THE STATUTORY REGULATION OF CHILDREN'S PARTICIPATION IN HIV-RELATED CLINICAL RESEARCH: MORE QUESTIONS THAN ANSWERS

1 Introduction

The HIV epidemic in South Africa shows no sign of declining. Statistics show that children and young adults are especially vulnerable to contracting the disease: female children and young adults between the ages of 15 and 24 have a HIV prevalence rate of 16,9% (HRC *South African national HIV prevalence, HIV incidence, behaviour and communication survey 2005* (hereafter "*HSRC survey*") 45). The situation for children and young adults between the ages of 15 and 24 who are living in informal settlements is particularly dire – they show a prevalence rate of 25,8% (*HSRC survey* 44). In this context, it is not only vital that clinical research is conducted to find interventions which may curb the spread of HIV, but it is imperative that such research includes children and young adults.

Clinical trials are underway to establish the efficacy and safety of anti-HIV microbicides, pre-exposure prophylaxes, preventive HIV vaccines and male circumcision (see generally Ramjee "Microbicides and other prevention technologies" – paper delivered at the XVI International HIV/AIDS Conference, Toronto, Canada, 13–18 August 2006; Ramjee *et al* "Challenges in the conduct of vaginal microbicide effectiveness trials in the developing world" 2000 *AIDS* 2553–2557; "Medicines Control Council approves first HIV vaccine trial in South Africa" SAAVI press release 18 June 2003). At present, the trials do not include child participants, but in light of the statistics demonstrating the vulnerability of children and young adults to HIV infection, they conceivably will be included in the near future.

In South Africa, clinical research on human subjects into establishing the efficacy or safety (or both) of new drugs (and new indications of existing drugs) is governed by legislation, and by international and local principles and guidelines for medical and research ethics. This note explores the regulation by section 71(2) and 71(3) of the National Health Act 61 of 2003 of children's participation in preventive HIV-related clinical research (the National Health Act entered into force in 2006, but chapter 9, which deals with issues related to health research, has not yet come into effect as of 30 November 2007). Reference is made to inconsistencies between statutory provisions and local ethical guidelines, such as the *Guidelines for good clinical practice in the conduct of clinical trials in human participants in South Africa: Clinical trial guidelines* (Department of Health, 2002, hereafter "*Good practice guidelines*") and the Medical Research Council's *Guidelines on ethics for medical research Book 1* (MRC, 2002, hereafter "*MRC guidelines*"). Because the emphasis is on preventive HIV-related research, or so-called "non-therapeutic" research, some attention is given to the distinction – reintroduced by the National Health Act – between "therapeutic" and "non-therapeutic research".

2 Section 71(2) and (3) of the National Health Act

Section 71(2) of the National Health Act governs the participation of minors in *therapeutic* health research. It provides:

> "Where research or experimentation is to be conducted on a minor for a therapeutic purpose, the research or experimentation may only be conducted – (i) if it is in the best interests of the minor; (ii) in such a manner and on such conditions as may be prescribed; (iii) with the consent of the parent or guardian of the minor; and (iv) if the minor is capable of understanding, with the consent of the minor."

Section 71(3) of the National Health Act governs the position of minors participating in *non-therapeutic* health research, such as preventive HIV-related research. It provides that

> "where research or experimentation is to be conducted on a minor for a non-therapeutic purpose, the research or experimentation may only be conducted – (i) in such a manner and on such conditions as may be prescribed; (ii) with the consent of the Minister; (iii) with the consent of the parent or guardian of the minor; and (iv) if the minor is capable of understanding, the consent of the minor".

Note the use in section 71(2) and (3) of the term "minor". In the past, a minor was taken to be anyone below the age of 21, while a "child" was anyone below the age of 18 (in terms of s 1 of the Child Care Act 74 of 1983). When the Children's Act 38 of 2005 comes into full effect, a minor will be taken to be anyone under the age of 18 (in line with the Constitution, 1996).

