ETHICAL-LEGAL CHALLENGES IN ADOLESCENT HIV VACCINE TRIALS

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South Africa is likely to enrol adolescents into a phase IIb proof of concept HIV vaccine trial in late 2007 or early 2008, which would make it the first country in the world to enrol adolescents into HIV vaccine trials. These healthy adolescents will be at high risk of HIV infection. They will have to undergo a general physical examination, answer questions about their personal HIV risk, be administered an experimental HIV vaccine or placebo via injection, have blood drawn for laboratory safety and immunogenicity testing, and have regular testing for HIV infection.[1] Many ethical/legal complexities exist, in part due to our fluctuating ethical-legal framework, the lack of legal guidance on issues such as adolescent privacy rights in research, and differing approaches towards child antonomy in child care and health legislation that enable children of a certain age to consent independently to medical treatment but not to research.

Against this backdrop, in 2005 a member of the UCT Research Ethics Committee (REC) initiated a process of research into the minimum legal requirements that need to be met to ensure that adolescent HIV vaccine trials are lawful. As a result, a unique collaboration was established between an ethics and law research unit, (the HIV/AIDS Vaccines Ethics Group – HAVEG); members of the UCT REC, and researchers at the Desmond Tutu HIV Centre, Cape Town, and the Perinatal HIV Research Unit, Soweto. This collaboration resulted in the development of a roadmap of issues that ought to be addressed in order to promote the rights and welfare of adolescent participants in HIV vaccine trials, which was published in *Biomedical Central: Medical Ethics* in 2007.[1] From November 2006 onwards, work began to apply these legal principles to a protocol for an adolescent HIV vaccine trial and its accompanying informed consent/assent forms. This article summarises the issues identified by this unique and on-going collaboration, published in an earlier article.[1]

CONSENT CHALLENGES

No provision currently in operation sets out when children may provide their own independent consent to research. In the future, in terms of Section 71 of the National Health Act (NHA),[2] consent for research participation will have to be obtained from a parent or legal guardian until the age of majority is reached. Other caregivers or custodians will not have the authority to provide consent for child research. Until 30 June 2007 minority ended at the age of 21.[3] However, section 71 of the new Children's Act[4] was implemented on 1 July 2007 which lowered the age of majority to 18.

A further complexity is that the NHA provides that adolescents will consent with their parents if they have sufficient understanding. This means that researchers must anticipate how they will assess adolescent understanding to determine when adolescents possess the higher standard of competence required for consent.

Finally, in order for adolescent participation in these trials to be lawful in South Africa, common law requirements must be met, namely, consent to such research must be legally permissible or in line with public policy.[5] A key issue in making this determination is to establish if the research interventions pose acceptable standards of risk. Ethical guidelines in South Africa are approaching agreement on this issue – three out of four South African ethical guidelines[6-8] assert that when the intervention or research *does not* hold out the prospect of direct benefit, the risk must be 'minimal' or 'negligible' (i.e. the risks of daily life or routine medical and psychological tests), although a minor increase over such risk is allowed. However, draft regulations[9] are slightly more restrictive, i.e. they do not appear to permit non-beneficial research or interventions to exceed minimal risk, which is out of step with the majority of our guidelines. RECs will have to make complex assessments about whether vaccine trial interventions meet acceptable risk standards in terms of our national framework. In addition, enrolling over-16-year-olds in an efficacy trial requiring them to be sexually active would not be contrary to public policy, given that sex over the age of 16 is lawful.[10]

PRIVACY CHALLENGES

Adolescents in these trials will not consent independently to trial enrolment, but will be assisted by their parent or legal guardian. Accordingly, a number of complex privacy issues must be managed. These include whether adolescents will enjoy confidentiality regarding their HIV status, sexually transmitted infection (STI) results, pregnancy test results and sexual risk information. Unfortunately neither the current nor the future law deals directly with a child's right to privacy in research. The lack of legal guidance means that the general legal principles relating to privacy must be applied to a research context to fill this vacuum. These principles provide

that the right to privacy only extends to those aspects of a person's life that the person him- or herself, as well as society, recognises should be kept private.[11] This means that adolescents will have the right to privacy for STI results (for example) if it can be shown (*i*) that they would expect these results to be private, and (*ii*) that this is reasonable because they would have this right outside of the research context provided they were over the age of 14 and could consent independently to such tests. Consent forms will need to delineate the boundaries of adolescent privacy rights.

