



The South African Medical Research Council's *Guidelines on Ethics for Medical Research* – implications for HIV-preventive vaccine trials with children

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Children are at risk of HIV infection, stand to benefit from the development of HIV preventive vaccines, and therefore should be enrolled in trials of HIV vaccines in order to generate relevant safety, immunogenicity and efficacy data. In South Africa, the national vaccine initiative is considering the future conduct of trials involving children; this requires an analysis of the current ethical framework, including elements that facilitate or constrain the conduct of such trials. In this article, we examine the Medical Research Council (MRC)'s *Guidelines on Ethics for Medical Research: General Principles*

(Book 1), and their provisions on research involving children. We argue that this set of influential guidelines includes provisions on research with children that are conceptually problematic and may prohibit critical research with healthy (but at-risk) child participants, including trials of HIV-preventive vaccines. We recommend that Book 1 provisions should be redrafted to reflect a balance between protecting children from research-related risks and testing interventions critical to their health.

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The participation of children in research honours their right to equal consideration by enabling their access to safe and effective health care products.¹ There has been an increasing call for research initiatives to involve children.² However, children are considered vulnerable³ and most ethical guidelines spell out protections for them. These generally include the absence of alternative methods or research participants, acceptable levels of research risk, consent by parents or legal guardians and child assent.¹

The South African AIDS Vaccine Initiative (SAAVI), a lead programme of the Medical Research Council (MRC), is currently focusing on healthy adult participants who can give independent consent for HIV vaccine trial participation. However, children in South Africa are at considerable risk of HIV infection. A recent study⁴ revealed that 7% of 2 - 9-year-olds and 5% of 10 - 18-year-olds are infected with HIV. HIV-preventive vaccines may constitute one critical preventive intervention for children. It will be necessary to enrol children in HIV vaccine trials to generate data on the safety, immunogenicity and efficacy of HIV vaccines for this population.

However, the participation of South African children in HIV vaccine trials presents a number of ethical-legal challenges. Challenges include the nature of research in which it is considered permissible to enrol children, and post-enrolment challenges such as management of child disclosure of high-risk

sexual behaviour or illegal activities.

In this article we restrict ourselves to the challenges presented by one set of influential ethical guidelines, the Medical Research Council (MRC)'s *Guidelines on Ethics for Medical Research: General Principles (Book 1)*⁵ to the enrolment of healthy children in HIV-preventive vaccine research, and make recommendations for revision of these guidelines.

MRC 2001 general principles: Book 1

Those who formulate guidelines and regulations have long struggled with the problem of how to promote the best interests of children as a group through research while protecting the rights and welfare of individual research subjects.¹

Book 1⁵ governs MRC-funded research, and researchers. Its provisions on research involving children appear to be more restrictive than other South African guidelines⁶ and rest on a number of conceptually confusing provisions. The latter relate to the classification of research as 'therapeutic' or 'non-therapeutic' and as 'intervention' or 'observation'.

According to Book 1, when research is classified as 'non-therapeutic' and as 'intervention', children are precluded from participation.

'Therapeutic' versus 'non-therapeutic' research

This distinction has been defined as the difference between research where the aim is essentially diagnostic or therapeutic for a patient, and research where the aim is purely scientific.⁷ 'Therapeutic' studies have been defined as those that seek generalisable knowledge but intend to provide medically

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beneficial and acceptable therapy for the individual, and 'non-therapeutic' studies have been defined as those that seek generalisable knowledge but do not intend to provide therapy to benefit the individual directly.¹

This is a contested distinction on the grounds that most trials will contain components or interventions that do not intend to confer a direct health-related benefit to individual volunteers, e.g. assignment to placebo, additional tests.⁸ A number of leading international guidelines have abandoned this distinction.^{9,10} However, MRC Book 1 structures its provisions on children around this distinction.

Book 1 appears to classify research as 'therapeutic' or 'non-therapeutic' according to the aim of the research and the health status of participants. Specifically, therapeutic research is defined as aiming to benefit the individual participant or patient by treating or curing his or her condition, or investigating an intervention that might be of therapeutic benefit to the patient. Book 1 states that in most cases, research on patients will be therapeutic research. Non-therapeutic research is defined as aiming to acquire knowledge and to benefit people other than the research participant. Book 1 states that 'by definition' healthy volunteers will *not* be participants in therapeutic research but will participate in non-therapeutic research.

It may be difficult to classify research according to these definitions, particularly research involving the participation of volunteers who may be healthy but, because of their risk or susceptibility to a condition, stand to benefit from the intervention under testing. For example, phase III HIV vaccine trials may test promising candidate vaccines that could be of direct benefit to (at-risk) individual volunteers although volunteers are healthy. These trials could, therefore, be seen to meet part of the MRC defining elements for therapeutic *and* non-therapeutic research.

