involve taking significant amounts of blood
- New drug trials often include pharmacokinetic studies which require additional blood sampling
- Protocols should always indicate what volumes of blood will be taken and this should be included in the information sheet (in ml and teaspoons/tablespoons)
- Guidelines are in place regarding the maximum amount of blood permissible at one time or cumulatively – this is especially relevant to neonates and young infants

GENETIC STUDIES

- There is great interest in the interaction of and individual's genetic makeup and response to medications
- Most new drug studies include storage of blood for future genetic studies and a separate consent/assent is needed for this
- Details of what studies will be done needs to be included in a separate information and consent sheet – unrestricted genetic studies will not be approved
- Any later studies must be submitted to the HREC for approval

STORAGE OF BLOOD SAMPLES

- Most clinical trials include consent/assent for storage of blood and other samples for future testing on issues that may only become relevant at a later stage

- Again a separate information and consent/assent is required to outline what studies will be required

- Such studies should be relevant to the trial being done – ethics committees will generally not approve information sheets that are entirely open ended regarding what future studies will be done

ETHICAL ISSUES ARE NOT STATIC

- What was regarded as acceptable 20 years ago may not be regarded as such now
- The Declaration of Helsinki has undergone several revisions over the years to accommodate changes in ethical values
- Countries my differ in their approach to issues depending on local circumstances
- In a number of industrialized countries retrospective studies on existing data require individual or parental consent but in SA purely retrospective studies do not due to the perceived difficulties in obtaining consent