

**HIV AIDS VACCINES ETHICS GROUP**

---

**DEBATE AND CONSENSUS BUILDING FORUM**

**ETHICAL-LEGAL REGULATION OF RESEARCH IN SOUTH AFRICA:  
IMPLICATIONS FOR HIV VACCINE TRIALS**

Venue: Karridene Hotel, Illovo Beach, KwaZulu-Natal

Dates: 22<sup>nd</sup> & 23<sup>rd</sup> July 2004

Hosted by the HIV AIDS Vaccine Ethics Group (HAVEG)

University of KwaZulu-Natal: [Haveg@ukzn.ac.za](mailto:Haveg@ukzn.ac.za)

**CONTENTS**

Background information	2
Forum objectives	2
Forum participants	2
Key questions	3
Summary of key themes, including recommendations	3
Summary of presentations and discussion	8-19
Appendices	20
• Participants list	
• Agenda	
• Questions for breakaway groups	
• List of resources provided to forum participants	

## 1. BACKGROUND INFORMATION

The ethical-legal framework in South Africa is in a period of transition with a number of new developments changing the substantive principles and procedures for health research in South Africa. This changing environment poses many complexities for researchers, RECs, NGOs and communities. Some of the changing dynamics include both law reform and the review of ethical guidelines.

### (1) Law reform:

The National Health Bill (NHB) was recently passed by Parliament but is not yet in operation. It will supplement existing scientific regulation of research with additional ethical and policy controls.

### (2) Institutional context:

The NHB makes provision for the establishment of 2 institutions – the National Health Research Ethics Committee (NHREC) and the Essential National Health Research Committee (ENHRC). These Institutions' roles and inter-relationships are evolving.

### (3) New ethical guidelines

- The Medical Research Council's (2004) Guidelines on ethics for medical research: *HIV preventive vaccine trials* are soon to be published.
- The NHREC (2004) *Ethics in health research: Principles, structures and processes* are soon to be published.

### (4) Ethical guidelines under revision:

- The Medical Research Council's (2002) Guidelines on ethics for medical research: *General principles* are soon to be revised.
- The Department of Health's (2000) *Guidelines for good practice in the conduct of clinical trials* are under revision.

## 2. FORUM OBJECTIVES

Based on the background described above, the forum aimed:

1. To identify the complexities posed by the current ethical-legal framework and implications for HIV vaccine trials, with a focus on child participation
2. To work towards consensus on how to enhance the current framework so that it facilitates sound research and protects trial participants

### **3. FORUM 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 50 participants attended the forum. Please see Appendix 1 for list of participants.

### **4 KEY QUESTIONS**

Critical questions discussed throughout the forum included:

1. What are the strengths and limitations of the ethical-legal framework, and what are the implications of the framework for stakeholders (RECs, researchers and participating communities) involved in the planning and review of HIV vaccine trials?
2. How could the framework be improved?

### **5 SUMMARY OF KEY THEMES, INCLUDING RECOMMENDATIONS**

#### **1. What are the strengths and limitations of the ethical-legal framework and implications for stakeholders?**

- a. In some cases the ethical-legal framework is ambiguous and inconsistent, posing a challenge to stakeholders planning and reviewing HIV vaccine trials
  - i. The implications of the NHB for HIV vaccine trials have begun to be articulated but there is some disagreement over the precise implications.

Possible implications:

In the National Health Bill, the distinction between “therapeutic” (TR) and “non-therapeutic” (NTR) research has been retained, but not defined. It is not clear how HIV vaccine trial phases could be classified.

The NHB asserts that for research (regardless of classification as TR or NTR) consent procedures must involve parents/ guardians *and* children, if they are capable of understanding. This implies that researchers must face logistical

problems of locating parents or excluding children from research where parents/ legal guardians cannot be found.

The NHB requires that a child's ability to understand the research must be ensured. How can this be done? Future work is required to develop appropriate means of reliably assessing child understanding.

If HIV vaccine trials are classified as NTR (as early safety/ immunogenicity trials might be), the risk standard of "not significant risk" must be met. Can HIV vaccine trials meet this standard? Some argue that the risks of trial interventions will exceed this standard. Others argue that this is not the case.

If HIV vaccine trials are classified as NTR, "authorisation from Minister" must be obtained. How could this provision best be implemented? Some argue that this function will be delegated to an appropriate authority such as the NHREC or RECs. Furthermore the Minister of Health may only grant authorisation for the research based on certain considerations including that the research is not contrary to "public policy". How can this be understood and operationalised? Further work must be done on this issue.

If research is classified as TR, it has to be in the child's "best interests". How can "best interests" be understood/ operationalised? Further work is required on the factors that should be taken into account to determine best interests, and developing a "test" for this.

- ii. The regulations to be enacted in terms of the Bill are being drafted. These will spell out procedural and substantive safeguards for research participants, including HIV vaccine trial participants. These are not likely to be published for 6 months (i.e. Jan 2005).

Inputs to the regulations are an opportunity to clearly define terms, elaborate on key concepts, and increase consistency with existing legal principles and processes.

- iii. Four ethical guidelines exist that are relevant to HIV vaccine research.

Certain guidelines have not been officially released (MRC 2004 Guidelines on ethics for medical research: *HIV preventive vaccine research*; and the NHREC 2004 Ethics in health research: *Principles, structures and processes*) and others are under revision (DOH 2000 *Guidelines for good practice in the conduct of clinical trials*) and others are soon to be revised (MRC 2002 Guidelines on ethics for medical research: *General Principles*).

For certain complex issues, such as child participation, the guidance is contradictory. The guidelines on child participation are not well harmonized on the following points:

- The approach taken towards the analysis of risk
- The name given to risk levels allowed for child research, and the substance of the risk level allowed for child research
- Who consents for child participation

- What parents are permitted to consent to, in terms of kinds of research designs
  - What parents are permitted to consent to, in terms of risks when there is NO direct benefit
  - What parents are permitted to consent to, in terms of risks when there IS direct benefit
- b. Due to the complex, changing ethical-legal framework, understanding and awareness needs to be heightened
- i. Stakeholders require opportunities to enhance their understanding of the laws and guidelines that regulate research, including the complex issue of child participation.
- c. Mechanisms to impact on the ethical-legal framework must be developed and strengthened.
- i. Stakeholders, including representatives of participating communities, require mechanisms to liaise and make inputs to the framework in order to better protect participants and vulnerable communities.
- d. On some issues, there is a lack of relevant data.
- i. How do community representatives view child participation in HIV vaccine trials?
  - ii. How can child understanding best be ensured?