3 Analysis

3 1 Section 71(2)

In the past a minor over the age of 14 was considered to be able to consent independently to medical treatment and therapeutic research (s 39(4) of the Child Care Act 74 of 1983 determined that a minor over the age of 14 could consent independently to medical treatment; and medical treatment was considered (wrongly, perhaps?) to be analogous to research (see van Wyk "HIV preventative vaccine research on children: Is this possible in terms of South African law and research guidelines?" 2005 *THRHR* 35 40)). According to section 71(2), that minor now needs the consent of a parent or guardian. This requirement is anomalous if one considers that, according to the Choice on Termination of Pregnancy Act 92 of 1996, a minor female of any age may consent to the termination of her pregnancy. Furthermore, section 129 of the Children's Act 38 of 2005 lowers the age of independent consent to medical treatment to 12 years of age (provided the child is of "sufficient maturity and has the mental capacity to understand the benefits, risks, social or other implications of the treatment or operation"). If, like in the past, certain research interventions are taken to be synonymous with medical treatment, the provisions of the Children's Act will be in clear conflict with that of section 71(2) of the National Health Act.

According to section 71(2), a minor may participate in therapeutic research only with the consent of the minor's parent or guardian, as well as that of the minor. The requirement that only a "parent" or "guardian" may consent to the minor's participation in research, and not another person that has the care of the minor, may present problems (according to the Child Care Act 74 of 1983, a "custodian" of a child was permitted to give consent in situations where children were in children's homes or other places of safety, or where their parents could not be found or were dead). This requirement may result in children without parents or guardians being denied access to research which may be of direct benefit to them.

Some academics are of the opinion that section 71(2) may be interpreted to mean that, in case of therapeutic research, the consent of the minor is needed, but only the *assent* of parents (see eg Strode *et al* "Ethical and legal challenges in enrolling adolescents in medical research in South Africa: Implications for clinical trials" 2005 *SA J Science* 224 225; Slack and Kruger "The South African Medical Research Council's Guidelines on Ethics for Medical Research – implications for HIV preventative vaccine trials with children" 2005 *SA Medical J* 269; Jaspan *et al* "Scientific justification for the participation of children and adolescents in HIV-1 vaccine trials in South Africa" 2005 *SA Medical J* 685; Slack *et al* "Implications of the ethical-legal framework for adolescent HIV vaccine trials – report of a consultative forum" 2005 *SA Medical J* 682). Such an interpretation is unlikely to be supported by the courts, as the subsection specifically uses the word "consent" and not "assent".

Section 71(2) further directs that minors can consent only if they are "capable of understanding". This requirement is contrary to the Children's Act, which determines that the minor's wishes are important and should be taken into consideration, even if she cannot understand.

Another consequence of the requirement of parental consent for a minor's participation in therapeutic research is the erosion of the minor's privacy. In the past, minors were able independently to consent to participation in research which,

for example, was aimed at finding more appropriate drugs to treat sexually transmitted diseases such as HIV. The minor did not have to tell her parent that she was sexually active, or that she suffered from a sexually transmitted disease, in order to gain consent to participate in research. Section 71(2), therefore, may indirectly impede important research to find drugs that are appropriate for use in adolescents, as adolescents will refuse to participate in research because seeking parental consent will necessitate a violation of their privacy.

3 2 Section 71(3)

The subsection sets a higher threshold that needs to be met when minors are participating in non-therapeutic research: the Minister of Health is to consent to participation in such research, additional to the consent of the parent or guardian of the minor. The minister may not consent to the minor's participation in non-therapeutic research if the objects of the research may be attained if that research were carried out on adults; and if the research poses a "significant risk" to the health of the minor; or "some risk", though there is a likelihood of "potential benefit", if it does not significantly outweigh that benefit (s 71(3)(b)).

