

HIV AIDS VACCINES ETHICS GROUP

DEBATE AND CONSENSUS BUILDING FORUM

FINAL VERSION

REPORT ON A STAKEHOLDER CONSULTATION:

ETHICAL CONSIDERATIONS RELEVANT TO THE PARTICIPATION OF CHILDREN AND ADOLESCENTS IN HIV PREVENTIVE VACCINE TRIALS IN SOUTH AFRICA

Venue: Karridene Hotel, Illovo Beach, KwaZulu-Natal

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Hosted by the HIV AIDS Vaccine Ethics Group (HAVEG)

University of Natal

Haveg@nu.ac.za

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1 BACKGROUND INFORMATION

At present trials of HIV preventive vaccines in South Africa are recruiting adults able to give independent consent for participation in such research.

However, children in South Africa are at great risk of HIV infection, therefore children stand to benefit from the development of preventive interventions, including HIV vaccines.

If HIV vaccines will be used in the future for children, then it will be necessary to include children in HIV vaccine trials to generate data relevant to them.

There is, therefore, the need to consider in advance the complex ethical and legal issues raised by the involvement of children in such trials, including the evaluation of rigorous scientific rationales for the research, assessments of the probability and magnitude of risks, and adequate informed consent procedures.

2 OBJECTIVES OF THE FORUM

The objectives of the forum were:

1. To identify and debate the scientific rationale for the participation of children in HIV preventive vaccine research.
2. To review and debate the current legal framework for health research with children in South Africa.
3. To review and debate current ethical guidelines regarding health research with children.
4. To provide an opportunity for key stakeholders to articulate the steps that would need to be taken for the participation of children in HIV vaccine trials to be ethical.
5. To raise awareness of the issues amongst key stakeholders.

3 PARTICIPANTS

Participants were drawn from Research Ethics Committees (RECs and the NHREC), the Regulatory body (MCC), Community Advisory Boards (CABs) at participating sites, Health Department officials, ethics institutes, Non Governmental and human rights organizations, and investigators in South Africa. A total of 54 participants attended the forum. Please see Appendix 1 for list of participants who attended the workshop.

4 KEY QUESTIONS

Critical questions to be discussed throughout the forum included:

1. What is the scientific justification for including children in HIV vaccine trials?
2. What elements of the current ethical framework facilitate or constrain HIV preventive vaccine trials with children as participants?
4. At what stage in the vaccine evaluation process should data from children be collected?
5. What data will the MCC require to license a vaccine for use in children?
6. Once children are enrolled, what challenges face researchers? (E.g. notification requirements in the event of child sexual activity, or HIV status).
7. What are the core concerns of stakeholder groups?
8. Under what conditions would the participation of children be considered ethical?

5 SUMMARY OF KEY THEMES

1 Children in South Africa are at considerable risk of HIV infection.

In 2002, UNAIDS reported that 3.2 million children under the age of fifteen were infected with HIV. Of 5 million newly infected persons in 2002, 800 000 were children under 15 years, 700 000 of whom were from sub-Saharan Africa (UNAIDS, 2002). Prevalence for South African female youth (15-24) has been estimated at 21.6% and for male youth (15-24) at 5.8% (Dorrington et al., 2002). The ASSA model estimated that, for the period 1st January to 31st December 2002, of approximately 1.1 million births, about 69 000 babies were infected at birth, while more than 20 000 were infected through breastfeeding during the year.

2 HIV preventive interventions relevant to South African children, including HIV vaccines, must be developed. Therefore, children should be enrolled in clinical trials of preventive HIV vaccines.

Interventions that are appropriate and relevant to children *must* be developed to reduce their risk of HIV infection. HIV vaccines are likely to play an important role in the control of HIV infection. If future vaccination programs are likely to target children then it is essential that children are enrolled in clinical trials to generate data relevant to them.

3 The enrolment of children in HIV preventive vaccine research should take place carefully and at certain specific stages in the vaccine evaluation process. It was proposed that children should be enrolled after satisfactory phase I/II trials, involving adult participants, have been completed.

More specifically:

- Adolescents should be enrolled after phase I and II trials in adults, and then enrolled in phase III adults trials – either at the start or “midstream”
- Neonates should be enrolled after phase I and II trials in adults and then phase I, II, III trials should be conducted with neonates.

4 Aspects of current ethical guidelines for research with children appear to both constrain and enable HIV preventive trials with children. It is critical that an ethical-legal framework be created that balances the need to protect children from research-related risks with the need to ensure that appropriate public health interventions are developed.

It is possible that a strict interpretation of current provisions in Medical Research Council Book 1: *Guidelines on ethics for medical research: General Principles* might not accommodate certain trials of HIV vaccines involving children.

1. MRC book 1 distinguishes between therapeutic (TR) and non-therapeutic research (NTR). TR is defined as research that enrolls patient-volunteers and aims to test interventions that may be of direct benefit to volunteers. NTR is defined as research that enrolls healthy persons and aims primarily to develop knowledge that may be of benefit to future generations, and may not be of direct benefit to the individual volunteer.
2. According to these guidelines, parents may give consent for their healthy children to participate in non-therapeutic research if it is “observation research” and involves no risk or risks commensurate with daily life in a stable society or the performance of routine medical and psychological tests and interventions, termed “negligible risk” (also sometimes referred to as the “everyday” risk standard). According to these guidelines, parents are precluded from giving consent to enrol their children in research classified as “non-therapeutic” if the research is intervention research (see book 1, 5.1 – page 8) that involves slight increases over “everyday” risks.
3. “Classifying” HIV vaccine trials:

- a. Trials of HIV preventive vaccines could be classified as NTR because these trials enrol healthy volunteers (a key element of the definition for NTR).
 - b. Early trials of HIV vaccines, such as phase I and II trials, are especially likely to be classified as NTR as the aim of such research is to develop knowledge to benefit future generations and will be of no direct benefit to the individual volunteer (another key element of the definition for NTR).
 - c. Phase III trials are difficult to classify according to current definitions, as while these trials involve healthy participants (a key element of the definition of NTR) these trials may hold out the prospect of direct benefit for individual volunteers (a key element of the definition of TR).
 - d. Trials of HIV vaccines that enrol pregnant HIV infected mothers in order to assess the use of HIV vaccines in preventing mother-to-child transmission enrol patient-volunteers and aim to test an intervention that may be of direct benefit, therefore such trials may be classified as TR.
4. A strict reading of MRC book 1 precludes parental consent for non-therapeutic research (NTR) that involves intervention research with risks that may exceed the risks associated with daily life (the latter is a typical feature of clinical trials of drugs or vaccines).
 5. These provisions of MRC book 1:
 - a. May preclude a range of important research interventions with children as participants
 - b. Appear conceptually problematic (e.g. TR versus NTR distinction and the manner in which these are defined)
 - c. Appear less flexible than other ethical guidelines (see below).
 6. Other ethical guidelines (e.g. DOH GCP guidelines) do not distinguish between TR and NTR, do not restrict children's participation in NTR to observation research, and allow a slight increase over "everyday" risks if this can be adequately justified.
 7. Currently, all SAAVI-funded vaccine research falls under MRC guidelines and the scope of MRC book 1.
 8. It is critical that MRC book 1 provisions on research with children are re-considered to accommodate relevant and appropriate research with children, and that provisions on research with children in MRC book 5: *Guidelines on ethics for medical research: HIV preventive vaccine research* balance the need to protect children with the need to conduct appropriate research relevant to their health problems.