## **2. How could the framework be improved (e.g. by law reform, guideline harmonisation, advocacy and capacity development)?**

### **1. *Impact on the ethical-legal framework***

The following recommendations were made:

- a. Make inputs to the regulations from the National Health Bill: Form a working group that could write submissions on the regulations to reduce inconsistencies with existing laws/ ethical guidelines, define ambiguous sections and improve drafting
- b. Advocate for law reform to strengthen the ethical-legal framework relating to research with child participants. Support a law reform proposal regarding the extension of s 76 of the Children's Bill to include provisions relating to research. Contact: strodea@ukzn.ac.za
- c. Impact on ethical guidelines for health research

- i. Advocate to the MRC for the publication and review of Book 5: MRC Guidelines on ethics for medical research: *HIV preventive vaccine trials*. Contact: [adri.labuschagne@mrc.ac.za](mailto:adri.labuschagne@mrc.ac.za)
- ii. Advocate for harmonization of ethical guidelines on critical issues, such as child participation.
- iii. Advocate for the revision of MRC Book 1 (2002): Guidelines on ethics for medical research: *General Principles*. Contact: [adri.labuschagne@mrc.ac.za](mailto:adri.labuschagne@mrc.ac.za)
- iv. Make inputs to the Department of Health's (2000) Guidelines for good practice in the conduct of clinical trials. Contact: Dr L Makubalo at [makubl@health.gov.za](mailto:makubl@health.gov.za)
- v. Send comments on the MCC phase I and II guidelines for HIV vaccine trials. Contact S Munbodh at [munbods@health.gov.za](mailto:munbods@health.gov.za)

**2. *Develop capacity and mechanisms for stakeholders to better understand the strengths, weaknesses and implications of the framework and to impact on it.***

a. Participating communities:

- i. Develop an accurate understanding of community perspectives and concerns through sensitive research
- ii. Develop ways to consult with communities on the issue of child participation, e.g. canvas the voices and perspectives of youth and parents on the issue of child participation in HIV vaccine trials
- iii. Build capacity of community representatives to understand the laws and guidelines, e.g. a workshop on the National Health Bill
- iv. Develop mechanisms whereby community representatives can network with each other on child participation in HIV vaccine research and contribute to an improved framework

b. RECs:

- i. Build capacity for RECs to understand the implications of laws and guidelines for the review of protocols, e.g. develop a working paper and host a "think-tank"
- ii. Develop mechanisms where RECs can liaise on the interpretation of laws/guidelines for protocol review in order to aspire towards consistent approach, e.g. regular contact, newsletter, national annual meeting

**3. *Conduct research and develop tools:***

- a. Develop tools for testing children's understanding of research participation
- b. Develop tests for the National Health Bill's requirement that "non-therapeutic" research is "not against public policy"
- c. Develop tests for the National Health Bill's requirement that "therapeutic" research be in a child's "best interests"

## 6 SUMMARY OF PRESENTATIONS AND DISCUSSION

### DAY ONE: THURSDAY 22<sup>ND</sup> JULY 2004

#### SESSION 1 INTRODUCTION AND KEY CONSIDERATIONS

Prof Graham Lindegger welcomed participants to the forum.

Participants introduced themselves and outlined their expectations for the forum, including:

- To gain a better understanding of the legal and ethical issues around HIV vaccine trials
- To pass this information on to organisations/ constituencies that participants represent
- To have a better understanding of the concrete implications the framework will have
- To be able to plan and conduct trials that meet ethical and legal requirements
- To hear the perspectives of other stakeholders on complexities and the way forward
- To learn how to involve community representatives more meaningfully
- To focus on the participation of children and adolescents in research, and achieve some clarity on current ethical and legal requirements
- To learn how to review HIV vaccine trial protocols better

Ms Ann Strode outlined the “challenging” ethical-legal environment for the conduct of research in SA.

She articulated key aims for the forum and key questions (see section 1,2, and 4).

The following issues were raised in discussion:

- Difficulties are faced by those planning HIV vaccine trials who must deal with existing laws and guidelines in the knowledge that these may soon change. Researchers emphasized their need for practical guidance
- The complex ethical and legal issues in HIV vaccine research are found in other HIV prevention trials with vulnerable communities such as microbicides therefore there is need for close collaboration between these initiatives
- Implications of the ethical-legal framework for participating communities are as critical as that for researchers and research ethics committees (RECs).
- There is a tension between the need to protect vulnerable persons and communities from harm as well as ensure their just access to research participation and health interventions. This is mirrored in tension between “protectionist” and “entitlement” groups.
- A number of potentially vulnerable groups may take part in HIV vaccine trials, including children and adolescents, and members of hierarchical organisations (miners). Protections discussed at the forum for children may have implications for other vulnerable groups.

#### SESSION 2 ETHICAL LEGAL FRAMEWORK FOR RESEARCH IN SOUTH AFRICA: IMPLICATIONS FOR HIV VACCINE TRIALS

##### HIV vaccine trials in South Africa: Current and future: G Gray

Note: Slides from this presentation will be emailed to forum participants.

Dr Glenda Gray reminded forum participants of the lengthy process that will be involved in developing, testing and licensing HIV vaccines. She presented on the phases of HIV vaccine trials. She presented on phase I trials - current trials (HVTN 040 and IAVI 001) and those planned for 2004 (HVTN 050, HVTN 059) and planned for 2005 (SAAVI DNA multigene subtype C; SAAVI DNA/MVA multigene subtype C; IAVI A002 subtype C). She described phase IIb trials planned for 2005 (VRC multiclade Adenovirus).

Dr Gray described the problems in interpreting whether HIV vaccines are effective – effectiveness may comprise the ability of vaccines to prevent OR alleviate HIV. The latter is more likely with vaccines designed to stimulate cellular immunity. These vaccines may be effective insofar as they prevent chronic infection, decrease the intensity of infection and reduce transmission.

Dr Gray highlighted that efficacy may wane over time, leading to a rebound of viral load or immune escape mutants.

Dr Gray highlighted the at-risk status of South African adolescents, and the need to develop relevant HIV vaccines for them – requiring their trial participation. She outlined requirements that RECs are likely to request:

- Community participation and assent to involve adolescent participants
- Evidence that vaccine is safe and promising from adult participants
- The informed consent of the adolescent and at least one parent

She asked RECs to consider innovative ways of relaxing some of these requirements, e.g. is parental consent required or can adolescents consent for themselves to be in trials?

### **Children and HIV vaccine trials in South Africa (H Jaspan)**

Note: Powerpoints were made available in the resource pack.