MANDATORY REPORTING CHALLENGES

South African children often live with high levels of violence, poverty and abuse. The law has responded by providing special protections for children who may be facing abuse, ill-treatment or neglect. The Child Care Act requires *medical practitioners*, among others, to report suspected ill-treatment, abuse or neglect of children to the Department of Social Development.[12] Failure to report is a criminal offence. Additionally, the Family Violence Act[13] states that *any person* who examines, treats, attends to, advises, instructs or cares for any child, and suspects that the child has been ill-treated, must report this to a Commissioner of Child Welfare, a social worker or the police. The future Children's Act[4] obliges *any person* to identify children in need of care and protection (e.g. living in a child-headed household, required to perform child labour, being maltreated, abused, or exploited) and to refer these to a social worker.[1] Site staff would have a legal duty to report abuse or ill-treatment disclosed by an adolescent in a trial. This means they would have to recognise when disclosures trigger a mandatory reporting response. Consent procedures will have to inform parents and adolescents about this limit to confidentiality.[1]

APPROVAL CHALLENGES

Approval challenges relate primarily to (*i*) the circumstances in which RECs would regard such trials as ethical, and (*ii*) the data that will be required by the Medicines Control Council (MCC) before approving such research. Regarding RECs, the NHA (Section 73) sets out the current legal obligations of RECs. It provides that RECs must approve research where it meets the ethical standards of the committee. RECs that will review adolescent HIV vaccine trial protocols will have to network with each other to build consensus about adolescent trials. In addition, they will have to debate their role in relation to establishing lawfulness, given that their primary brief is to ensure that protocols are ethical and they may already be burdened. In many cases, RECs that comply with the principles set out in ethical guidelines may be simultaneously abiding by legal values, and researchers who craft their protocols with thoughtful attention to ethical guidelines may meet most, if not all, of the legal requirements. Where the law is unclear, researchers should consult with their REC or get legal advice from a lawyer trained in research ethics and law.[1]

With regard to the MCC, in terms of the regulations on the control and conduct of clinical trials, all trials must be conducted in accordance with Good Clinical Practice guidelines.[14] The MCC has also prepared a set of guidelines for phase I trial applications.[15] However, they have not issued any guidance on adolescents. They should be requested to articulate the data they will require, *firstly* to allow adolescents into trials and *secondly* to license an adolescent vaccine.

Finally, if such trials are classed as 'non-therapeutic', when Section 71 of the NHA is implemented, 'non-therapeutic' research on minors may not be done without first obtaining consent from the Minister of Health. This requirement has a number of ambiguities, including which research falls into its scope, and its place in the sequence of approvals.[16] This detail is also not provided in the draft regulations.[9] South African researchers will have to anticipate the public policy assessment that the Minister will have to undertake by framing their protocols in a way that assists the Minister, or a delegated authority, to make a speedy determination. They can do this by explicitly addressing the four factors the Minister must consider in terms of the Act when deciding whether to authorise such trials.

CONCLUSIONS

This collaboration between researchers and law/ethics advisors has facilitated research into the minimum legal requirements for lawful research with adolescents, and consideration of how to apply these requirements in a way that facilitates research and protects participants' rights. It has identified that South African investigators and RECs will have to deal with: (*i*) consent challenges (e.g. who must consent? what can be consented to?); (*ii*) privacy challenges (determining the boundaries of adolescent privacy rights for STI, HIV and other test results); (*iii*) challenges around obligations to protect children from abuse and maltreatment (e.g. responding to disclosures by adolescents that they have been raped); and (*iv*) procedural challenges (e.g. need for guidance from the MCC and the impending 'Ministerial Consent' requirement). Additional networking, tool development and training processes are needed to make sound adolescent trials a reality.

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