The intention of this subsection is clearly the protection of minors against unscrupulous research practices. However, by making ministerial approval compulsory, where in the past it was left to individual ethics committees to decide whether a proposed research project is ethically justified, section 71(3) not only lengthens the approval process of such protocols, but also removes the discretionary powers of research ethics committees. Moreover, no definition is given in the Act of "some risk" and "significant risk".

Furthermore, section 71(3)(b) creates confusion, as it presents a different risk standard from that in South African ethical guidelines: in the case of children's participation in non-therapeutic research, the Act requires that the risk should not be "significant", whereas the *MRC guidelines* require that the risk is "negligible".

3 3 General

Subsections 71(2) and 71(3) reintroduce the distinction between so-called "therapeutic" and "non-therapeutic" research. Although the National Health Act provides no definition of these terms, generally "therapeutic" research aims "to benefit the individual research participant or patient by treating or curing their condition" (*MRC guidelines* para 2 1 2 1). Therapeutic HIV-related research, for example, is research to develop an effective antiretroviral agent against HIV infection. "Non-therapeutic" research aims to "benefit people other than the research participant . . . [t]he acquisition of knowledge may be of no immediate benefit to the participant or healthy volunteer" (*MRC guidelines* para 2 1 2 2). Importantly, participants in therapeutic HIV-related research will be living with HIV/AIDS, whereas participants in non-therapeutic preventive HIV-related research will be HIV-negative.

The distinction maintained by the National Health Act between therapeutic and non-therapeutic research has largely been discredited. It is understood that therapeutic research contains many non-therapeutic elements (that have no benefit to the individual research participant), and that, after all, in the case of placebo trials, the therapeutic trial research participant may not benefit at all. Similarly, therapeutic research has at best merely the *potential* to benefit the individual research participant – an unproven drug or intervention is being tested.

These arguments make it difficult to distinguish precisely between "therapeutic" and "non-therapeutic" research.

Furthermore, the distinction in the National Health Act between "therapeutic" and "non-therapeutic" research fails to take into account different risk standards: research which is considered therapeutic may have more severe risks attached to it than so-called non-therapeutic research. Conversely, non-therapeutic research may have very little risk attached to participation, making the added requirement of ministerial permission unnecessary (in this regard, see also Strode "How well does South Africa's National Health Act regulate research involving children?" 2005 *SA Medical J* 265 267). If the intention was to protect minors against potentially high-risk research interventions, the legislator should rather not have used these terms, and instead defined different categories of risk as is done in the various local and international ethical guidelines, or, instead, defined the research permissible in minors in terms of well-defined risk standards (see eg Guideline 9 12 4 4 of the *MRC guidelines*).

Preventive HIV-related research, by definition, should fall squarely under the heading of non-therapeutic research. Volunteers in preventive HIV-related clinical trials are HIV-negative at the start of the trial; they are healthy volunteers, and, nominally, have nothing to gain from their participation. Is it, however, possible to argue that some preventive HIV-related research is "therapeutic" research?

In South Africa, as elsewhere, preventive HIV-related research participants need to be at high risk of HIV infection to ensure that the effectiveness or not of the intervention may be proven statistically. They are at increased risk of infection because of their lifestyle, or because of their social, cultural and economic circumstances (see eg Van Niekerk "Moral and social complexities of AIDS in Africa" in Van Niekerk and Kopelman (eds) *Ethics & AIDS in Africa: The challenge to our thinking* (2005) 53ff). For this reason, it may be argued that participants in preventive HIV-related research benefit from the object of the research – finding an effective preventive HIV vaccine, microbicide or other intervention – and that such research should therefore be considered "therapeutic". What is more, even if participants at high risk of HIV infection do not personally benefit, the class of subjects to which they belong – be it injection drug users, men who have sex with men, or the particular community in which they live – potentially may benefit from the research as they will be given counselling on high-risk behaviour (a "therapeutic" intervention), and thus (it is hoped) reduce their chances of infection.