Dr Heather Jaspan outlined statistics pointing to the risk of children in SA for contracting HIV, either through sexual transmission or mother-to-child transmission, particularly during breastfeeding.

She described previous HIV vaccine trials in children, beginning with the controversial Zairian HIV vaccine trial. Two well-controlled trials in the United States have subsequently involved infants to investigate the role of vaccines in reducing mother-to-child transmission (PACTG 326a; PACTG 230) and one is planned for Uganda. While no HIV vaccine trials to date have involved adolescents, adolescents have taken part in SPV trials – a sexually transmitted disease.

Dr Jaspan discussed the differences between adults and children in the way foreign substances are metabolised, distributed and excreted. Dr Jaspan also presented on differences in the immune system between children and adults, including antibodies and cytokine profiles. These are likely to mean different safety and immune profiles for HIV vaccines in children and adults. She presented examples of children's differing responses from adults to other vaccines. She briefly outlined other relevant issues, such as pre-existing immune patterns ( - differences in vaccination history) and passively acquired maternal antibodies.

She described the South African situation with regard to HIV vaccine trials in children:

- Collaborations have been formed
- Reciprocal visits have been planned
- Laws and ethical guidelines are under examination
- Community participation mechanisms are being formed.

She ended with some recent news that product manufacturers have agreed to allow one of their products to be considered for adolescent trial participation – VRC – which might encourage other vaccine developers to come forward.

### **Discussion:**

Discussion centered around the following issues:

- The vaccine product has been administered to US adults.
- A possible sequence for SA is that the product will undergo safety and immune response testing in SA adults, and then adolescents will be enrolled in trials to test safety and immune responses for adolescents.

### **Ethical-legal regulation of research in South Africa (J Singh)**

Note: Slides from this presentation will be emailed to forum participants.

Dr Jerome Singh outlined the current ethical-legal framework for research in SA, and its application to HIV vaccine trials. He presented the statutory councils, institutions and centres that regulate research, including the Department of Health and Department of Science and Technology.

He outlined regulation by national policy, national guidelines and law.

#### National policy:

1. DOH (2001) Patient Rights Charter
2. DOH (2001) Health research policy in SA

#### National guidelines:

1. Research-specific
  - a. DOH GCP (2000): applies to all clinical trials, minimum standards for conduct
  - b. MRC (1993, 2002): covers MRC research/ers only but widely used; some tension exists about their broad applicability
  - c. NHREC Structures and Processes: applies to all health research (pending release)
  - d. MRC (2004): HIV vaccine trial guidelines (pending release)
  - e. HSRC Code of research ethics: applies to social-behavioural science research which may be attached to HIV vaccine trials; covers HSRC research/ers only.
2. Clinical
  - a. DOH HIV AIDS guidelines (relevant for treatment of participants who become infected)
3. (HPCSA guidelines, SAMA guidelines, SAC for Social Science Guidelines pertain to clinicians and professionals involved in research).

#### Law:

1. Current research specific
  - a. Constitution of RSA (relevant to participants and researchers – freedom of academic activity and expression)
  - b. SA MRC Act (empowers the MRC Board to set ethical standards)
  - c. Human Tissues Act (will be superseded by provisions in the NHB; relevant to HIV vaccine trial products)
  - d. SA Medicines Medical Devices Regulatory Authority Act
2. Imminent research specific
  - a. National Health Bill (passed but not proclaimed)
3. Non-specific but relevant
  - a. RSA Constitution
  - b. Child Care Act (being revised – see Children’s Bill; focuses on treatment and not research directly; does not define “medical treatment” allowing some to interpret “therapeutic research” as equal to “medical treatment”; begs the question of how some phases of HIV vaccine trials could be defined – “therapeutic” or “non-therapeutic”)
  - c. Health Professions Act (relevant if the HIV vaccine trial researcher is a registered health professional)
  - d. Mental Health Care Act (only relevant if mental health care users were to be participants)

- e. Promotion of Equality act (prohibits discrimination in the workplace; relevant to participants who may test antibody positive from HIV vaccine)
4. Common law relevant to research with humans
  - a. Contract law
  - b. Delict

Dr Singh concluded by stating that SA has a fairly comprehensive set of laws and guidelines regulating research.

### **Good practice for clinical trials (H Rees)**

Note: Powerpoints will be emailed to forum participants.

Prof Helen Rees outlined that she would prefer to consult with the forum participants than make a formal presentation.

She outlined that the Department of Health's *Guidelines for good practice in clinical trials* have been used forcibly since their release in 2000 to protect trial participants and protect the integrity of trial data.

Subsequently, issues have been raised by researchers, ethicists and industry prompting a revision process. Prof Rees outlined several areas for revision including:

1. Principal investigators – under consideration is the redefinition of what PI's core responsibilities might be, and whether PIs need be SA citizens
2. Children – under consideration are the requirements for the kinds of interventions children can be exposed to and requirements for consent and assent.
3. Women
4. Vulnerable communities
5. Standard of care – under consideration are requirements for the tests and interventions trial participants should receive
6. Death reporting – under consideration are requirements for determining “unnatural death”, and subsequent post-mortem, and implication for consent

Prof Rees asked forum participants to contribute to the process of revision, and send written comments to Dr Lindiwe Makubalo at makubl@health.gov.za

## **SESSION 3 THE CHANGING LEGAL FRAMEWORK: IMPLICATIONS FOR HIV VACCINE TRIALS**

### **The National Health Bill (P Carstens)**

Note: Powerpoints were made available in the resource pack.

Prof Pieter Carstens stated that the National Health Bill (NHB) will be Act 61 of 2003.

He emphasized that the NHB – statutory law – must be balanced against other sources of law, e.g. the Child Care Act, and is subordinate to the Constitution of South Africa. He argued that the essential quest is for an ethical-legal framework that “will pass Constitutional muster”.

Prof Carstens took participants through various sections of the NHB, including the definitions e.g. of “health research”, and Chapter 8 – control of human tissues; and Chapter 9 – including section 71 dealing with consent to research and the permissible boundaries of research.

He stated that the regulations that will refine elements of the NHB are being drafted and will only be available in 6 months.

He stated that the Bill is controversial and will be challenged in the Constitutional Court.

### **National Health Bill: Children: Implications for RECs/ researchers (C Grant)**

Note: Powerpoints were made available in the resource pack

Ms Catherine Grant outlined various strengths and limitations of section 71 of the National Health Bill and some of the implications for researchers and RECs.

