Minors as Research Participants*

Central Ethical Issues in Research with Children in the South African Context

Children are vulnerable
Their physical, cognitive and emotional development is incomplete.
They are dependent on others for their wellbeing.
They are legally unable to make independent decisions about whether to take part in research.
Children living in poverty are particularly vulnerable; for example, parents may have a poor understanding of research and may be more susceptible to pressures of enrolment, such as access to better health care.

Generally, children ought not to bear the burdens of research unless absolutely necessary; yet, if they are to benefit from health-related advances then children must take part in relevant health research
Researchers face the ethical dilemma of how to balance protection and access: fairness demands protection and opportunity for inclusion. The extensive off-label use of diagnostic and therapeutic interventions to treat children has led to the conclusion that children are already being used as research participants without the benefit of ethical and regulatory oversight, or a systematic commitment to discover what works best. Some argue that off-label use of diagnostic and therapeutic interventions has become the standard of care for many children. If new interventions are only tested in adults but are used in children, then children are exposed to risks from interventions not specifically proven safe and effective in this population. Clinicians face difficult choices when treating children. If they use untested interventions they face dangers of underdosing, overdosing or prescribing unsuitable paediatric formulations. If, on the other hand, clinicians use only proven interventions, they are severely limited in their diagnostic and therapeutic options. So, in our efforts to protect children from harm, we may actually deprive them of the benefits of medical research.

Researchers must resolve the tension between advancing knowledge to benefit future children and limiting potential harm to individual children
The most intractable ethical issues arise in non-beneficial research where there is no prospect of direct benefit to individual minor-participants but there is risk of harm. Is it a greater wrong to use individual children where there is no prospect of individual benefit (i.e. to serve societal rather than the child’s own interests) or to fail to obtain vitally important information that may benefit all children, such as vaccine research? Researchers must balance the best interests of the individual child with the best interests of children as a class.
Determining the minimal risk standard in research with children.

Minimal risk is a useful sorting mechanism which draws attention to riskier research and acts as a threshold limiting the amount of non-therapeutic risk in research. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in research are not greater than the harms or discomfort ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. This is also called the ‘everyday risks standard’ or the ‘routine examination’ standard. The ‘everyday risks standard’ raises the ethical question of what risks count as the risks of daily life: should risks of daily life be measured against the risks healthy children typically face in everyday life (i.e. an absolute interpretation) or against actual risks in the background of children who take part in research (i.e. a relativistic interpretation). Arguments against a relative standard of minimal risk claim that it would impose a disproportionate burden of research on sick or disadvantaged children. According to this view, children with a specific disease or condition face certain risks such as extra lumbar punctures or MRIs because they have a specific disease or condition. Hence these risks are already part of their daily lives, that is to say they are already risks of daily life. This raises the ethical question of how a relativistic argument could be justified without violating the principle of justice. Justice demands that research not unduly involve groups unlikely to benefit from research; but in this case children with a specific disease or condition may benefit from the research. If the only way to provide some benefit is to conduct research among these groups of children then a relative standard may be justified by the prospect of future benefits among those most likely to gain from the findings of the research. In summary, reasonable differences exist regarding the interpretation of the minimal risk standard in research involving children.

Policy Considerations

Research involving children requires additional ethical, regulatory and legal protections. However, the existing South-African ethical-legal framework for research with children is in a state of flux as key legislation governing research with children must still be enacted (National Health Act 61 of 2003 Section 71 (2)(3)). Furthermore, there are inconsistencies between the proposed legislation and existing ethical guidelines including those of the Department of Health. If it transpires that in the future children will be unfairly excluded from important research clinicians, researchers and Human Research Ethics Committees (HRECs) may need to adopt an advocacy role aimed at promoting the inclusion of children and adolescents in relevant research which is not against their best interests.

Definition of Health Research

‘Health research’ is broadly defined in the National Health Act of 2003, (see point ‘a’ below), and the extent to which the Act’s legal obligations will affect other disciplines, for instance research in psychology or the social sciences, remains unclear.
Health research includes any research which contributes to knowledge of:

a. the biological, clinical, psychological or social processes in human beings
b. improved methods for the provision of health services
c. human pathology
d. the causes of disease
e. the effects of the environment on the human body
f. the development or new application of pharmaceutical, medicines and related substances
g. The development of new applications of technology.