6 RECOMMENDATIONS

The following recommendations were made:

- 1. There is a need to develop HIV vaccines that are relevant for children; therefore children should be enrolled in trials of HIV preventive vaccines in South Africa.**
- 2. The enrolment of children should occur at certain phases of the evaluation process. More specifically, children should be enrolled only after satisfactory phase I and II data has been obtained from HIV preventive vaccine trials with adults as participants.**
- 3. The ethical framework for the participation of children in research should reflect a balance between the need to protect children from research-related risks and the need to conduct research relevant to children. Working groups should be established to take forward inputs to the ethical-legal framework. These include inputs to the National Health Bill, and inputs to**

Medical Research Council book 1: *Guidelines on ethics for medical research: General principles*, and other relevant ethical guidelines.

- 4. A brief working paper should be developed that outlines the scientific justification for the participation of children in trials (both neonates and adolescents) and a working party should take this forward.**
- 5. A brief working paper should be developed that critically examines ethical arguments, and philosophical justifications, for the participation of children in such research.**
- 6. Structures and forums for future dialogue should be established:**
 - a. Between regulatory and scientific bodies regarding data that MCC would require to license a vaccine for use in children, and the scientific arguments for the participation of children.**
 - b. Between investigators and community to engage communities in this debate.**
- 7. Research should be conducted on critical issues bearing on the enrollment of children, including research into the ethical-legal framework, and post-enrollment ethical-legal obligations that investigators may have to child-participants.**
- 8. Research should be undertaken with parents and adolescents regarding their expectations, willingness to participate, and how to optimize their experience of participation, and research should be conducted into community cultural beliefs and practices regarding children and the involvement of children in medical research in South Africa.**
- 9. There should be future forums on this issue to facilitate increased debate and to allow working groups to report back on their progress.**
- 10. The South African AIDS Vaccine Initiative (SAAVI) should give out consistent messages to communities and the broader public, regarding the need to enrol children in trials, the stage of the evaluation process at which children should be enrolled, and the protections that will be in place to safeguard the welfare of children.**

7 SUMMARY OF PRESENTATIONS AND DISCUSSION

FORUM: DAY 1

HIV vaccine development and the HIV/AIDS & STD strategic plan for SA (Dr N Simelela)

Dr Simelela gave apologies on behalf of the Minister of Health.

She described a number of major ethical considerations for trial participation, including the need for:

1. Consent from informed parents.
2. Informed and involved communities, and the development of partnerships with communities.
3. Trial participants who are aware of their rights and responsibilities.
4. Science to value the lives, rights and expectations of people.
5. Proper treatment and care for trial participants who develop adverse effects related to trial participation.
6. The development of ethical guidelines for research in children as if the children were our own.

She noted that deliberations from the current forum would be important to inform policy.

SESSION 1: WHY INCLUDE CHILDREN IN TRIALS OF HIV PREVENTIVE VACCINES?

Clinical trials of HIV preventive vaccines and international efforts towards the involvement of children in HIV preventive vaccine trials (Dr A Grimwood)

Dr Grimwood outlined pending Phase I HIV vaccine trials for South Africa, as well as other HIV vaccine trials in the pipeline.

He noted that international HIV vaccine trials to date have focussed on adults, a few on neonates, and none with adolescents.

He said that there were many challenges to involving adolescents/children in HIV vaccine trials, but that these should not be viewed as obstacles to the research.

Two approaches to including children in research were described:

1. Sequential: Adult trials are undertaken to obtain safety, immunogenicity and efficacy data for adults. Licensure is obtained for adults. Post licensure studies are done with children to obtain safety, immunogenicity and efficacy data for adolescents. Licensure is sought and obtained for adolescents. Phase I,II,III to licensure for adults can take 7-10yrs, Phase I to licensure for adolescents could take as long, therefore this approach could mean a 14 year wait.
2. Parallel but staggered: Adult phase I and II trials are undertaken. Adolescents are introduced after phase II a or II b trial, into a phase III trial with adults. Licensure is sought for adults and adolescents simultaneously.

Some of the empirical data demonstrating the need for HIV vaccines for minors was described, e.g. that in SA a 15 year old boy has almost a 70% chance of a life time risk of death from HIV infection.

Some ethical considerations were outlined, including that more than any other group, youth stand to benefit from preventive interventions, therefore involvement in trials is an issue of justice.

Clinical trials of HIV preventive vaccines: The prevention of mother-to-child transmission (Dr C Tiemessen)

Dr Tiemessen provided empirical data to argue for the importance of developing vaccines to prevent mother-to-child transmission (MTCT) of HIV, e.g., the majority of MTCT in the developing world is through breast-feeding.

The rationale for involving infants in trials of HIV vaccines is clear, i.e. To assess if vaccines prevent the transmission of HIV from mother to infant during breastfeeding, that is, late transmission of HIV. Therefore, one of most feasible ways to reduce HIV transmission is to immunise in this period.

She described that immune systems in infants differ from those in adults, and that vaccines may work differently in infants than in adults; emphasising the need for a specific neonatal vaccine.

She outlined planned, ongoing and completed paediatric HIV vaccine trials to date, including 2 trials that have been completed in the United States, with infants. There was not consensus as to whether these trials had followed adult safety trials or not.

Clinical trials of HIV preventive vaccines with adolescents: Scientific rationale (Dr G Gray)

Dr Gray summarised the epidemiological evidence for HIV risk of adolescents in SA (data on age of sexual debut; proportion of youth that are sexually active; coercive sexual practices and transactional sex; and prevalence of HIV in under-20 year olds at 15%).

The aim of HIV vaccine trials in adolescents would be to establish whether vaccines could prevent HIV infection through sexual transmission. Adolescents and youth are, and should be, the target population for HIV vaccination (before they become sexually active).

If vaccines are to be used in adolescents, then they will have to be licensed by the MCC for use with children, therefore the MCC will require data for an adolescent indication. The issue is what data will the MCC require? The issue of children in HIV vaccine trials is essentially a regulatory issue.

When should children be enrolled? Do researchers enrol small numbers of adolescents in early Phase I trials? Or should adolescents be enrolled in Phase II/ III trials after early trials in adults? Or is the vaccine just administered to adolescents once proven effective in adults?

The UNAIDS guidelines (2000) promote the conduct of HIV vaccine trials in children and adolescents. However, the participation of adolescents will involve complex ethical, legal, regulatory dimensions, including:

- VCT in adolescents, and the potential ethical and legal obligations of researchers to disclose HIV status and sexual activity of minors
- Evolving capacity of adolescents to be involved in decisions.

Discussion

The following key questions and points of discussion were raised:

- It was agreed that the issue of inclusion of minors in HIV vaccine trials was a justice issue. This vulnerable group, at high risk of HIV infection, may gain more than other societal groups from effective HIV vaccines. A situation must be avoided where safe and effective vaccines cannot be used in younger persons at highest risk for infection, or where there is insufficient data to administer vaccines safely and beneficially to this group.

- To what extent can one generalise data generated in adult trials to children?
 - Adolescents: *Response 1*: Physiologically there is little difference in immune response between post-pubescent adolescents and adults, therefore, adult data could be extrapolated to adolescents. That is, “bridging studies” would be necessary, where phase I and II data from adults could be gathered and a phase III adult trial begun, enrolling a proportion of adolescents, where safety and immune responses for adolescents are assessed at the same time. *Response 2*: The immunological correlates of protection of HIV are not known, therefore it is very difficult to extrapolate data from adults to adolescents via a “bridging study”.
 - Neonates? Paediatric HIV vaccines would require Phase III data, because one cannot extrapolate adult data to infants because of the different immune responses.

- What data would the regulatory authority require to licence a vaccine for use in children? *Response*: Regulatory decisions are informed by science. Investigators would need to argue for why data from adults would *not* be applicable to children, and why the latter group need to be enrolled in trials to get data relevant to them. The South African regulatory authority would value discussion on this issue, are currently finalising their Phase 1 trial guidelines, and this forum will inform the MCC future work on HIV vaccine trial research with children.