These included:

Strengths:

1. The NHB creates a platform for regulations to provide a wide range of safeguards for research participants

Limitations:

1. Section 71 largely focuses on consent as an ethical protection and excludes other protections
2. It may be inconsistent with other laws – in terms of consent, such as the Child Care Act, and proposed laws such as the Children’s Bill
3. It maintains the controversial distinction between “therapeutic” research (TR) and ‘non-therapeutic” research (NTR), which has been abandoned in many ethical guidelines
4. It may be inconsistent with some ethical guidelines in terms of allowable research risk levels for NTR
5. It may create additional bureaucratic procedures such as “consent from the Minister” for NTR
6. There is non-uniform approach to some sections, e.g. “best interests” of the child standard is only invoked in relation to TR
7. The wording is confusing in places, e.g. “non-therapeutic” research is allowable when it is likely to improve understanding of a minors “condition” – can this accommodate research with healthy children that will not confer direct benefit?
8. The section uses “minor” and “child” interchangeably

Implications for stakeholders

1. Consent procedures will have to involve parents/ guardians *and* children
2. If HIV vaccine trials are classified as NTR, “authorisation from Minister” must be obtained, on the consideration of various factors. Work needs to be done to understand how this will take place, and if delegated to whom?
3. If HIV vaccine trials are classified as NTR, the research cannot be “against public policy”. Additional work is required to develop a “test” for this requirement.
4. The NHB requires that a child’s ability to understand the research must be ensured. Future work is required to develop instruments to assist with this requirement.
5. If research is classified as TR, it has to be in the child’s “best interests”. Future work is required to spell out the kind of factors that should be taken into account to determine best interests.

### **Discussion:**

Discussion items included the following:

- In the event of inconsistencies between the National Health Bill and the Children's Bill, which will prevail? It was submitted that the values in the Children's Bill may trump.
- Inconsistencies stemming from the National Health Bill could be remedied through recourse to international jurisprudence
- The interaction between law and guidelines: How will the National Health Bill impact on the more nuanced approach certain ethical guidelines wish to take?
- The convention of rights of the child foregrounds the views and opinions of children therefore children need to be consulted!

### **Small group discussions:**

Participants divided into 3 groups and responded to a list of key questions.

Please see Appendices for questions.

Please see Powerpoints for detailed responses.

### **Summary:**

#### **Group one:**

- a. General implications of the National Health Bill for HIV vaccine trials: Include that the Bill appears to act as a barrier to HIV vaccine research with children.
- b. Specifically
  - a. Implications of TR versus NTR: The group felt they did not have a choice regarding whether they agreed with the distinction between TR and NTR, and needed to work within this broad distinction. They felt the Minister should define these terms broadly, and that phase I and II trials are likely to be classified as NTR and phase III trials as TR
  - b. Implications of consent procedures required by NHB: Children with no parents or legal guardians, such as orphans, will be excluded from research. However parents should be involved as they will have to take responsibility for Adverse Events. Children may be dissuaded from participation, however, consent for participation could still allow confidentiality of various issues
  - c. Implications of "not significant risk" standard for NTR in NHB: The group felt that HIV vaccine trial procedures would involve levels of risk exceeding those allowed by the NHB for NTR. However, there was not agreement on how "significant" could be defined or whether the interventions (venupuncture, stigma) were "significant". If phase III trials were classified as TR then trials could proceed. The NHB could be challenged as excluding children from trials might not be in their "best interests" and could be viewed as overly protectionist. Instead an informed risk-benefit analysis should be done
  - d. Implications of "authorization from the Minister" for NTR: The group felt that this function could be delegated to the Director of HIV; committee of experts.
  - e. Implications of "not against public policy" for NTR: Not addressed

- f. Implications of child understanding requirement in NHB: Instruments/ Tools must be developed before enrolment of children that are culture and age sensitive
  - g. Implications of “best interests” standard for TR: Group argued that this assessment must be made on an individualised case-by-case basis
- c. Recommendations:
- a. Persons with expertise in paediatrics are required on RECs
  - b. Inputs to the regulations should be made for definitions of TR versus NTR
  - c. Capacity building is required
  - d. Develop paper on criteria and tools to test child understanding.

**Group two:**

- 1. General implications: Not addressed
- 2. Specifically:
  - a. Not addressed
  - b. Not addressed
  - c. Not addressed
  - d. Implications of “authorization from the Minister” for NTR: Minister should delegate this function to the NHREC which could delegate this to local RECs
  - e. Implications of “not against public policy” for NTR: The group stated that the research would have to be socially acceptable as demonstrated by liaison with civil society structures and community based research
  - f. Implications of child understanding requirement in NHB: Develop tools to test understanding
  - g. Implications of “best interests” standard for TR: Not addressed.
- 3. Recommendations:
  - a) Build capacity to understand the NHB, science of trials and trial procedures, and get regular updates from PIs and sponsors
  - b) Enhance liaison and networking between RECs (national networking meeting; newsletter) to ensure more uniformity in approach. Outcomes of this meeting should be presented at the National Meeting 10<sup>th</sup> September 2004
  - c) Strengthen infrastructure for review: e.g. human resources, administration, monitoring capacity, transparency around funding from sponsors

**Group three:**

- 1. General implications of the National Health Bill: Include an emphasis on community involvement and consultation (2,3,4,5,6). Strengths of the NHB include community involvement and the emphasis on informed consent. Weaknesses include that there is no detail on how to involve communities; community members are not aware of the NHB, and the English language presentation is an obstacle
- 2. Specifically:

- a. Implications of NHB stating parental consent and child assent: Work should begin with parents and adolescents, to build trust and engage communities on this issue
- b. Implications of NHB requiring children to understand: Disseminate information widely to youth, mass media, road show etc; find the most appropriate tool to test understanding, be sensitive to age
- c. Implications of NHB requiring “best interests” if TR: Best interests could be evaluated in light of “is the child going to be a beneficiary” or “is this for public benefit” for children as a whole?

3. Recommendations:

- a. The regulations to come out of the NHB should specify in more detail how communities can become involved
- b. The NHB should be workshopped with communities
- c. Consideration must be given to when there is conflict between child assent and parental consent
- d. Strategies should be formed to build trust with communities, parents and adolescents, and begin discussion on this issue
- e. Communities should mobilise around this issue of child participation
- f. Protocols should include finances for consultation with communities
- g. Peer educators should be involved
- h. The views and expectations of communities should be researched.

**DAY TWO: FRIDAY 23<sup>RD</sup> JULY 2004**

**SESSION 4: ETHICAL GUIDELINES: IMPLICATIONS FOR RESEARCH AND HIV VACCINES**

**National guidelines for research: The interim National Health Research Ethics Committee Guidelines (A Dhai)**

Note: Powerpoints were made available in the resource pack

Prof Ames Dhai outlined core principles of research ethics and traced the history of research ethics review in South Africa.

