Ethical issues in research with human volunteers: Preventive HIV Vaccine Trials

MRC KZN AIDS Forum

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SOUTH AFRICAN AIDS VACCINE INITIATIVE

Aims & objectives

- To present ethical principles & requirements for health research with human volunteers
- To discuss their application to trials of preventive HIV vaccines in South Africa
- To create a discussion forum

SAAVI

- South African AIDS Vaccine Initiative (SAAVI):
  - To develop safe affordable and locally relevant HIV vaccines and to coordinate this process
- Main focus activities of SAAVI are:
  - Candidate vaccine development
  - Vaccine evaluation and immunology
  - Clinical trials
  - Education, human rights & mobilization
  - Ethics research and training

See SAJS (2000) Vol 96, 318 - 351

Clinical trials of HIV vaccines

- Pre-clinical tests: Is this vaccine safe? promising?
- Phase 1: Is this vaccine safe in humans?

  (18 months; smaller numbers of participants at lower risk of HIV)
- Phase 2: Does this vaccine produce the desired immune responses?

  (24 months; larger numbers)
- Phase 3: Is this vaccine effective? Does it prevent HIV infection or disease progression ?

  (36 months +; with large numbers of participants at higher risk of HIV infection)
- Randomized, placebo controlled, double blinded

What is the role of ethics in research with human subjects?

- The objective of clinical research:
  - To develop generalizable knowledge to improve health and/ or increase the understanding of human biology
  - The aims of research are a recognized good, but research has the potential to treat participants as just "means to an end"
- The aim of ethics is:
  - To ensure that participants are treated with dignity and respect
  - While they contribute to the social good

What is the role of ethics in research? cont'd

- Ethics aims to:
  - Protect participants from harm
  - To promote their welfare
  - acts to restrain science

- However, ethics also promotes good science as participants who feel respected may:
  - Follow research requests
  - Answer truthfully
  - Return for follow up
  - Therefore increasing the quality of the data

What are the key principles in research ethics?

- NON-MALEFICENCE: “Do no harm”:
  - There should be no intentional injury or harm to participants as a result of participation
- BENEFICENCE:
  - Minimize potential harms & maximize expected benefits of the research (Certain research bears no direct benefit for the participant, but benefits to society)
- RESPECT FOR AUTONOMY: “Self-rule”:
  - Respect freedom of thought & action
  - Take special measures to protect the vulnerable or those with no capacity to choose

What are the key principles in research ethics cont'd?

- JUSTICE: Fair balance of risks and benefits

- Those who stand to benefit from research must contribute to its risks and discomforts
  - No group of persons should bear more than their fair share of the *burdens* of research; No group should be asked to bear research risks so that other groups enjoy benefits (knowledge/ products)
  - No group should be deprived of fair access to the *benefits* of research; No group should be unfairly excluded from research, as this denies them relevant knowledge/ health interventions

What makes research ethical?

The requirements for ethical research:

1 Social value
2 Scientific validity
3 Fair selection of participants
4 Favorable risk – benefit ratio
5 Independent review
6 Adequate informed consent
7 Ongoing respect for dignity (confidentiality)
8 (Community participation)

Emanuel, Z, Wendler, D and Grady, C (2000) "What makes clinical research ethical?" JAMA, 283, 2701 – 2711

What makes research ethical? 1. Social value & 2. Validity

1. Social value: Society should gain important generalizable knowledge

2. Validity: Research must also be well designed and conducted

3. Why? Research that is of no benefit to society or is poorly designed & conducted exposes subjects to risks and inconvenience for no purpose

What makes research ethical? 3. Fair choice of participants

- Participants should be chosen for participation fairly:
- 1) Selection should be based on scientific goals
  - not convenience or vulnerability

- Eligibility criteria for HIV vaccine trials

- Complexities:
  - Later efficacy trials of HIV vaccines, eligibility to participate includes *higher risk of HIV infection*
  - High risk may be linked to vulnerability; due to a range of factors (e.g. limited access to health care, socially stigmatized activities etc)

What makes research ethical? 3. Fair choice of participants

- Obligations of investigators:
  - To justify why vulnerable groups are involved; and what safeguards will be take to offset specified vulnerabilities
- 2) Individuals and commuities should be chosen so that burdens and benefits are fairly distributed:
  - The burdens of HIV vaccine research should be distributed fairly among various populations
  - Those who bear the burdens should access the benefits:
    - Early trials = knowledge; later trials = products
    - SAAVI: Access; negotiated price controls

What makes research ethical? 4. Favorable risk- benefit ratio

- The potential risks to individual participants must be identified and minimized
- The potential benefits of the research must be identified and maximized
- The potential risks to individual subjects should be *outweighed* by the benefits to the individual or society
- “Favorable risk-benefit ratio”