- When should children be enrolled, at what stage of the vaccine evaluation process? Should small numbers of adolescents be enrolled in phase III trials at the same time as adults? Or should early trials be conducted only with less vulnerable groups like adults?
 - Generally, safety or even immunogenicity of a candidate vaccine should be demonstrated with adults before involvement of children. E.g. Phase I and II data should be obtained from adults, then adolescents should be included from the onset of phase III trials (This would allow phase I & II data to be obtained on safety, dosage etc with adolescents). Phase I and II data should be obtained from adults, then clinical trials should begin with neonates.

- Other issues raised:
 - Are there any examples of previous vaccine research that can be drawn from to assist us to make these determinations in HIV vaccine trials? *Response*: There are, but HIV is more complicated than many other conditions. E.g. with Hepatitis it was easy. Adult data on Hepatitis B used to extrapolate a dosage for children (a half dose). Immune responses to Hepatitis are quantifiable.
 - There is a need for closer dialogue between the scientists and the MCC across all phases of HIV vaccine trials.
 - There is a need to know if we can make a start in conscientising adolescents and engaging parents and schools. *Response*: Any engagement should be carefully planned and appropriate.
 - Will the trials investigate participants from all race groups? *Response*: Data will be collected across race groups. The HLA/genetic differences between race groups are not yet understood. In addition, nutritional differences may impact on results, or the burden of other diseases, e.g. TB/hookworm.

SESSION 2 ETHICAL LEGAL FRAMEWORK: SOUTH AFRICA

Health research in South Africa: Rights of child participants (Prof D McQuoid-Mason)

Prof McQuoid-Mason provided a broad background to the legislative and ethical guideline requirements for health research in children in South Africa.

He made reference to the following:

- Convention of the Rights of the Child, 1989 (and Universal Declaration of Human Rights).
- South African Constitution (Act 108 of 1996).
- MRC Guidelines: Book 1.
- SA Common Law.
- Child Care Act (Act 74 of 1983).
- Termination of Pregnancy Act (Act 92 of 1996).

A number of legal and ethical dilemmas were outlined, including:

- Consent to medical research with children.
 - By parents or legal guardian.
 - Who gives consent for AIDS orphans?
 - Can unmarried mothers, under the age of 14 give consent for their children?
- Disclosure of research-related risks.
- HIV/AIDS research:
 - Voluntary counselling and testing, and reporting duties.

S12 of the constitution states that persons have a right not to be subjected to medical or scientific experimentation without their informed consent. One literal interpretation of “their” suggests that no proxy consent is allowed (e.g. where parents consent for their children).

Children under the age of 21 usually require the assistance of their parents or legal guardian in decision making.

“Therapeutic research”: The Child Care Act of 1974 allows that children can give independent consent if they are 14 years and older, and wish to consent to medical treatment. Children of 14 years and older can consent to medical research that involves treatment, so called “therapeutic research”.

“Non-therapeutic research”: Some SA legal experts (e.g. Strauss and Van Oosten) have suggested that NTR should not be permitted with children unless there is no risk or danger to the child. One interpretation of the Constitution would preclude proxy consent by parents for NTR. An alternative view is that NTR with children should be permitted if:

- Risks are minimal.
- Research will benefit society.
- Parental consent is obtained, and there is no objection/ assent by the child.

The ethical framework in South Africa: Under what conditions can parents consent to enrol their children in non-therapeutic research? (Prof C van Wyk)

Prof van Wyk presented the framework for research in children in South Africa, based on the South African Constitution, the Medical Research Council guidelines (Book 1) and the National Health Bill.

Section 12(2)c of the South African Constitution was scrutinised. The following points were considered:

- The Constitution states that persons may not be subjected to “experimentation” without “their informed consent”.

- A literal reading of this would mean that research can only be conducted on persons able to give first person consent. This would render South Africa out of step with international trends that allow research on incompetents (persons not legally able to give their own consent).
- Current MRC ethical guidelines classify research into “therapeutic” and “non-therapeutic”. research:
 - TR: involves patient-volunteers and tests an intervention that may be of direct benefit to them.
 - NTR: involves healthy volunteers and while the individual may inadvertently benefit, the primary aim of the research is to benefit others, or future generations.
- Therapy, and by extension TR, can be conducted on children (if it presents remote chance of serious injury or death) who are:
 - 14 and older, with the consent of the child, and permission of parents.
 - Younger than 14, with the assent of the child and the consent of the parents.
- NTR can be conducted on children if it meets certain strict requirements.
 - NTR divided into observation and intervention research.
 - Intervention research: Involves the introduction of fluid or agents into the body, and interferes with the physical or psychological integrity of a child. Involves risks the magnitude of which is unpredictable. This kind of research should *never be allowed* on children.
 - Observation research: Of an invasive nature (interferes with the integrity of research subjects) or a non-invasive nature (does not interfere with integrity of research subjects). Both are permissible provided that they present no risk or risks commensurate with daily life in a stable society (termed “negligible”).
- In terms of the Constitution and existing MRC guidelines (book 1), parents can only give consent to enrol their healthy children in NTR if it is observation research with risks commensurate with daily life.
- HIV vaccine trials (especially early trials) are non-therapeutic, intervention research with risks exceeding this level.
- Therefore it is not currently possible for parents to give consent to enrol their children in such research.
- Such trials should focus on adults, perhaps even those who are 21 and older.

She noted that there are ways to move ahead with trials involving children:

1. Ask for a Declaratory order from the High Court.
2. Redraft the Health Bill.
3. Amend 12(2)c of Constitution.

Acceptable risks for the participation of children/minors in preventive HIV vaccine research: Legal, ethical and human rights considerations (Mr T Smit)

Mr Smit identified 2 cautionary principles regarding research in children:

1. Presumption against children in research.
2. The threshold of risk that children can be exposed to in research.

There is broad agreement that children can only be subjected to a certain threshold of risk, but less agreement about how this threshold should be fixed. Determining whether research risks meet standard for acceptable risk is difficult, and depends not only on the risk per se, but also efforts made to minimize the risks.

The issue is not “Who can consent?” But “What can be consented to?”

Two approaches can be discerned:

- The protectionist model (children are vulnerable and society must protect them from harm):
 - Research involving risks above the threshold is automatically rejected without risk-benefit assessment.
- The “empowerment” model (aims to secure for children adult rights and responsibilities):
 - Research involving risks should include children.

The protectionist model appears to predominate in South Africa.

History: UK:

- 1963: UK MRC: NTR on children ruled out if any risk.
- 1973: Royal College of Physicians: NTR allowed if “negligible” risk.
- 1980: British Paediatric Society: NTR allowed if “minimal risk”.
- 1991: MRC guidelines: If no more than negligible risk of harm.

Comparative perspective: US Code of federal regulations:

- Research with children could be approved if it involves minimal risk, or slight increase over minimal risk if there will be benefit to child, or the research will generate generalizable knowledge about the condition.
- Research with children could be approved even if it cannot meet these requirements if it presents an opportunity to alleviate a serious problem affecting the health of children.

SA DOH GCP: Does not use TR and NTR distinction, sets minimal risk as standard.

SA MRC Book 1: Asserts that NTR should be observation research and negligible risk.

HIV preventive vaccine research is NTR because NTR involves healthy volunteers, and therefore HIV vaccine research with children could be interpreted as not strictly possible under current MRC book 1 standards.

A possible solution is to propose that HIV vaccine research with children be reviewed as an exceptional circumstance, because of the HIV epidemic, or to revise guidelines.