She described the process whereby the NHREC has developed guidelines: *Ethics in Health Research: Principles, Structures and Processes*.

The implications for HIV vaccine trials are that these will have to comply with NHREC Ethics in Health Research. Research Ethics Committee membership will have to comply with requirements set out in these guidelines. RECs reviewing HIV vaccine trials will have to be “level 2” committees (which review more than minimal – everyday- risk research, drug research, human tissue research, hi-tech, multi-centered, collaborative, long-term research).

**The Medicines Control council’s guidelines for HIV vaccine trials (T Smit)**

Note: Powerpoints will be forwarded to participants

Mr Thomas Smit described the acts conferring authority on the MCC to form policies.

He described 2 sets of guidelines the MCC has developed for phase I and phase II HIV vaccine trials. The phase I guidelines have been accepted. However the phase II guidelines are available for comment.

He described concerns raised at a stakeholder meeting hosted by the MCC on 21<sup>st</sup> February 2003 to debate the phase I guidelines, including:

- The guidelines set “golden standards”
- Child/ adolescent participation
- The status of the section on ethics: is the development of ethics guidelines within the role of the MCC? The MCC did not want to ignore ethical issues, especially in the absence of guidelines applicable to all RECs.

The main role of the MCC is to see that risks are appropriately described.

Mr Smit described the content of the guidelines, and major sections.

He outlined that the MCC will not approve HIV vaccine trials without approval from RECs. The MCC may still consider ethical issues (e.g. the “therapeutic misconception”) but their main role is to ensure that ethical approval has taken place.

### **The Medical Research Councils’ ethical guidelines for HIV vaccine trials: A focus on child participation (C Slack)**

Note: Powerpoints will be forwarded to participants

Ms Catherine Slack presented on the MRC’s (2004) guidelines on ethics for medical research: *HIV preventive vaccines* (so-called “book 5”) – specifically the guidance point on children – and compared it to other South African research ethics guidelines. These were MRC (2002) guidelines on ethics: *General principles* (“book 1”); the DOH (2000) *guidelines on good practice in clinical trials*; and the NHREC (2004) *Ethics in Health Research: Principles, structures and processes*.

She outlined in Table form numerous inconsistencies between these guidelines in terms of what can be consented to and who gives consent for child participation.

She outlined that the MRC’s book 5 permits child participation in HIV vaccine trials when core requirements can be met including that the research cannot be conducted on less vulnerable participants, the research investigates a problem of direct relevance to children, risk-benefit ratio’s are appropriate and legal and ethical requirements for consent can be met.

She recommended harmonization between the major guidelines, so that RECs charged with filtering out unacceptable studies are not face with conflicting guidance.

#### **Discussion:**

Discussion items included the following:

- The difference between law, ethics and human rights
- Clarification of the future of the DOH (2000) *Guidelines for good practice in the conduct of clinical trials*: It was clarified that these guidelines are under revision and will still hold when the NHREC publishes their *Principles, structure and processes*.
- The need to conduct sensitive research around community and cultural notions of childhood, young adulthood and family, in order to prevent culturally insensitive trial practices

#### **Small group discussions:**

Participants remained in plenary, and responded to a list of questions.

Please see Appendices for questions.

**Summary:**

The discussion and inputs yesterday made many forum participants increasingly aware of the need for better consultation with communities, on the need to enhance community capacity to engage with these issues. Input from community members in the plenary needs to be increased.

Suggestions for how to enhance community participation in forums such as this one included:

- A preliminary capacity building input prior to the main forum
- Interpreters
- A program to build capacity, perhaps taken on by the SAAVI community preparedness program (CPP)

The most obvious weaknesses of the ethical-legal framework include lack of co-ordination and harmonisation between guidelines on issue of child participation; the legal framework is fragmented; there are some inconsistencies between large pieces of legislation such as the National Health Bill and Children's Bill on issues such as child understanding and "consentors" on child's behalf; the National Health Bill focus on consent and not other ethical protections and retention of the TR and NTR distinction. Furthermore, there is no consensus on the ideal ethical-legal system.

The National Health Bill's standard for NTR as "not significant" risk was identified as a legal "weasel" word that may serve the purpose of drawing on and harmonising with other ethical guidelines. That is, it could be interpreted to be the same risk standard as that found in existing ethical guidelines.

**Thanks and close**

Prof Lindegger and Ms C Slack summed up some major themes and recommendations for a way forward. (Please see sections 3 and 4 of the report). Prof Lindegger thanked participants for sacrificing valuable time to be at the forum and for their contributions. He added that the workshop report would be drafted and the draft sent to participants for comment.

It was decided that the forum report should be available in isiZulu and Sotho.

## Appendices

- Participants list
- Agenda
- Questions for breakaway groups
- List of resources provided to forum participants

