Implications of the ethical-legal framework for adolescent HIV vaccine trials – report of a consultative forum

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The ethical-legal framework in South Africa is in a period of transition, with a number of new developments changing the substantive principles and procedures for health research in the country. Some of the changing dynamics include both law reform and the review of ethical guidelines. This changing environment poses many complexities for researchers, research ethics committees and participating communities involved in planning, implementing and reviewing research with child participants, including HIV vaccine trials. This paper presents the major themes and outcomes of a consultative meeting convened by the HIV AIDS Vaccines Ethics Group in July 2004 for key stakeholder groups. At this forum participants discussed the complexities posed by a transitional and sometimes contradictory ethical-legal framework and how the framework could be improved to simultaneously promote critical research and the welfare of child participants.

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Adolescents in South Africa are at high risk of HIV infection. In 2002 it was estimated that 9.3% of youth (15 - 24 years) were HIV infected.[1] Another survey in 2003[2] reported that 10.2% of this same age group were infected. In the 15 - 19-year age group, 4.8% of youths were reportedly infected with HIV.[2] The participation of children in research, including HIV vaccine trials, ensures their fair access to safe and efficacious products. Adolescents are, however, a vulnerable group and their participation raises complex ethical and legal issues.

South African ethical-legal framework

The ethical-legal framework governing child research in South Africa is currently in transition. Firstly, a comprehensive new legislative framework for health research is being implemented through the National Health Act.[3] Secondly, the legislation relating to children is being reviewed and consolidated into a Children's Bill.[4] Thirdly, a number of new ethical guidelines have been published and a series of others are being revised. Fourthly, the institutional framework for establishing research priorities and regulation of ethical review is being strengthened with the establishment of new institutions such as the National Health Research Ethics Committee.

The South African ethical-legal framework and its implications for adolescent HIV vaccine trials were debated at a forum convened by the HIV AIDS Vaccine Ethics Group (HAVEG), funded by the South African AIDS Vaccine Initiative (SAAVI). Representatives from a variety of stakeholder groups including research ethics committees (RECs) and community advisory boards were invited to the forum that aimed to: (*i*) identify the complexities posed by the current ethical-legal framework and implications for HIV vaccine trials, with a focus on child participation (including adolescents); and (*ii*) work towards consensus on how to enhance the current framework so that it would facilitate sound research and protect trial participants.

The major themes and recommendations of the forum are presented here.

Key outcomes

The South African ethical-legal framework is in a state of flux due to legislative and ethical guideline changes

Key problems raised at the forum included: (*i*) although the National Health Act[3] has been passed by parliament not all aspects of the Act have been implemented; (*ii*) the regulations that accompany the Act[3] and that contain much of the detail regarding its practical application have yet to be finalised; (*iii*) the Children's Bill,[4] which proposes considerable amendments to the health rights of children, has not yet been passed by parliament; and (*iv*) it is uncertain when the revision of key ethical guidelines will be finalised.[5,6]

As a result investigators, RECs and other stakeholders face an uncertain ethical-legal environment. For example, Section 71(2) of the National Health Act[3] requires consent from both the parent/guardian and the child, regardless of age, for all research including 'therapeutic' research. Unlike existing and proposed children's legislation, the Act does not provide for a child of a specified age or capacity to give independent consent. For example, section 39 of the Child Care Act (Act No. 74 of 1983) allows a child of 14 years to consent independently to 'medical treatment', which legal scholars and RECs have

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interpreted as allowing children over 14 to consent independently to 'therapeutic' research.[7]

Researchers will now face new legal requirements that may affect recruitment and informed consent processes. Although the National Health Act[3] will not operate retrospectively, once it is implemented researchers may have to change current practices if they are not in line with the new provisions.

Aspects of the emerging ethical-legal framework are ambiguous and inconsistent

Key problems raised at the forum included:

1. The National Health Act[3] retains the contested distinction between 'therapeutic' and 'non-therapeutic' research in its provisions relating to research with children, despite the fact that most research contains interventions not intended to confer direct benefit to participants. It does not define either term.
2. It is not clear how the different phases of HIV vaccine trials would be classified in terms of the above distinction.
3. If HIV vaccine trials are classified as 'non-therapeutic' research (as early trials might be) the risk standard of 'not significant' risk must be met. There was some debate as to whether the above term introduced a more relaxed standard of risk for research involving children or alternatively whether it was substantively identical to current risk standards (routine tests or daily life). There was some debate as to whether the risks of HIV vaccine research (such as vaccine administration, risk assessments) could meet this standard set by the National Health Act.[3]
4. There are many inconsistencies between the National Health Act[3] and other critical pieces of legislation such as the Children's Bill.[4] For example, the National Health Act[3] requires dual consent for research from parents or legal guardians and where children are capable of understanding, children themselves.[8] This differs from the approach taken in the Children's Bill[4] which provides for independent consent by a child of a specified age and capacity (albeit in the case of medical treatment and operations and not research), which creates a wider category of persons who are able to act on a child's behalf,[9] and which requires that the views of a child be given due consideration bearing in mind the age, maturity and stage of development of the child.[10]
5. The National Health Act[3] requires 'therapeutic' research to be conducted only if it is in the 'best interests' of the child.[11] No guidance is provided in the Act on how one establishes what these 'best interests' are.
6. Both the National Health Act[3] and the Children's Bill[4] provide that in the event of an inconsistency their provisions will prevail.
7. Four ethical guidelines relevant to HIV vaccine research[5,6,12,13] offer some contradictory guidance regarding child participation on the following points: (*i*) the approach taken towards the analysis of risk and classification of research; (*ii*) the name given to risk levels allowed for child research, and the substance of the risk level allowed for child research; (*iii*) who has the authority to consent for child participation; and (*iv*) what risk parents or guardians are permitted to consent to on behalf of children when there is no direct benefit to the child and when there is a direct benefit.

It is the MRC's General Principles[6] that are most disjunctive with the other three increasingly well-harmonised guidelines.[5,12,13] As a result of these ambiguities and inconsistencies REC members reviewing trials and researchers planning trials may struggle to screen out 'unethical' or unlawful research practices involving child participants.

In some instances, the ethical-legal framework does not protect child welfare or promote critical research as effectively as possible

The following issues were discussed:

1. Section 71 of the National Health Act[3] purports to deal with the rights of children participating in research; however, it focuses on informed consent without considering other protections such as a child's right to privacy. As a result, there are many instances in which child research participants do not have explicit legal protection in South African law.
2. The National Health Act[3] creates additional procedural requirements that may burden investigators and RECs, e.g. when 'non-therapeutic' research is conducted on children then 'authorisation from the Minister' must be obtained.[14] Furthermore, the Minister is obliged to follow guidelines set down in the Act, in determining whether authorisation for non-therapeutic research should be approved. Concerns were raised regarding: (*i*) how this provision would operate in practice; (*ii*) whether it would delay research classified as 'non-therapeutic'; and (*iii*) how the Minister would interpret poorly drafted requirements such as that research may only be authorised if the parent or minor's reasons for consenting to the research are not contrary to public policy.
3. Certain ethical guidelines are restrictive in their approach, e.g. the Medical Research Council's General Principles[6] permit parents to enroll their children in 'non-therapeutic' research only if it is 'observation' research, and research with risks not exceeding everyday life. This approach may prevent the enrolment of healthy children in intervention research such as clinical trials of prevention products.

Recommendations

A number of recommendations were made at the forum to promote a more coherent framework that facilitates critical research with child participants, including adolescents, while promoting their rights and welfare. These included the following.

Capacity should be built for stakeholders to better understand the strengths, weaknesses and implications of the framework, and mechanisms should be developed to allow them to impact on the framework

It was recognised that in many instances stakeholders felt unable to participate in the ethical-legal framework or impact on its development because of a lack of capacity. Accordingly it was recommended that: (*i*) the capacity of community representatives, RECs and investigators should be developed to enable them to understand the relevant laws and guidelines, and their interpretation in relation to HIV vaccine research; (*ii*) an accurate understanding of the perspectives and concerns of participating communities should be established through sensitive research and consultation; and (*iii*) mechanisms should be developed whereby stakeholders, such as RECs, can liaise on the interpretation of laws or guidelines in order to aspire towards consistent protocol review.

Law reform and the revision of ethical guidelines is required

The following was recommended: (*i*) input should be made to the regulations that will accompany the National Health Act in order to resolve certain inconsistencies and ambiguities in the Act;[3] (*ii*) proposals to include the rights of child research participants in the Children's Bill[4] should be supported; and (*iii*) revisions should be made to ethical guidelines[5,6] that ensure their harmonisation and ability to protect child participants while accommodating sound research.

Appropriate tools should be developed

It was recommended that tools and tests should be developed to facilitate the appropriate implementation of a number of the new requirements set out in the National Health Act including: (*i*) children's 'understanding' of research participation; (*ii*) determining 'public policy'; and (*iii*) determining the 'best interests of the child'.

In conclusion, a transitory and inconsistent framework complexifies research involving adolescent or child participants. Considerable training, law reform, guideline amendment and tool development are required to better protect these participants and to facilitate critical research to promote their health.

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