Discussion

The following key questions and points of discussion were raised:

- It appears that generally the standard of risk considered acceptable for children to be exposed to in research is that of “everyday” risk, alternatively termed “negligible” or “minimal” in ethical guidelines.
- “Therapeutic” versus “non-therapeutic” research: The distinction between TR and NTR, and some of the complexities and shortcomings, were discussed:
 - It is sometimes very difficult to classify research as TR or NTR:
 - TR is defined, in MRC book 1, as research conducted with patient-volunteers where the primary aim of the research is to test interventions that may be of direct benefit to the volunteer.
 - NTR is defined, in MRC Book 1, as research conducted on healthy volunteers where the primary aim to generate knowledge that will benefit others or future generations, even though the individual may inadvertently benefit directly.

- Some research on healthy volunteers may have direct potential benefits, where for e.g the volunteers may be at great risk of acquiring the condition.¹
 - It was reported that many ethical guidelines both international (Declaration of Helsinki, CIOMS) and national (SA DOH GCP) have dropped this distinction and instead classify research as having the possibility of “direct benefit” or “no direct benefit” for a volunteer.
 - In current South African MRC guidelines, Book 1: *Guidelines on ethics for Medical Research: General Principles*, parents can only consent to the participation of their children in NTR if it is “observational research”. Furthermore, the risk cannot exceed risks associated with daily life (“negligible risk”). Other SA guidelines, such as the DOH GCP guidelines do not restrict the participation of children in non-therapeutic research to “observation research”. They also allow a slight increase over everyday risk if this can be justified.
 - Whether research is classified as TR or NTR has critical implications. There was some debate regarding whether current research would be considered TR or NTR according to current definitions in South African guidelines. E.g. 1: Nevirapine studies: If the child is considered “healthy”, the research satisfies a core requirement for being classified as “non-therapeutic”. If it is considered that the primary aim of the research is to benefit the child, the research satisfies a core requirement for being classified as “therapeutic”. If classified as NTR, then it is possible that parents would not be permitted to consent for their children to participate in this drug interventional research. E.g. 2: Pneumococcal vaccine and BCG trials: These trials enrol children who do not currently have the condition, and are currently “healthy” and therefore satisfy one of the core requirements for classification as “non-therapeutic” (even if they are at risk of acquiring the condition). If so classified, parental consent would be precluded, according to current MRC guidelines.
- The implications of current guidelines for HIV preventive vaccine trials were raised. Can a parent give consent for their adolescent to participate in HIV vaccine trial research, and would an ethics committee approve this research? It was posited that, according to Book 1, currently parents are not able to give proxy consent to enrol their healthy children in non-therapeutic research unless it is observation research, and presents no risk, or risks associated with daily life/ routine medical or psychological testing.
- The stage of the evaluation process at which children should be enrolled was discussed. It was questioned whether if phase I & II trials in adults indicate a good safety profile the research would constitute “everyday” risk? It was clarified that generally all clinical trials of drugs and vaccines are considered to exceed everyday risk, however, in many countries these trials in children are justified usually by benefit to child or society. In South Africa, current MRC Book 1 guidelines assert that if this risk threshold is reached in NTR, children cannot be enrolled, not allowing for a minor increase over this level of risk even if justified.
- The level of risk to which children can be exposed in research was debated. One of the risks of daily life in South Africa for children is the risk of HIV infection. Is this risk not a key factor in determining an acceptable level of risk in research? Should we not be re-evaluating the level of risk healthy children can be exposed to, given the enormous risks of infection and disease they currently bear?
- A number of options to make the framework more accommodating of HIV vaccine trial research in children were discussed. These included that:
 - Inputs must be made to the revision of MRC book 1.
 - Investigators could go to the Constitutional Court for a declaratory order.

¹ This illustrates how some research appears to satisfy certain of the core elements for the definition of both TR and NTR or does not meet all elements of one definition.

- A submission could be made to the draft National Health Bill, or to the regulations that will come after the Bill has been through parliament.
- It was noted that the current framework appears to emphasize individual rights and de-emphasise public health or the social good. The legal framework is protectionist of individuals, and the benefit to others is of less concern in this framework.

SESSION 3: ETHICAL-LEGAL FRAMEWORK: INTERNATIONAL

Children and clinical trials of HIV preventive vaccines: The international ethical-legal perspective (Dr R Lie)

Dr Lie presented international guidelines and regulations on risk-benefit evaluations in relation to research with children, and discussed the difficulties with making risk assessments.

International guidelines allow that risks to individuals are weighed against benefits to individuals or to society, therefore containing an inherent asymmetry (this can make us uncomfortable: that individuals assume risks for the benefit of society at large).

“Therapeutic” and “non-therapeutic research”:

International ethical guidelines tend to use either the “therapeutic” versus “non-therapeutic” distinction, or “research that holds out the prospect of direct benefit to the individual”, or research that does not. That is, the distinction rests on whether there may be direct benefit for the volunteer or not.

Accordingly, Phase I and II trials of products, including HIV vaccines, are generally classified as “non-therapeutic” (there will be no direct benefit for the participant). However, phase III trials are more complex to classify and could be regarded as TR, as they may hold out the prospect of direct benefit to the participant.

“Minimal risk”:

International ethical guidelines tend to refer to “minimal” versus “more than minimal” risk. “Minimal risk” is defined as the level of risk associated with daily life or performance of routine medical and psychological examinations. “Daily life” as an index is somewhat problematic as the risks of daily life are not uniform. And there has been some debate regarding whether allowable risks should be place-relative or place-independent.

Dr Lie summarised a number of international guidelines on risk levels with “incompetents” or persons not able to give informed consent.

- ICH GCP: Research with incompetents: Foreseeable risks should be “low”; trial should investigate a condition that affects them (at risk of the condition) or that they have; also allows for a general exception clause.
- EC GCP: Research with persons incapable of giving consent: Refers to “patients” and that direct benefits should outweigh the risks (this would rule out NTR with children; phase I trials with children; might not exclude phase III trials with children where one could demonstrate that anticipated benefits may outweigh potential risks).
- Council of Europe: Research with incompetents: Can do research with no direct benefit to the child, if scientific, of benefit to other persons in the same risk category; or other persons with the same condition.
- EU GCP: Research with children: Allowed if direct benefit for patients is obtained, or relates to the clinical condition under study.

- United States: Research with children: This is acceptable if the research presents “minimal risks”, or a slight increase over minimal if the research will be of direct benefit to subjects or there is the likelihood of generalizable knowledge about the subjects condition.
- CIOMS: Incompetents: Research allowed if the risks will not be greater than those associated with routine medical and psychological examinations, a slight increase over these risks are allowed if there is scientific justification and an REC approves.

Implications for HIV vaccine trials:

Clinical trials of HIV vaccines will always be classified as “more than minimal” risk; or greater than risks associated with performance of routine medical or psychological exams. All drug and vaccine trials are classified as more than minimal risk. Administering an investigational product to someone is not part of their daily life! Don’t justify HIV vaccine trials with children by trying to argue that these trials are minimal risk. Rather, researcher can justify this research by arguing that the risks appear low (e.g. from adult data) and are outweighed by the expected benefits.

Phase I and II trials of HIV vaccines are likely to be classified as “non-therapeutic” research or research that does not hold out the prospect of direct benefit for the volunteer.

However, phase III trials of HIV vaccines are may indeed hold out the prospect of direct benefit for the individual volunteer, and therefore could be viewed as “therapeutic”.