FINAL FORUM REPORT: slackca@ukzn.ac.za

Surname	Name	Organisation	Telephone	Facsimile	Email
<b>Chairs:</b>					
Kleinsmidt	Anita	Wits Univ:Bioethics Centre	27 11 717 2720	27 11 643 1264	kleinsmidta@medicine.wits.ac.za
Mellors	Shaun	Independent HIV AIDS Consultant	27 31 260 4725	27 31 260 4725	s-mellors@mweb.co.za
Morar	Neetha	HIV Prevention Research Unit (HPRU), MRC, SAMRI	27 31 242 3630	27 31 242 3800	nmorar@mrc.ac.za
<b>Facilitators</b>					
Mkhize	Nhlanhla	HIV AIDS Vaccines Ethics Group	27 33 260 5693	27 33 260 6167	Mkhize@ukzn.ac.za
Wassenaar	Doug	HIV AIDS Vaccines Ethics Group	27 33 260 5373	27 33 260 6167	wassenaar@ukzn.ac.za
<b>Participants</b>					
Bekker	Linda-Gail	Desmond Tutu HIV Centre	27 21 650 6959	27 21 650 6963	linda-gail.bekker@hiv-research.org.za
Cheevers	(EJ) Sean	HVRU, MRC, Durban:SI Merck	27 31 203 4738	27 31 203 4707	scheevers@mrc.ac.za
Dollie	Farida	South African Human Rights Commission	27 11 484 8300	27 11 484 1746	fdollie@sahrc.org.za
du Plooy	Willem	Medunsa:REC	27 12 521 4123	27 12 5214121	wimduplooy@medunsa.ac.za
Engelbrecht	Sherella	HIV AIDS Vaccines Ethics Group	27 33 260 6165	27 33 260 6065	engelbrecht@ukzn.ac.za
Fleischer	Theodore	UCT: Bioethics Centre:Dept of Medicine	27 21 406 6195	27 21 448 6815	terryf@uctgsh1.uct.ac.za
Hassim	Adila	AIDS Law Project	27 11 717 8635	27 11 4032341	hassima@law.wits.ac.za
Hlabisa	Velenkosini	CAB:Hlabisa	-	27 35 838 1015	no email
Horn	Lyn	Stellenbosch Univ:Division for Research Development & Support	27 21 938 9075	27 21 933 6330	lhorn@sun.ac.za
Kagee	Shaheen(Ashraf)	Stellenbosch Univ:Dept. of Psychology	27 21 808 3442	27 21 8083584	skagee@sun.ac.za
Kruger	Mariana	Kalafong Hospital:Dept. of Paediatrics	27 12 373 1009	27 12 373 7977	mariana@kalafong.up.ac.za
Levendal	Elise	SAAVI: CPP	27 21 938 0826	27 21 938 0823	elise.levendal@mrc.ac.za
Lindegger	Graham	HIV AIDS Vaccines Ethics Group	27 33 260 5335	27 33 260 5809	Lindegger@ukzn.ac.za
Lutge	Elizabeth	NMSM: Dept. Community Health	27 31 2604287	27 31 2604211	Lutgee1@ukzn.ac.za
Madonsela	Abednigo	CAB:Africa Centre	-	27 35 550 7565	no email
Makubalo	Lindiwe	DOH: Sub-Directorate :HSRREC	27 12 312 0774	27 12 323 5003	makubl@health.gov.za
Mgoduso	Nomsa	HIV Prevention Research Unit (HPRU), MRC, SAMRI	27 31 242 3689	27 31 242 3800	nmgoduso@mrc.ac.za
Milford	Cecilia	HIV AIDS Vaccines Ethics Group	27 33 260 6164	27 33 260 6167	milford@ukzn.ac.za
Mkhize	Nonhlanhla	CAB:DBN HVRU	27 31 301 2145	27 31 301 2145	gaycentre@mweb.co.za
Mogale	Matilda	CAB:HAVD, PHRU	27 11 989 9822	27 11 938 3973	mogalem@hivsa.com
Mohlakoana	Joseph	CAB:Orkney Site	27 18 478 3620	27 18 478 3046	wellness.wv@aghs.co.za
Moodley	Keymanthri	Tygerberg Division of the Unit for Bioethics	27 21 938 9600	27 21 932 7712	km@sun.ac.za
Msweli	Abel	CAB:Africa Centre	-	27 35 550 7565	no email
Munbodh	Shyamli	Medicines Control Council	27 21 959 2190	27 21 959 1379	munbods@health.gov.za
Naidoo	Shan	Wits Univ: REC	27 11 717 2614	27 11 717 2084	naidoosh@sph.wits.ac.za
Ngwenya	Nomusa	HIV AIDS Vaccines Ethics Group	27 33 260 5566	27 33 260 6167	ngwenyan@ukzn.ac.za
Nqojana	Lungelo	CAB:Cape Town Vaccine Trial Site	-	27 21 785 7317	no email

FINAL FORUM REPORT: slackca@ukzn.ac.za

Surname	Name	Organisation	Telephone	Facsimile	Email
Ogunbanjo	Gboyega	Medunsa:Research Ethics & Publications Committee	27 12 521 4321	27 12 521 5811	gao@intekom.co.za
Ramjee	Gita	HIV Prevention Research unit	27 31 2034770	27 31 203 4702	ramjeeg@mrc.ac.za
Stobie	Melissa	HIV AIDS Vaccines Ethics Group	27 33 260 5565	27 33 260 5652	stobiemi@ukzn.ac.za
Toohey	Jacintha	HIV AIDS Vaccines Ethics Group	27 33 260 6166	27 33 260 6167	tooheyj@ukzn.ac.za
Van Niekerk	Anton	Stellenbosch Univ:Dept. of Philosophy:Centre for Applied Ethics	27 21 808 2055	27 21 808 3556	aavn@maties.sun.ac.za
Vawda	Cati	Children's Rights Centre	27 31 307 6075	27 31 307 6074	<a href="mailto:cati@crc-sa.co.za">cati@crc-sa.co.za</a>
Wambugu	Jacob	HIV AIDS Vaccines Ethics Group	27 33 260 5566	27 33 260 6167	wambugu@ukzn.ac.za
Xaba	Xolani	HIV AIDS Vaccines Ethics Group	27 33 260 6164	27 33 260 6167	xabax@ukzn.ac.za
<b>Speakers</b>					
Carstens	Pieter	Univ. of Pretoria: Health Law	27 12 420 4067	27 12 420 2991	pcarsten@hakuna.up.ac.za
Dhai	Ames	NMSM:REC	27 31 260 4448	27 31 260 4427	dhaia1@ukzn.ac.za
Grant	Catherine	HIV AIDS Vaccines Ethics Group	27 11 442 5298	27 11 442 5298	Kittyb@mweb.co.za
Gray	Glenda	HAVD, PHRU	27 11 989 9703	27 11 989 9762	grayn@hivsa.com
Jaspan	Heather	Desmond Tutu HIV Centre	27 21 650 6960	27 21 650 6963	heather.jaspan@hiv-research.org.za
Rees	Helen	Wits Univ:RHRU	27 11 989 9208	27 11 9899271	h.rees@rhrujh.co.za
Singh	Jerome	NMSM:Bioethics and Health Law Programme:CAPRISA	27 31 260 4561	27 31 260 2837	singhj9@nu.ac.za
Slack	Cathy	HIV AIDS Vaccines Ethics Group	27 33 260 5751	27 33 260 6167	slackca@ukzn.ac.za
Smit	Thomas	SAAVI CPP	27 21 938 0528	27 21 938 0823	thomas.smit@mrc.ac.za
Strode	Ann	HIV AIDS Vaccines Ethics Group	27 33 260 5731	27 33 260 5015	strodea@ukzn.ac.za

DEBATE AND CAPACITY BUILDING FORUM  
ETHICAL-LEGAL REGULATION OF RESEARCH IN SOUTH AFRICA:  
IMPLICATIONS FOR HIV VACCINE TRIALS