Definitions and Distinctions in Research with Children

Child
A child is a person under the age of 18 years. The terms minor and child are used interchangeably. A child becomes a legal major at the age of eighteen. This means that from the age of 18 young persons can consent independently to any form of research.

Guardianship
Every person <18 years requires a legal guardian to assist with decisions with legal consequences, such as consent to research participation. Both parents, if married, are legal guardians. If a child is born out of wedlock, the mother is natural guardian. If the unmarried mother is herself a minor, her mother (i.e. the maternal grandmother) would be the child’s guardian. An unmarried father may apply to be a child’s guardian. If parents are dead, a guardian may be appointed by way of a will or the High Court. Occasionally, a child without a parent or guardian is placed in the custody of a person (e.g. a foster parent) or institution (e.g. a children’s home) without a guardian being appointed. In this case, the High Court may act as the guardian of a child.

Assent
Assent derives from the ethical principle of respect for persons. In the case of children, the investigator must respect a minor-participant’s emerging autonomy which translates into the requirement for assent, respect for dissent and respect for a participant’s confidentiality (within legally allowable parameters). It includes respect for diminished autonomy and a child’s right to protection through the legal requirement for parental or a legal guardian’s consent.

Assent means a minor’s affirmative agreement to participate in research. Mere failure to object should not be interpreted as assent. A child’s refusal must be respected. The earliest age at which assent is recommended is arbitrarily set at 7 years. However, the assent process should be developmentally appropriate depending on a child’s age, maturity and experience with a disease or condition. The child must agree whether the research as he or she understands it is an activity he or she wants to take part in. Researchers must be sensitive to a child’s non-verbal cues reflecting his or her willingness or unwillingness to take part. The older the minor, the more an assent form will mirror a parental consent form. According to
Section 71(2)(d) in the National Health Act, if a minor is capable of understanding, the child must provide consent.

**Best Interests Criterion**

The Constitution in Section 28(2) requires the best interests of the child to be the paramount consideration in all matters concerning the child and this would include decisions relating to whether a child should take part in medical research.

According to Section 7 of the Children’s Act No. 38 of 2005, the following are among the criteria which must be considered when determining a child’s ‘best interests’:

- age, maturity and stage of development
- background
- the child’s intellectual, emotional, social and cultural development
- any disability a child may have
- any chronic illness from which a child may suffer

**Therapeutic and Non-therapeutic Research**

Section 71 of the National Health Act of 2003 (not yet enacted) includes special protections for children related to the degree of risk involved in a study and the extent to which the research is likely to benefit the minor-participant. In line with the Act, researchers and HRECs will need to categorise research as therapeutic or non-therapeutic.

Therapeutic research would include studies which provide direct health-related benefits to minor-participants. HRECs may only approve non-therapeutic research with children if:

- The Minister of Health gives consent;
- A parent or legal guardian provides consent; and
- A minor who is capable of understanding provides consent.

The Minister may not give consent in circumstances where:

- The objectives of the research can be achieved if conducted on adults;
- The research is not likely to significantly improve scientific understanding of the minor’s condition, disease or disorder and there is no significant benefit to the minor or other minors;
- The reasons for the consent to the research by the parent or guardian are contrary to public policy;
- The research poses a significant risk to the health of the minor; or
- There is some risk to the health or wellbeing of the minor and the potential benefit of the research does not significantly outweigh that risk.

In practice, the distinction between therapeutic and non-therapeutic research is misleading as most studies include a mixture of therapeutic and non-therapeutic components. For example, in HIV prevention research, risk reduction counselling, high quality voluntary testing and counselling, and diagnosis and treatment of sexually transmitted infections are direct benefits of participation. In comparison, extra blood tests, storage of biological specimens for future research and completing questionnaires are non-therapeutic
interventions with no direct benefit for minor-participants. Researchers and HRECs need to evaluate these components separately using the appropriate risk standards as defined in the National Health Act.

Informed Consent in Research with Children: Ethical and Legal Framework

Who may consent to a minor’s participation in research?