Discussion

The following key questions and points of discussion were raised:

- Risks:
 - Any clinical trial of drugs or vaccines would be defined as exceeding everyday risk (termed “minimal risk” in international guidelines and SA GCP). This is even if the trials have been conducted in adults first.
 - Therefore HIV vaccine trials would de defined as exceeding everyday risk.
 - Investigators who are justifying clinical trials of drugs or vaccines must show that the risks are outweighed by the benefits to the child or to society.
- TR and NTR research:
 - TR generally refers to the notion that there may be direct benefit for the individual participant. NTR generally refers to the notion that there may be no direct benefit to the individual. According to this definition, phase I and II HIV vaccine trials are likely to be classified as “non-therapeutic”.
 - However phase III trials where a safe, immunogenic vaccine will be administered to persons at high risk of acquiring HIV infection could, according to some definitions, be classified as “therapeutic” – that is, holding the potential for direct benefit.² According to SA MRC book 1, if research is classified as NTR, then children can only be enrolled in observation research, presenting risks equal to those of everyday life in a stable society. This appears more inflexible and conservative than other guidelines that allow healthy children to be enrolled in intervention research with risks exceeding minimal/ everyday risks, if this is a minor increase

² According to current definitions in South African MRC book 1 phase I and II clinical trials of HIV vaccines will be classified as NTR. Phase III trials could also be classified as NTR because they involve healthy volunteers, which is one element for classification asNTR. However the application of the second element for classification as NTR is not clear, namely that the research aims to generate knowledge that will benefit future generations

and can be justified by benefits to the child or society (e.g. US Code of Federal Regulations, CIOMS).

FORUM: DAY 2

SESSION 4: SPECIAL CONCERNS

The following groups provided feedback on key questions:

1. Scientist-investigator group.
2. Regulatory and licensing group.
3. Ethical-legal group.
4. Community representative group.

Scientist-Investigator group feedback

Key concerns:

- Children are at risk therefore their participation in trials is indicated:
 - Infant responses are likely to differ from adults.
 - It is not clear if adolescents will differ from adults in terms of immune responses; therefore we need phase I and II data to assess this.
 - Safety, dosage, and immune responses must be assessed for infants and adolescents.
- Dialogue between scientists and the regulatory body is required.

Regulatory and licensing group feedback

Key concerns:

- Outcome measures have not been defined.
- Safety data is required however adverse effects may only be detected with large samples such as those in post marketing phase.
- Perception that precedent wavers appropriate decisions.

Children should be enrolled in trials; the question is when to enrol children?

- Ethics committees and MCC should have paediatricians and immunologists who can give guidance in terms of different age categories.
- Adolescents: Post phase I and II data from adults, then “bridging trial” at phase III (mid-stream phase III could utilise interim analysis phase III safety data, or at same time as phase III, as long as phase I and II safety data acceptable).
- Neonates: Post phase I and II from adults, then start at phase I Type of data required by MCC for

licensing:

- Safety, quality, efficacy.

Ethical-legal group feedback

MRC Book 1 standard for enrolling children in NTR (where participants are healthy and the aim of the research is to benefit future generations) is observational research presenting risks equal to everyday life

- This appears to be an unreasonable standard.
- It precludes intervention research with healthy children (even if valuable) that may have risks slightly higher than everyday risks, even if balanced by benefits.
- It precludes parental rights to enrol their healthy children in certain kinds of research.
- Observation research is often used as an example of research risks that are “everyday”, but observation research should not become the standard.

It would not be fair to exclude children from important research, including research aimed at developing interventions for them to reduce their risk of HIV infection.

At what stage in the vaccine evaluation process should data from children be collected?

- Adolescents: phase I and II data should be gathered from adults before enrolling children.
- Neonatal and infant use: Perhaps children could be enrolled prior to data from adults (however vaccines will be of use to adults therefore no reason not get safety data from adults first).

What are the obligations of researchers to parents: Voluntary testing and counselling:

- Over 14, parents have no right to the information about their children’s status, the child provides independent consent to VCT.
- Under 14, parents would give consent for the VCT and may have a right to this information, if the child agrees.

What are the legal obligations of researcher in terms of disclosures of sexual activity from children under 16?

- Obligated to report in terms of the Child Care Act to the Director General of Social Welfare; the choice exists to report to police (CPU); no obligation to report to the parents.
- These duties must be contextualized in terms of other revealed information (e.g. truancy, other high-risk information).

Limits of confidentiality should be part of the consent process.

Community and child rights feedback

Key concerns:

- Community participation:
 - Interface between researchers and community.
 - Parents need to give input on the trial process and procedures.
 - Open and honest education to community.
- Consent:
 - Informed Consent practices must be supported with education, be culturally and religiously sensitive and in an appropriate language.
 - Assessment of understanding should be undertaken to determine whether one needs to go back to training or proceed.
- Cultural issues:
 - Norms, religion and class within each community; the role of the child; how families are constructed must be taken into account.
 - Lines of authority into the community must be followed.
 - Research needs to consider culture in evolution.

How promote the meaningful involvement of communities in this debate?

- Broad community meetings to discuss pertinent issues.

Ethical and appropriate incentives for trial participation:

- Benefits should be community-wide (e.g. upgrade of school grounds or schools, building their skills to establishing food gardens) and negotiated to be ethical and appropriate.

Child participants in research and the obligations of researchers (Prof L Richter)

Prof Richter outlined the variety of challenges in research with children, exacerbated by gaps between law, ethics and the implementation of research.

Challenges include:

- While it may be easy to meet the letter of legal obligations to report/ notify, it is much more difficult to meet the spirit of these requirements. E.g. Section 42 of the Child Care Act (74 of 1983) has an ambiguous requirement, for the Director-General to be notified of certain factors (such as ill treatment of a child). Sending a letter will meet this requirement, but it is insufficient to protect a child, or benefit them. Notification requirements are also complicated by field-worker lack of resources to make decisions in the field; often capacity of the system to respond is limited.
- Balancing reporting requirements with assurances of confidentiality: Notification requirements must be part of the consent information.
- Acting appropriately on disclosures of sexual activity, and making judgements of whether disclosures meet definitions of "child abuse" or "rape"?

Examples of current research projects with child-participants were described, including options such as notification, requesting the DG of Social Development to waive notification, referral to professional services; and setting up an internal counselling and clinical service; and building in disclosure to a supportive adult as part of what a child-participant must consent to.

SESSION 5: PERSPECTIVES FROM KEY STAKEHOLDERS: UNDER WHAT CONDITIONS WOULD THE PARTICIPATION OF CHILDREN BE CONSIDERED ETHICAL?

Microbicides: The ethical challenges of research in adolescent populations (Dr K Dickson presenting on behalf of Prof H Rees)

Dr Dickson presented a paper drafted by Prof H Rees.

Prof Rees's paper stated that youth should be involved in trials of preventive products because they are an at-risk group. Furthermore, there will be regulatory requests for registration of these products for use in youth.

In Microbicides research, a less mature genital tract in youth could pose distinctive safety issues.

Her paper described differences between Microbicides and HIV vaccine research:

- Microbicides can be used for STI prevention and unwanted pregnancy.
- Safety is not independent of sexual activity in Microbicides research.
- Demonstration of safety may include speculum examination with or without colposcopy (key: vaginal examination).

It would be most efficient to conduct parallel adult and adolescent studies.

Prof Rees's paper outlined certain challenges of adolescent Microbicides research, including:

- Recruitment of adolescent females.
- Confidentiality.
- Trial procedures: insertion of vaginal products, subjection to vaginal examination.
- Trial procedures: Disclosing sexual experiences.
- Consent for sexual activity is 16; what if an adolescent is under the age of consent for sex?
- Consent for the trial: Ability of young person to understand?