HIV vaccine trials, however, might be crudely categorised as non-therapeutic, because Book 1 asserts that 'by definition' healthy volunteers will not be participants in therapeutic research, or because they comprise early safety or immunogenicity studies.

'Observation' versus 'intervention' research

MRC Book 1 classifies research as 'intervention' or 'observation' research. Intervention research is defined as research that interferes with a research participant's mental or physical integrity, and always involves risks of unpredictable magnitude. Examples given include the removal of bodily material, or the introduction of fluids into the body. Observation research is not defined *per se* but is classified further as non-invasive research involving no interference with mental or physical integrity and no risk (e.g. unlinked

anonymous specimen gathering), and 'invasive' research that invades mental or physical integrity but involves 'negligible risk' foreseeable from routine medical practice (e.g. the collection of urine, nail clippings, hair, one blood sample, weight measurements). 'Negligible risk' is defined as equal to the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives of people in a stable society or in the routine performance of physical or psychological examinations or tests — so-called everyday risk.

It is not simple to classify research according to these definitions. To do so, procedures must be examined (namely, do the procedures invade the integrity of the participant?). Invasive procedures characterise both 'types' of research, therefore it is risks that appear more important — both risk level (are risks commensurate with those of routine medical or psychological examinations or not?) and risk foreseeability (are the risks foreseeable from routine medical practice?).

However, using the research types, risk levels and examples, it would appear that trials of HIV vaccines would be classified as 'intervention' research, because such trials do interfere with the bodily integrity of participants, will exceed 'negligible' risk (also defined as risk so small it may be ignored) and involve the introduction of fluids or agents into the body.

Child participation in non-therapeutic research — observation only

MRC Book 1 does not permit the participation of children in non-therapeutic intervention research. It only permits the participation of children in non-therapeutic observation research of an invasive or non-invasive nature.

'Non-therapeutic research on minors is not permissible, except where parental consent (and the assent of the minor) is obtained for observation research of a non-invasive nature ... and observation research of an invasive nature ...' pp. 12 - 13).

Parental consent and child assent are restricted to this kind of study. Therefore, Book 1 provisions as currently drafted may preclude parental consent to enrol healthy children in clinical trials of HIV vaccines.

Parental consent for non-therapeutic research is also restricted to research with a risk threshold of 'no or negligible risk'. This appears more restrictive than other regulations and guidelines. For example, the US Code of Federal Regulations¹¹ allows that parents may give proxy consent to non-beneficial research if the risks are reasonably commensurate with those of a child's non-research life; however, a minor increase over such risk may be considered acceptable if the research holds out the prospect of potential benefit to others in the same class.¹² The guidelines of the Council for International Organisations of Medical Sciences (CIOMS)¹⁰ explicitly allow children to be enrolled in research representing a minor increase over everyday risk, even where the research interventions do not



hold out the prospect of direct benefit for the subject, when there is an overriding scientific or medical rationale, or where the research is designed to be responsive to conditions to which children are particularly susceptible.

Conclusions and recommendations

Current MRC 2001 provisions may have consequences that the drafters did not foresee.⁸ In order to justify intervention research on preventive agents with healthy children, under current MRC provisions, investigators might have to argue that such trials are in fact 'therapeutic research'. This would be difficult because of the assertion that healthy volunteers do not participate in 'therapeutic' research. Alternatively, investigators might have to acknowledge that trials of preventive agents involving healthy children are likely to be classified as 'non-therapeutic' research, but might try to argue that such research is not 'intervention' research, but rather observational research of an invasive nature. Meeting the outlined risk standard or the examples will prove a challenge.

Instead, we recommend that the MRC consider a careful revision of these provisions on research with children to reflect a balance between the need to protect children from research-related risks while permitting critical research for the health of children. Specific recommendations include the following.

1. The classification of entire protocols as 'therapeutic' or 'non-therapeutic' should be omitted and replaced with a focus on beneficial versus non-beneficial interventions.¹³
2. Risk standards and risk-benefit ratios for interventions with children should be carefully framed, e.g. the risks from non-beneficial interventions should be commensurate with routine examinations or tests, or slighter higher when there is an overriding scientific or medical rationale.¹⁰ Risks from beneficial interventions should be outweighed by the benefits.
3. Trials of HIV vaccines involving healthy child participants

should be permitted when certain safeguards prevail, e.g. (i) if the research cannot be conducted equally well on adults; (ii) if interventions meet risk standards and risk-benefit ratios outlined above; (iii) legal requirements for consent and assent are obtained; and (iv) due consideration is undertaken by research ethics committees with appropriate child expertise.

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