There are discrepancies between the requirements of the National Health Act of 2003 and the Department of Health’s ethical and good clinical practice guidelines:

National Health Act of 2003

If a study is categorised as therapeutic, the researcher must obtain written consent from the:
- Parent or guardian; and
- Minor, if capable of understanding.

If a study is categorised as non-therapeutic, the researcher must obtain written consent from the:
- Minister of Health; and
- Parent or guardian of the minor; and
- Minor, if capable of understanding.

Once enacted into law, these requirements will override existing ethical guidance. Furthermore, Section 71(1)(b) of the Act requires written informed consent for all research.


These guidelines require consent from the:
- Parent or legal guardian; and
- Minor if competent to decide; and
- Any person required by law.
- No other caregiver can consent on behalf of a child to participate in research.

Unassisted Consent

At present, researchers may request that adolescents be allowed to provide ‘unassisted consent’ to take part in research. In certain research situations such as sensitive surveys about high risk behaviours, adolescents may not want their parent or legal guardian to know they are taking part in a study. HRECs may approve the use of ‘unassisted consent’ if a study meets the following conditions:
- The study is no more than minimal risk; and
- The nature of the research is acceptable to the Committee, parents or legal guardians or the community at large. The Committee’s opinion must be based on information from the community concerned and lay Committee members; and
- Justification for why adolescents are needed in the study; and
- Justification for why adolescents should consent unassisted.
Once Section 71 of the National Health Act is enacted, HRECs will no longer have discretion to permit unassisted consent for minors’ participation in any kind of research. Written consent from a parent or legal guardian will be a legal requirement for their inclusion.


According to the Minister of Health, ‘These Guidelines will support the regulatory requirements of the Medicines Control Council and regulations related to Health Research in the National Health Act’ (p. 2). These guidelines require:

- Consent from a parent or legal guardian in all but exceptional circumstances (e.g. emergencies)
- Consent from a caregiver
- Consent from a caregiver

A ‘caregiver’ is defined as any person other than a parent or guardian who factually cares for a child and includes
- A foster parent
- A person who cares for a child with the implied or express consent of a parent or guardian of the child
- A person who cares for a child whilst the child is in temporary safe care
- The person at the head of a child and youth centre where a child has been placed
- The person at the head of a shelter
- A child and youth care worker who cares for a child who is without appropriate family care in the community

The provision for consent from a caregiver conflicts with earlier research ethics guidance provided by the Department of Health (2004).

Consent for Research when Minors Reach Eighteen

Minors taking part in ongoing or long-term studies must provide independent informed consent when they become adults at eighteen. Participants must be reminded of their right to withdraw, including rights to use of their stored human tissue, where this is possible.

Consent, Medical Treatment and Participation in Research

For purposes of consent, treatment and research are treated differently under the law. Under existing law a child can consent independently to medical treatment from the age of 12, but can only consent independently to take part in research at the age of eighteen. All children of 12 years of age, or below 12 years of age with sufficient capacity, may consent independently to HIV testing. This means that if a study includes HIV testing, participants from age 12 will be able to consent independently to this procedure. HIV testing must include pre and post test counselling.
General Pointers for Developing a Protocol

- Children may be included in research only if their participation is necessary to answer the scientific question being investigated. This means that researchers must justify the inclusion of children in a study.

- Consider potential benefits, harms and discomforts from the child's perspective:
  - The research environment should be child-friendly with age-appropriate furniture, play equipment and food.
  - Where possible, coordinate the collection of clinical and research samples.
  - Only research staff with paediatric expertise and/or experience should perform research-related procedures.
  - Where possible, use topical anaesthesia such as EMLA during potentially painful procedures.
  - Researchers may not make more than two attempts to draw blood intended solely for research purposes.
  - Where appropriate, protocols must include data monitoring mechanisms that allow rapid termination in the face of unexpected problems or adverse events.
  - Where possible, use laboratories experienced in handling small volumes of blood.