Interim National Health Research Ethics Committee: Ethics in research: Principles, structures and processes (Prof L Mazwai)

Prof Mazwai summarised that because the Interim NHREC is a national body, its guidelines are broad, and that there are sections dedicated to research involving children.

The various types/levels of review bodies in South Africa were listed. These make use of variety of guidelines, human rights requirements, and legislation.

The National Health Bill is currently before parliament. A section of this Bill will inform the structure of the National Health Research Council.

The contents of NHREC guidelines were outlined in detail.

A task group should be convened to get clarity and consistency across guidelines on key terminology and substantive definitions, e.g. "minimal risk".

Research on Children: A MRC perspective (Prof D du Toit)

Prof du Toit noted that the MRC specifically made their booklets available in five volumes to allow for comments to be incorporated into working documents.

The following points were included in the presentation:

- Distinction between therapeutic and non-therapeutic research: This is often a difficult distinction to draw (research is a mix of both!) but it is an important distinction for the protection of incompetents.
- Deontological versus consequentialist moral philosophies, and their application to research: The former approach underlies the thinking that persons should be used as means to an end therefore only persons who can identify with the aims of research and personally consent to be involved should participate in research, therefore research should not take place with children (regardless of the social benefits); and the latter underlies the thinking that research with children is acceptable if there is a risk-benefit calculus, and low risks.

MRC Book 1 will have to re-examine its provisions of the participation of children in research.

UCT REC: Ethical issues and concerns in children and adolescents: Some experiences of an REC (Prof T Zabow)

Prof Zabow provided a summary of certain issues relating to research with children dealt with by the UCT REC, including:

- Procedures for obtaining consent, and the legality of the consent

- Parental permission (active or passive?).
- Identification of the legal guardian?
- Child/adolescent assent:
 - How to assess competence?
 - Age, maturity and psychological state.
- Child consent and legal age of consent given the type of investigation (therapeutic or non-therapeutic).
- Research on sensitive issues may expose children to stigmatisation, abuse, danger.
- Research may cause negative emotional reactions, or alarm, in the child.
 - Need to minimize this.
- Research that detects or exposes illegal activities:
 - Drugs or sexual activity or abuse.

Medicines Control Council (Dr G Steele; Dr E Khomo)

Drs Steele and Khomo outlined:

- Less than 5% of clinical trials involve children. 79% of paediatric medications have never been tested in children.

Children should be included in HIV vaccine research; the question is when and how?

Children should be included in HIV vaccine research because:

- Disease may manifest differently in adults and children.
- Children have less mature organ systems, therefore there is the potential for variation in vaccine performance.

Concerns include that little is known about the safety of current vaccines, and deleterious effects of vaccine exposure may be delayed for many years; psycho-social risks include apprehension and anxiety.

Researchers could make use of bridging trials to determine how well the results of adult research relate to a cohort/ population in which licensure is required (e.g. adolescents). Bridging trials are simplified, and quicker, they could be completed within 1.5 years.

The MCC's main concern in approving vaccine trials is to ensure that there is safety, quality and immunogenicity of a product, and to ensure that design and conduct of trial is scientific.

Questions

The following questions/points of clarification were raised with regards to the above presentation:

- If phase I & II data are available from adults, and then a bridging study is undertaken, what questions are asked? *Response:* The primary question would be safety, but one would also ask about immunogenicity markers. Efficacy would be more difficult. If adolescent and adult immune responses are similar, then there would not be a need for adolescent efficacy studies.
- Would the bridging studies have to be placebo controlled? Researchers should already know adverse events. *Response:* Generally these are not. There would have to be a strong justification for including a placebo in bridging studies.

CAB: HIV Vaccine Trial Unit, Medical Research Council, Durban (Ms N Mkhize)

Ms Mkhize elaborated on issues relevant to the community when considering HIV vaccine trials in minors.

These included:

- When would children be involved? What data would there be from adults? Safety data?
- Issues of consent:
 - Clear appropriate jargon free information.
 - Clear purpose or reason for the research.
 - When can parents consent?
 - How will children assent to be in such research?
- Meaningful involvement of communities in research:
 - Communities must be involved early in the research, and clearly understand the research objectives.
- Issues around cultural and religious sensitivity.
- Research must be responsive to the potential social harms and there must be support mechanisms, including referral mechanisms.
 - What protection/support will be available, e.g. children are harmed or abused in trials?

CAB: HIV AIDS Vaccines Division, Chris Hani Baragwanath: Participation of children and adolescents in HIV vaccine trials (Mrs M Mogale)

Mrs Mogale described the trial site in Soweto before outlining the concerns of the community regarding HIV vaccine trials in children. These included:

- How safe are these vaccines?
- Will the trials follow the same stages/phase as adult trials?
- Will adolescents be coerced into participating, taking advantage of their vulnerabilities:
 - Lack of knowledge about HIV vaccines.
 - Cultural conventions that may override the wishes and desires of youth.

These were evaluated in the context of the vulnerabilities of the community, including:

- Lack of legal parents/guardians?
- Need for support post-trial for harms: Will children have someone to turn to if things go wrong after the trial is completed?
- The community needs to be educated about this research.
- There needs to be research into parental expectations and concerns.

Discussion

- Overall, there is support expressed by the CAB for research in children, in light of the HIV infection rates. Concern rests on safety of the vaccine and avoidance of exploitation of the children.

Children's rights and preventive vaccine trials: Where are children? (Ms C Vawda)

Ms Vawda said that to date, the Children's Rights Centre had not been involved in HIV vaccine issues. She emphasised the need to take Convention of the Rights of the Child into account when reviewing the ethics of the vaccine trials.

42% of South Africans are under 18 years of age.

Children are different from other groups. They are inherently dependent and are the most vulnerable members of society, therefore, as adults we have an added responsibility to protect them. Specific points of concern included:

- Are there simpler, more effective measures to reduce the risk of children? E.g., MTCT programs that already exist and are of known benefit?
- What inducements would there be for parents?
- If a child has additional vulnerabilities, they should be excluded, because they are at greater risk of being exploited.
- Monitoring of long-term effects of trial participation.

Discussion

The following key points of discussion were raised:

- The Health Bill is being tabled soon. Inputs must be made quickly.
- Is a revision of MRC book 1 underway? *Response:* Once it is out of print, and the new Health Bill passed, it may be revised.
- Can researchers proceed with process of engaging adolescents in HIV vaccine research? *Response:* Appropriate work needs to be done. A declaratory order from the court, and amended ethical guidelines would assist in the process of allowing work on such protocols to begin.
- For a single ethics committee to gain expertise in reviewing HIV vaccine trial protocols is difficult. A central group should filter and pass on information to local ethics committees.

SESSION 6: Key themes and recommendations (Dr R Lie)

Dr Lie noted that a only a very literal reading of the MRC guidelines would preclude HIV vaccine research with on healthy children, and that these guidelines need more work, including key definitions (such as types of research, and TR versus NTR). Legal clarification is also required.

Dr Lie said that HIV AIDS research is driving a lot of revision of national and international guidelines, however it is probably wiser to consider amendments to ethical guidelines that facilitate ethical paediatric research in children generally rather than HIV research per se.

Discussion

The following key questions and points of discussion were raised:

- There is a need for small task groups to refine some of the outstanding issues.