<b>DAY ONE:</b>	<b>THURSDAY 22<sup>nd</sup> JULY 2004</b>
0830-0900	Tea/ coffee and registration
<b>Session 1</b>	<b>INTRODUCTION AND KEY CONSIDERATIONS</b>
	<b>Facilitators:</b> Nhlanhla Mkhize and Doug Wassenaar HAVEG, UNP
0900-0910	<b>Welcome</b> (G Lindegger, HAVEG)
0910-1000	<b>Participant introductions and expectations</b> (Facilitators)
1000-1010	<b>Key questions and potential outcomes</b> (A Strode, HAVEG)
1010-1030	<b>Comments and questions</b> (Facilitators)
1030-1100	Tea Break
<b>Session 2</b>	<b>ETHICAL-LEGAL FRAMEWORK FOR RESEARCH IN SOUTH AFRICA: IMPLICATIONS FOR VACCINE TRIALS</b>
	<b>Chair:</b> Neetha Morar, HIV Prevention Research Unit
	<b>Key outcomes for participants:</b> An enhanced ability to evaluate the status of current and planned HIV vaccine trials in South Africa and the legal-ethical context for research
1100-1115	<b>HIV vaccine trials in South Africa: Current and future</b> (G Gray, HAVD PHRU, and SAAVI)
1115-1130	<b>Children and HIV vaccine trials in South Africa</b> (H Jaspan, Desmond Tutu HIV Centre, and SAAVI)
1130-1145	Questions (Chair)
1145-1215	<b>Ethical legal regulation of research in South Africa</b> (J Singh, CAPRISA)
1215-1230	<b>Good practice for clinical trials: Guidelines and revision</b> (H Rees, RHRU)
1230-1300	Discussion (Facilitators)
1300-1400	Lunch
<b>Session 3</b>	<b>THE CHANGING LEGAL FRAMEWORK: IMPLICATIONS FOR HIV VACCINES</b>
	<b>Chair:</b> Anita Kleinsmidt, Wits Bioethics Centre
	<b>Key outcomes for participants:</b> An understanding of the current National Health Bill, its scope, strengths, weaknesses, practical implications for investigators and RECs; and application to HIV vaccine trials and child participation in research
1400-1445	<b>The National Health Bill:</b> (P Carstens, UP)
1445-1500	<b>National Health Bill: Children: Implications for RECs/researchers</b> (C Grant, HAVEG)
1500-1530	Questions and discussion (Chair and Facilitators)
1530-1545	Tea Break
1545	Briefing for small groups (Facilitators)
1545-1700	Small group discussions - chairs & rapporteurs: expert groups to address questions
1700	Housekeeping thanks and close

FINAL

**DAY TWO: FRIDAY 23<sup>rd</sup> JULY 2004**

0800-0830	Tea/Coffee
0830-0915	Plenary report-back from breakaway small group discussions (Facilitators)
<b>Session 4</b>	<b>ETHICAL GUIDELINES: IMPLICATIONS FOR RESEARCH &amp; HIV VACCINES</b>
	Chair: Shaun Mellors, Independent HIV Consultant <u>Key outcomes for participants:</u> An enhanced sense of current ethical guidelines that govern SA research and implications for HIV vaccine trials; a focus on guideline strengths, gaps, inconsistencies, and practical implementation.
0915-0930	<b>National guidelines for research: The Interim National Health Research Ethics Committee Guidelines</b> (A Dhai, Interim National Health REC).
0930-0945	<b>The Medicines Control Council's guidelines for HIV vaccine trials</b> (T Smit, MCC, and SAAVI)
0945-1000	Questions (Chair)
1000-1030	Tea Break
1030-1045	<b>The Medical Research Councils' ethical guidelines for HIV vaccine trials: A focus on child participation</b> (C Slack, HAVEG)
1045-1115	Discussion (Facilitators)
1115	Briefing for small groups (Facilitators)
1115-1215	Small group discussions - chairs & rapporteurs for expert groups to address specific questions (to be provided)
1215-1300	Plenary report-back from breakaway small group discussions (Facilitators)
1300-1315	Thanks, way forward and close (G Lindegger, C Slack, HAVEG)
1315	LUNCH

QUESTIONS FOR BREAKAWAY GROUPS – DAY ONE:

GROUP ONE

1. According to your group, what are the general implications of the National Health Bill (NHB) for the conduct of HIV vaccine trials in South Africa?
2. More specifically please consider the following:
  - a. In the National Health Bill, the distinction between “therapeutic” (TR) and “non-therapeutic” (NTR) research has been retained, but not defined.
    - i. Do you agree with retaining the distinction between the two types of research?
    - ii. How should the Minister, in regulations, define this to give good guidance?
    - iii. What are the implications for HIV vaccine trials of the NHB retention of the distinction between TR and NTR? E.g. how are they likely to be classified?
  - b. The NHB asserts that for research (regardless of classification as TR or NTR) consent procedures must involve parents/ guardians *and* children, if they are capable of understanding. What are the implications for trials, e.g. logistical problems?
  - c. If HIV vaccine trials are classified as NTR (as early safety/ immunogenicity trials might be), the risk standard of “not significant risk” must be met. Can HIV vaccine trials meet this standard?
  - d. If HIV vaccine trials are classified as NTR, “authorisation from Minister” must be obtained, on the consideration of various factors. How could this provision best be implemented? E.g. if the power to provide consent were delegated, which authority should it be delegated to? What guidance would the authority need to make this decision?
  - e. If HIV vaccine trials are classified as NTR, the research cannot be “against public policy”. How can this be understood and operationalised?
  - f. The NHB requires that a child’s ability to understand the research must be ensured. How can this be done?
  - g. If research is classified as TR, it has to be in the child’s “best interests”. How can “best interests” be understood/ operationalised? E.g. what kind of factors should be taken into account to determine best interests?
3. What is required to assist researchers to comply with and implement the National Health Bill?

## GROUP TWO

1. **According to your group, what are the general implications of the National Health Bill (NHB) for the review of HIV vaccine trials in South Africa, and for the protection of participants?**
2. **More specifically please consider the following:**
  - a. In the National Health Bill, the distinction between “therapeutic” (TR) and “non-therapeutic” (NTR) research has been retained, but not defined.
    - i. Do you agree with retaining the distinction between the two types of research?
    - ii. How should the Minister, in regulations, define this to give good guidance?
    - iii. What are the implications for HIV vaccine trials of the NHB retention of the distinction between TR and NTR? E.g. how are they likely to be classified?
  - b. The NHB asserts that for research (regardless of classification as TR or NTR) consent procedures must involve parents/ guardians *and* children, if they are capable of understanding. What are the implications for trials, e.g. logistical problems?
  - c. If HIV vaccine trials are classified as NTR (as early safety/ immunogenicity trials might be), the risk standard of “not significant risk” must be met. Can HIV vaccine trials meet this standard?
  - d. If HIV vaccine trials are classified as NTR, “authorisation from Minister” must be obtained, on the consideration of various factors. How could this provision best be implemented? E.g. if the power to provide consent were delegated, which authority should it be delegated to? What guidance would the authority need to make this decision?
  - e. If HIV vaccine trials are classified as NTR, the research cannot be “against public policy”. How can this be understood and operationalised?
  - f. The NHB requires that a child’s ability to understand the research must be ensured. How can this be done?
  - g. If research is classified as TR, it has to be in the child’s “best interests”. How can “best interests” be understood/ operationalised? E.g. what kind of factors should be taken into account to determine best interests?
3. What is required to assist reviewers to comply with and implement the National Health Bill?