On the whole, it is difficult to fit preventive HIV-related clinical research into the category of either "therapeutic" or "non-therapeutic" research. Consequently, it will be difficult to decide whether the minister's permission is needed for minors' participation in preventive HIV-related research. Moreover, some types of preventive HIV-related research (such as research to find a microbicide against HIV-infection) might be considered "therapeutic" research, whereas other types of HIV-related clinical research (such as preventive HIV-vaccine research) might be considered "non-therapeutic".

From the discussion above, it is clear that the provisions of the National Health Act are inconsistent with existing and proposed legislation and ethical guidelines. In order to point to the inconsistencies between the different Acts and

the ethical guidelines, the relevant Acts and ethical guidelines are represented in tabular form:

	Age of independent consent	**Formalities**	**Who may give surrogate consent**	**Risk standards mentioned – determine independent consent**
National Health Act	> 18	In writing	"Parent" or "guardian"	Therapeutic and non-therapeutic; not defined
Children's Act	"treatment": >12 and of sufficient maturity; "surgical operation": >12 and is assisted by parents or guardian	None mentioned	"Parent", "guardian" or "care-giver" of a child	None mentioned
Choice on Termination of Pregnancy Act	Any age	None mentioned	N/A	N/A
MRC guidelines	> 18 and of sound mind; "in certain circumstances persons below the age of 18 years are considered able to give their own consent"	"record of their explicit consent should be obtained, through the signing of the informed consent form"	Proxy consent by a "parent" or "legal guardian"	Distinguish therapeutic and non-therapeutic research Terms defined
Good practice guidelines	None mentioned	Both written and verbal IC; if participant is illiterate, verbal consent "in the presence of and countersigned by a literate witness".	None mentioned	None mentioned

3 4 The draft health research regulations

In terms of section 90 of the National Health Act, "Regulations relating to research on human subjects" (*GG* 29637, published 23 February 2007, hereafter "Draft health research regulations") have been published for comment in the *Government Gazette*.

Although its purpose is to supplement the requirements for the participation of minors in research in terms of section 71(2)(ii) of the National Health Act, clause 4 of the draft health research regulations neither elucidates, nor elaborates on the position set out in section 71. It stipulates that children can only participate in health research in instances where "the parent or legal guardian of the child gives consent for such a child to participate" and that "refusal to participate by the child should precede the consent of the parent/legal guardian" (cl 4(c) draft health research regulations). As seen above, section 71(2) of the National Health Act requires the consent of the parent or guardian in the case of therapeutic research and, in the case of non-therapeutic research, the consent of the minister (s 71(3)(ii)). The draft health research regulations are therefore problematic: in terms of clause 4, is the minister's consent for non-therapeutic research on minors no longer necessary? Moreover, clause 4 does not clarify the uncertainty surrounding who is permitted to consent in cases of minors who are without parents or guardians and who are looked after by "care-givers". The addition of the word "legal" in the clause does not offer a solution because a "care-giver" is not a "legal" guardian in terms of South African law.

The second part of clause 4 also needs clarification. Although "refusal to participate by the child should *precede* the consent of the parent/legal guardian" (my emphasis), it appears that refusal may be overridden by the parent or guardian's consent, creating the situation in which a minor may be forced by her parents to participate in research against her will. This possibility is not only out of step with current legislation (see eg s 29(2) and (3) of Act 38 of 2005), but is also likely to be considered *contra bonos mores*. The sense of the clause would be more transparent if it were to read "*consent* to participate by the child should precede the consent of the parent/legal guardian".

4 Conclusion

Preventive HIV-related research which includes children as participants is likely to take place in light of recent statistics showing children's and young adults' increased vulnerability to HIV infection.

The position regarding children who participate in preventive HIV-related clinical research appears unclear at the moment, as South African law and ethical guidelines are contradictory and inconsistent. The National Health Act has reintroduced confusing and discredited terms, such as the distinction between "therapeutic" and "non-therapeutic research", and is not in line with ethical guidelines. Moreover, the draft health research regulations recently published for comment, instead of clearing up the uncertainties and inconsistencies, create more confusion.

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