Appendices

- Participants list
- Agenda

Participants List

SURNAME	NAME	TITLE	ORGANISATION	TELEPHONE	FACSIMILE	E-MAIL
Bekker	Linda-Gail	Dr	Western Cape Clinical Trials Consortium	021-406 6856	021-406 6896	lgbekker@cormack.uct.ac.za
Dhai	Ames	Dr	Wits Bioethics Division and Wits Medical School Research Ethics Committee	011-717 2720	011-643 1264	dhai@webmail.co.za or dhaia@medicine.wits.ac.za
Dickson	Kim Eva	Dr	Microbicides Initiative South Africa	011-989 9207	011-989 9298	kimdt@rhrujhb.co.za
Engelbrecht	Sherella	Mrs	School of Psychology, University of Natal, UNP (HAVEG)	033-260 6165	033 260 6065	Engelbrecht@nu.ac.za
Gerntholtz	Liezel	Ms	AIDS Law Project and Treatment Action Campaign	011-717 8631	011-403 2341	gerntholtzl@law.wits.ac.za
Hlongwa	Khethani	Mr	School of Psychology, University of Natal, UNP (HAVEG)	033-260 6164	033-260 6167	hlongwak@nu.ac.za
IJsselmuiden	Carel	Prof	South African Research Ethics Training Initiative	012-841 3240	012-841 3308	carel@medic.up.ac.za
Khotu	Shaheen	Dr	DOH: National Health Information Systems	012-312 0791/0	012-312 0812	khotush@health.gov.za
Lindegger	Graham	Prof	School of Psychology, University of Natal, UNP (HAVEG)	033-260 5335	033-260 6167	lindegger@nu.ac.za
Manegold	Julie	Ms	School of Psychology, University of Natal, UNP (HAVEG)	033-260 6166	033-260 6167	imanegold@hsrc.ac.za
Mhlambiso	Ayanda	Mr	Western Cape: Clinical Trials Consortium CAB	021-785 0902	021-406 6896	None
Mlisana	Koleka	Dr	Centre for the AIDS Programme of Research in South Africa	031-260 4562	031-260 4566	mllisanak@nu.ac.za
Milford	Cecilia	Ms	School of Psychology, University of Natal, UNP (HAVEG)	033-260 6164	033-260 6167	Milford@nu.ac.za
Netshidzivhani	Pakiso	Mrs	DOH: Health Systems Research, Research Coordination and Epidemiology	012-312 0995	012-312 0784	netshp@health.gov.za
Phillips	Jacintha	Ms	School of Psychology, University of Natal, UNP (HAVEG)	033-260 6166	033-260 6167	phillipsj@nu.ac.za
Rajcoomar	Urvarshi	Ms	Lawyers for Human Rights	033-342 1130/80	033-394 9522	varshi@sn.apc.org
Reddy	Vimla	Ms	Medical Research Council: Durban: HIV Vaccine Trial Unit CAB	031-203 4740	031-203 4707	vimla.reddy@mrc.ac.za
Reynolds	Louis	Prof	UCT:School of Child and Adolescent Health	021-658 5354	021-689 1287	reynolds@ich.uct.ac.za
Robinson	Andrew	Dr	Medical Research Council HIV Vaccine Trial Unit	031-2034 738	031-2034 707	andrew.robinson@mrc.ac.za
Rollins	Nigel	Dr	Nelson R Mandela School of Medicine: Research Ethics Committee	031-260 4352	031 260 4388	rollinsn@mrc.ac.za
Singh	Jerome	Dr	School of Law, University of Natal, (Durban)	031-260 1231	031-260 1464	singhj9@nu.ac.za
Stobie	Melissa	Ms	Unilever Ethics Centre, University of Natal, UNP (HAVEG)	033-260 5565	033-260 5652	StobieML@nu.ac.za
Tyhali	Michael	Mr	Western Cape: Masiphumelela CAB	021-785 2442	021-785 5632	admin@ukhanyops.school.wcape.za

Vardas	Eftyhia	Dr	Perinatal Health Research Unit: The HIV/AIDS Vaccine Division	011-989 9756	011-938 3973	vardase@mweb.co.za
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SPEAKERS

Du Toit	Danie	Prof	Medical Research Council: Research Ethics Committee	012-318 6265/7	012-318 6262	dtoitd@techpta.ac.za
Gray	Glenda	Dr	Perinatal Health Research Unit: The HIV/AIDS Vaccine Division	011-989 9703	011-989 9762	gray@pixie.co.za grayn@hivsa.com
Grimwood	Ashraf	Dr	South African HIV Vaccine Action Campaign	021-938 0826	021-938 0823	ashraf.grimwood@mrc.ac.za
Khomo	Esther	Dr	MCC:Clinical Trials Committee	011-871 7446	011-871 7527	dirhealth@ekurhuleni.com
Lie	Reidar	Dr	Department of Clinical Bioethics, National Institutes of Health, Bergen University	091 301-496-2429	091 301-496-0760	RLie@cc.nih.gov
Mazwai	Lizo	Prof	Interim National Health Research Ethics Committee	047-502 2233	047-502 2235	medicine@getafix.utr.ac.za
McQuoid-Mason	David	Prof	Howard College School of Law, University of Natal (Durban)	031-260 2558	031-260 2559	mcquoidm@nu.ac.za
Mkhize	Nonhlanhla	Ms	Medical Research Council: Durban: HIV Vaccine Trial Unit CAB	031-301 145/9	031-301 2147	gaycentre@mweb.co.za
Mogale	Matilda	Mrs	Perinatal Health Research Unit: HIV AIDS Vaccine Division CAB	011-989 9700	None	mogalem@hivsa.com
Rees	Helen	Prof	Reproductive Health Research Unit	011-933 1228	011-959 1379	l.moodaley@rhrujhb.co.za / h.rees@rhrujhb.co.za
Richter	Linda	Prof	Human Sciences Research Council	031-273 1419	031-273 1403	skhonyane@hrsc.ac.za/ritcherl@nu.ac.za/lrichter@hrsc.ac.za
Slack	Cathy	Ms	School of Psychology, University of Natal, UNP (HAVEG)	033- 260 5751	033-260 6167	slackca@nu.ac.za
Simelela	Nono	Dr	DOH: HIV AIDS & TB	012-312 0121	012-328 5743	simeln@health.gov.za
Smit	Thomas	Mr	AIDS Legal Network, South African HIV Vaccine Action Campaign	021-447 8435	021-447 9946	aincpt@mweb.co.za
Steel	Gavin	Mr	MCC:HIV Vaccine Clinical Trial Working Group	043-708 2244	043-708 2244	steelgav@hlthcmh.escape.gov.za
Tiemessen	Caroline	Dr	National Institute for Communicable Diseases	011-321 4285	011-882 0596	carolinet@nicd.ac.za
Tshabalala-Msimang	Mantombazana Edmie	Hon. Dr.	Ministry of Health	021-465 7407/8	021-465 1575	khodzaz@health.gov.za
Van Wyk	Christa	Prof	Department of Jurisprudence: UNISA	012-429 8380	012-429 3442	vwykcw@unisa.ac.za
Vawda	Cati	Ms	Childrens Rights Centre	031-307 6075	031- 307 6074	cati@childrensrightscentre.co.za
Zabow	Tuviah	Prof	University of Cape Town: Faculty of Sciences: Research Ethics Committee	021-404 2164	021-448 8158	zabowt@curie.uct.ac.za

CHAIRPERSONS & FACILITATORS

Kruger	Mariana	Prof	Department of Paediatrics: Kalafong Hospital	012-373 1008/9	012-373 7977	mariana@kalafong.up.ac.za
McClain	Charlotte Vuyiswa	Ms	Human Rights Commission	011-484 8300 Ext. 2292	011-484 8403	cmclain@sahrc.org.za
Mkhize	Nhlanhla	Mr	School of Psychology, University of Natal, UNP (HAVEG)	033-260 5963	033-260 6167	mkhize@nu.ac.za
Wassenaar	Doug	Dr	School of Psychology, University of Natal, UNP (HAVEG)	033-260 5373	033-260 5809	wassenaar@nu.ac.za