### GROUP 3

1. According to your group, what are the general implications of the National Health Bill (NHB) for communities involved in HIV vaccine trials?
2. More specifically please consider the following:
  - a. The National Health Bill asserts that for research (regardless of classification as “therapeutic” or “non-therapeutic”) consent procedures must involve parents/ guardians *and* children. What are the implications for trials, e.g. logistical problems?
  - b. The NHB requires that a child’s ability to understand the research must be ensured. How can this be done?
  - c. If research is classified as “therapeutic”, it has to be in the child’s “best interests”. How can the child’s “best interests” be understood and operationalised? E.g. what kind of factors should be taken into account to determine best interests?
3. What is required to assist communities to apply the NHB in the protection of participants and communities?

**SAAVI: HAVEG: Forum: 22<sup>nd</sup> & 23<sup>rd</sup> August 2004**  
**ETHICAL-LEGAL REGULATION OF RESEARCH IN SA**

#### QUESTIONS FOR BREAKAWAY GROUPS – DAY TWO:

##### For all 3 groups

1. After this morning’s presentations, have any of your views on Day 1’s questions changed, and if so, how?
2. According to your group, what are the most obvious strengths, weaknesses, and inconsistencies in the current ethical-legal framework for research in South Africa?
3. We would value your group’s perspective on the following issues:

The South African NHB implies that children in “non-therapeutic research” (NTR) should be exposed to research risk that is “not significant”.

South African ethical guidelines state that children in non-therapeutic research (or a non-beneficial intervention) should only be exposed to levels of research risk that is similar to the “risks of daily life” (DOH GCP) or the risks of daily life *in a stable society* (MRC, 2002) or the risks of routine physical and psychological tests/ examinations (MRC 2002, DOH 2000) or slight increase over these.

- a. Are the 2 standard similar, or is the National Health Bill a more relaxed risk standard than the one in ethical guidelines?

# FINAL

## Resource List

1. Agenda
2. Emanuel, E.J, Wendler, D, Killen, J., Grady, C. (2003). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of the American Medical Association* 283 (20): 2701–2711.
3. Francis, D.P, Heyward, W.L, Popvic, V, Orozco-Cronin, P. (2003). Candidate HIV/AIDS vaccines: Lessons learned from the world's first phase III efficacy. *AIDS* 17: 147-156.
4. HIV AIDS Vaccines Ethics Group. (2004) Information sheet.
5. Kuther, T.L. (2003). Medical decision-making and minors: Issues of consent and assent. *Adolescence* 38 (150): 343, 16p.
6. Lidz, C.W, Appelbaum, P.S, Grissot, T., Renuad, M. (2004). Therapeutic misconception and appreciation of risks in clinical trials. *Social Science & Medicine* 58: 1689-1697.
7. Mac Queen, K, Sugarman, J. (2003) HIV prevention trials network. Ethics guidance for research.
8. Mays, R.M, Sturm, L.A, Gregory, D.Z. (2004). Parental perspectives on vaccinating children against sexually transmitted infections. *Social Science & Medicine* 58: 1405-1413.
9. McClure, C, Gray, G, Rybczyk, G.K, Wright, P.F. (2004). Challenges to conducting HIV preventative vaccine trials with adolescents. *Acquir Immune Defic Syndr* 36:726-733
10. Medicines Control Council (2004). Draft HIV vaccine trial guidelines: Phase two.
11. Medicines Control Council. (2002). Guide to completing a clinical trial application of a vaccine.
12. Miller, F.G. (2003). Clinical research with healthy volunteers: An ethical framework. *Journal of Investigative Medicine* 51 (supplement1): S2-S5.
13. Miller, G.F, Wendler, D, Wilford, B. (2003). When do the federal regulations allow placebo-controlled trials. *Journal of Pediatrics* 142: 102-107.
14. Monday, B. (2002). AIDS vaccinations insurance implications. *South African Medical Journal* 92 (11).
15. MRC (2002). Guidelines on ethics for medical research: *General Principles*
16. National Council of Provinces (2003) National Health Bill.
17. Participants List
18. Richardson,H.S, Belsky, L. (2004). The ancillary-care responsibilities of medical researchers. *Hastings Center Report*, January-February: 25-33.
19. SAAVI, FAQ's. (2004). Basic questions and answers on HIV vaccines. <http://www.saavi.org.za/basicfaq.htm>.
20. SAAVI, FAQ's. (2004). Questions and answers about the MVA.HIVA AIDS vaccine candidate in human trial in South Africa. <http://www.saavi.org.za/mvafaq.htm>.
21. SAAVI, FAQ's. (2004). Questions and answers on the VEE candidate vaccine. <http://www.saavi.org.za/veefaq.htm>.
22. Safrit, T.J. (2003). HIV vaccines in infants and children: Past trials, present plans and future perspectives. *Current Molecular Medicine* 3: 303-312.
23. Society for Adolescent Medicine. (2003). A position paper of the society for adolescent medicine: Guidelines for adolescent health research. *Journal of Adolescent Health* 33:396-409.
24. Stanford, P.D, Monte, D.A, Briggs, F.M, Flynn, P.M, Tanney, M. (2003). Recruitment and retention of adolescent participants in HIV research: Findings from the REACH (reaching for excellence in adolescent care and health) project trials in children? *Journal of Adolescent Health* 32: 192-203, 2003.
25. Van Wyk, C. (2004). Clinical trials, medical research and cloning in South Africa. *Journal of Contemporary Roman Dutch Law* 67:1-21
26. Van Wyk, C. (2005). HIV preventative vaccine research on children: Is this in terms of South African law and reform guidelines. Unpublished work. *Journal of Contemporary Roman Dutch Law*
27. Weijer, C. (2000). The ethical analysis of risk. *Journal of Law, Medicines and Ethics* 28:344-361.