- Informed consent is a process of communication between the researcher, parent and minor-participant. The protocol must indicate:
  - Who will request assent and consent (preferably someone with paediatric expertise or experience).
  - How and when assent and consent will be requested. This is particularly important when children with a serious and/or critical condition and their parents are approached to enrol in research. If standard therapy has failed, parents may see a clinical trial as the only option for survival. In such a situation, the informed consent document must describe possible burdens of participation and alternative forms of care such as palliation.
  - If a parent or guardian will be present when assent or consent is obtained. Sometimes it may be appropriate for the researcher to spend time alone with a child or adolescent. This may make it easier for a child or adolescent to ask questions and not feel pressured or inhibited by a parent or guardian.
  - How the researcher will assess a minor-participant’s decision-making capacity.
  - How the researcher will assess the minor-participant’s understanding of information exchanged during the assent or consent process.
  - How assent will be documented:
    - Signature on assent form
    - Oral response
    - Combination of both
  - The researcher should carefully consider the age of child participants. Self-evidently, most young children (for argument’s sake ≤12 years) are less capable of independent decision-making than children ≥12 years. This is confirmed by the law’s recognition that children ≥12 years can independently consent to certain medical interventions. The views of older children should carry substantial weight in decisions to take part in
research. This is also consistent with the Children’s Act 38 of 2005 which states that children’s voices must be heard in all matters affecting them.

- The burden of ensuring that parents, guardians and minor-participants understand what will happen during a study rests with the investigator.
- Researchers need to explore innovative and creative approaches to obtaining assent or consent from minor-participants. Examples might include:
  - Videotapes or photographs of research procedures.
  - Pre-visits to the research site to see equipment such as MRIs.
  - Design comics or illustrated assent/consent forms that explain the nature of the research.
  - Encouraging families to speak to other families and minor-participants who have taken part in similar research.

Statutory Reporting Requirements for Neglect and/or Abuse

If during a study a researcher learns that a minor-participant is being neglected or abused, the researcher has a legal obligation to report the circumstances to the relevant authorities. Depending on the nature of a study, researchers need to inform children and parents or legal guardians in the assent and consent documents of their obligations to report ill-treatment. Based on this information, parents and minors may choose not to take part in a study.

The Criminal Law (Sexual Offences and Related Matters) Amendment Act No.32 of 2007 states that a person who has knowledge that a sexual offence has been committed against a child must report such knowledge to a police official. In similar vein, Section 110 of the Children’s Amendment Act No.41 of 2007 imposes a duty on medical doctors and others to report sexual abuse. The implications of these reporting requirements for research (and confidentiality) are discussed in the Recommended Readings 1 and 6.

Privacy Rights of Minor Research Participants

Since the law does not deal directly with a minor’s privacy rights in research, researchers must rely on general legal principles relating to privacy. Researchers must specify what privacy rights a parent or legal guardian and a minor-participant have in a research study. Although a parent or a legal guardian must consent to a minor’s participation based on a detailed description of all diagnostic and therapeutic interventions in the study, the minor-participant retains privacy rights with respect to medical interventions to which he or she consents independently in the study, provided this is in the minor’s best interests. South African courts have ruled that a person has the right to privacy if the person can show that:

- He or she has a legitimate expectation of privacy; and
- This expectation would be considered reasonable by the community.

The privacy rights of adolescents in research are especially challenging, as it would have to be determined for each element of a study whether adolescents have an expectation of privacy and whether society would regard this expectation as reasonable. For example, adolescents
may have an expectation of privacy regarding treatment of a sexually transmitted infection if they have consented independently to such treatment. Besides, if they are over the age of 16 and having lawful sex this expectation of privacy may be regarded as reasonable by society. In contrast, if an adolescent tests HIV positive, even if she has consented independently to the test and expects privacy, society may not regard this as reasonable since HIV is a life-threatening condition requiring long-term chronic care. There is no blanket right to privacy for adolescents in research; their best interests would always have to be considered and rights can be waived in certain circumstances (Anne Strode. Personal Communication).

*Based on the Standard Operating Procedure for Research with Children, Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town http://www.health.uct.ac.za/research/humanethics/sop/

Recommended Reading

1. Bhana A, Swartz S, Davids A. Standards for the reporting of sex/sexual activity of minors in a research context. SAMJ 2010;100:642-3


Lesley Henley PhD.
Research Directorate, Faculty of Health Sciences, University of Cape Town
11 February 2011