OBSERVERS

Kemilembe	Joyce	Mrs	SARETI Fellow: University of Natal / University of Pretoria	033-260 6162	033-260 5809	MaraisD@nu.ac.za
Mapfumo	Owen	Mr	SARETI Fellow: University of Natal / University of Pretoria	033-260 6162	033-260 5809	MaraisD@nu.ac.za
Nyika	Aceme	Dr	SARETI Fellow: University of Natal / University of Pretoria	033-260 6162	033-260 5809	MaraisD@nu.ac.za
Uzoma Manafa	Ogenna	Dr	SARETI Scholar: University of Natal / University of Pretoria	033-260 6162	033-260 5809	MaraisD@nu.ac.za

DEBATE AND CONSENSUS BUILDING FORUM:

ETHICAL CONSIDERATIONS RELEVANT TO THE PARTICIPATION OF CHILDREN AND ADOLESCENTS IN HIV PREVENTIVE VACCINE TRIALS IN SOUTH AFRICA

DAY ONE: THURSDAY 7th AUGUST 2003

0800-0830 Tea/ coffee and registration

INTRODUCTION AND KEY CONSIDERATIONS

Facilitators: Nhlanhla Mkhize and Doug Wassenaar HAVEG, UNP

0830-0835 **Welcome** (Graham Lindegger, HAVEG, University of Natal, Pmb)

0835-0920 **Participant introductions and expectations of the forum** (Facilitators: Nhlanhla Mkhize and Doug Wassenaar, HAVEG)

0920-0930 **Key questions and potential forum outcomes** (Cathy Slack)

0930-0945 **HIV vaccine development and the HIV AIDS & STD strategic plan for South Africa** (Nono Simelela, HIV/AIDS & TB, Department of Health)

Session 1 WHY INCLUDE CHILDREN IN TRIALS OF HIV PREVENTIVE VACCINES?

Facilitators: Nhlanhla Mkhize and Doug Wassenaar HAVEG, UNP

Key outcomes for participants: An enhanced ability to evaluate the scientific arguments for the inclusion of children in HIV preventive vaccine trials (such as why data from adult participants may not provide data relevant to children) and arguments for when in the evaluation process data from children should be collected.

0945-1000 **Clinical trials of HIV preventive vaccines and international efforts towards the involvement of children in HIV preventive vaccine trials** (Ashraf Grimwood, South African AIDS Vaccine Initiative)

1000-1020 **Clinical trials of HIV preventive vaccines: The prevention of mother-to-child-transmission** (Caroline Tiemessen, NICD)

1020-1045 Tea/Coffee break

1045-1105 **Clinical trials of HIV preventive vaccines with adolescents: Scientific rationale** (Glenda Gray, HAVD, Chris Hani Baragwanath)

1105-1200 Discussion (Facilitators)

DAY ONE (cont'd) THURSDAY 7th AUGUST 2003

Session 2 ETHICAL - LEGAL FRAMEWORK: SOUTH AFRICA

Chair: Lizo Mazwai Interim National Health Research Ethics Committee

Key outcomes for participants: An enhanced sense of the current ethical-legal framework in South Africa, including the levels of risk currently considered acceptable to expose children to in non-therapeutic research in SA and for which parents may properly give proxy consent, and the rights of child participants in relation to research in South Africa

1200-1220 **Health research in South Africa: Rights of child participants** (David McQuoid-Mason, School of Law, University of Natal Dbn)

1220-1240 **The ethical legal framework in South Africa: Under what conditions can parents consent to enrol their children in non-therapeutic research?** (Christa Van Wyk, Department of Jurisprudence, UNISA)

1240-1330 Discussion (Facilitators)

1330-1415 Lunch

Session 3 ETHICAL - LEGAL FRAMEWORK: INTERNATIONAL

Chair: David McQuoid-Mason School of Law, University of Natal, Dbn

Key outcomes for participants: An enhanced sense of the international ethical-legal framework, including the levels of risk currently considered acceptable to expose children to in non-therapeutic research

1415-1445 **Children and clinical trials of HIV preventive vaccines: The international ethical-legal perspective** (Reidar Lie, Department of Clinical Bioethics, NIH and University of Bergen)

1445-1515 Discussion - Chair

1515-1630 Small group discussions (x4) – 4 Chairs & rapporteurs for 4 expert groups to address specific questions (to be provided)

1630 Housekeeping

1640 Thanks and close of day one (Graham Lindegger, HAVEG, University of Natal, Pmb)

FINAL DRAFT

DAY TWO: FRIDAY 8th AUGUST 2003

0800-0830 Tea/Coffee

0830-0915 Plenary report-back from breakaway small group discussions

Session 4 SPECIAL CONCERNS

Chair: Charlotte McClain Human Rights Commission

Key outcomes for participants: An enhanced sense of key considerations relevant to child participants, and the special obligations that researchers may have to child participants

0915-0930 **Acceptable risks: Legal, ethical and human rights considerations** (Thomas Smit, AIDS Legal Network, SA HIV Vaccines Action Campaign, SAAVI)

0930-0945 **Child participants in research and the obligations of researchers**
(Linda Richter, Human Sciences Research Council)

0945-1000 Discussion - Chair

1000-1030 Tea break

Session 5 PERSPECTIVES FROM KEY STAKEHOLDERS: UNDER WHAT CONDITIONS WOULD THE PARTICIPATION OF CHILDREN BE CONSIDERED ETHICAL?

Chair: Ashraf Grimwood SA HIV AIDS Vaccine Action Campaign, SAAVI

Key outcomes for participants: An enhanced sense of the perspectives of stakeholders (REC members, regulators, community representatives and allied research initiatives) regarding their concerns, and the conditions under which the enrolment of children in trials of HIV vaccines would be considered ethical

1030- 10h45 **South African Microbicides Initiative**
(Helen Rees, Reproductive Health Research Unit)

10h45-1100 **Interim National Health Research Ethics Committee**
(Lizo Maswai)

1100-1130 **Research Ethics Committee Chairs**
(Danie Du Toit, Toviah Zabow)

1130-1200 **Medicines Control Council**
(Esther Khomo, Clinical Trials Committee, MCC;
Gavin Steele, HIV Vaccine Trial Working Group, MCC)

1200-1230 **Community Advisory Boards**
(Matilda Mogale, Community Advisory Board, HIV AIDS Vaccines Division, Chris Hani Baragwanath
Nonhlanhla Mkhize, HIV Vaccine Trial Unit, Medical Research Council, Durban).

1230-12h45 **Civil Society: Child Rights**
(Cati Vawda, Children's Rights Centre)

1245-1315 Discussion - Chair

1315-1415 Lunch

DAY TWO (cont'd) FRIDAY 8th AUGUST 2003

Session 6 KEY THEMES AND RECOMMENDATIONS

Chair: Mariana Kruger Department of Paediatrics, University of Pretoria and Kalafong Hospital

Key outcomes: An opportunity to reflect on the scientific and ethical-legal themes that have emerged, the concerns of stakeholders and the circumstances under which the enrolment of children in trials of HIV preventive vaccines would be considered ethical, and to evaluate whether HIV vaccine trial participation could meet standards for the enrolment of children in the current framework; or to develop key tasks for a way forward

- 1415-1430 **Key themes, responses to guiding questions and recommendations**
(Catherine Slack, HIV AIDS Vaccines Ethics Group, University of Natal, Pmb, SAAVI)
- 1430-1440 Respondent: Reidar Lie
- 1440-1500 Plenary Discussion (Facilitators)
- 1500 Close (Graham Lindegger, HAVEG, University of Natal, Pmb)
- Tea/Coffee