What makes research ethical? 4. Favorable risk-benefit ratio

- What are some of the potential risks of HIV vaccine trial participation?:
  - Physical side effects
  - False sense of security and possible increased risk behaviour
  - Trial related stigma
  - Exclusion from other HIV vaccine trials

Allen, M et al (2002). Trial related discrimination in HIV vaccine clinical trials. AIDS research and human retroviruses, 17, 667-674

What makes research ethical? 4. Favorable risk-benefit ratio

- Vaccine induced sero-positivity:
  - It is hoped that candidate vaccines will induce an immune response in volunteers, including the production of antibodies against HIV
  - A “positive” response could be produced from a standard HIV test that only looks for antibodies against HIV. *This will only happen if the test seeks antibodies for the same proteins found in the HIV vaccine*
  - Potential for negative consequences

What makes research ethical? 4. Favorable risk-benefit ratio

- What are risk minimization measures that should be undertaken?:
  - –Ongoing monitoring for effects
  - –Risk reduction counselling (optimal)
  - –Counselling around negative consequences (e.g. stigma) of disclosure
  - –Provision of support counselling
  - –Differential testing: antibody response and natural infection; ID card; psycho-legal support; advocacy

Grady, C (1994). HIV preventive vaccine research: Selected ethical issues. Jnl of Medicine & Philosophy, 19, 595 – 612;

Chesney, M et al., Strategies for addressing social & behavioural challenges in HIV vaccine trials. Jnl of Acquired Immune Deficiency Syndrome & Hum Retrovir 9, 30– 35.

What makes research ethical? 4. Favorable risk-benefit ratio

- What are expected benefits of HIV vaccine trials?:
  - Determining safety, immunogenicity, or efficacy of candidate HIV vaccines for South Africa
  - Access to counselling and interventions to reduce risk of HIV infection
  - Access to medical monitoring and care

What makes research ethical? 4. Favorable risk-benefit ratio

- The potential risks to individual subjects should be outweighed by the benefits to the individual or society:

- Who decides this?
  - Research ethics committees at every participating institution
  - Participating communities via establishment of representative participatory structures
  - Each and every individual via informed consent

Debate: Minimizing risk of HIV infection

- What complexities exist in phase III efficacy trials for risk reduction?:
  - Phase III trials aim to assess if vaccines can prevent HIV infection, by comparing rates of infection in vaccinated and non-vaccinated groups
  - Determinations of efficacy rest on the exposure of a proportion of participants to HIV
  - Simultaneously, researchers have to minimize potential harms and provide participants with risk reduction counselling. This should be optimal
  - Potential conflict of interest?

Ijsselmuiden, CB (1995) Ethical aspects of HIV vaccine research. AIDS Bulletin, 4, 13-16

Debate: Maximizing benefits: Access to treatment

- In all phases of HIV vaccine trials some participants may become infected with HIV, despite risk reduction measures:

- Ensuring access to treatment:
  - –Are investigators and sponsors obligated to ensure access to treatment for volunteers who become HIV infected?
  - –At what level e.g. access to Antiretroviral Treatment (ART) ?

Guenter, Esparza & Macklin (2000). Ethical considerations in international HIV vaccine trials: Summary of a consultative process conducted by UNAIDS. Jnl of Medical Ethics, 26, 37-43,

Debate: Maximizing benefits: Access to treatment cont'd

Arguments:

- Potential for distorted belief in efficacy of the experimental vaccine ("therapeutic misconception") false sense of security & "behavioural disinhibition"
- Favourable balance of risks and benefits
- Justice considerations: Equity for participants from sponsor and host countries; obligations to proactively reduce inequities in health care

Schüklenk, U. (2000). Protecting the vulnerable: testing times for clinical research ethics. *Social Science and Medicine*, 51, 969-977. Schuklenk U, Ashcroft RE. International Research Ethics. *Bioethics* 2000; 14: 158-172; Reider Lie (1998). Ethical issues in clinical trial collaborations with developing countries with special reference to preventive HIV vaccine trials with secondary endpoints. http://www.ethica.uib.no/who.pdf ; Harris, J (1998) 'Ethical Implications of Phase III Clinical Trials of HIV Vaccines: Justice issues : burdens, benefits and availability' Working Paper for UNAIDS. Geneva: UNAIDS

Debate: Maximizing benefits: Access to treatment cont'd

- Best proven or "highest attainable"
- Considerations
  - Undue inducement
  - Research related inequities in health care

Benatar, S & Singer, P. (2001). A new look at international research ethics. *BMJ, 321*, 824-826.

London, AJ. (2001). Equipoise and international human subjects research. *Bioethics*, 15 (4), 313-332. Also Bloom, B (1998) The highest attainable standard: Ethical issues in AIDS vaccines. Science, 297, 186-188

What makes research ethical? 5. Independent review

- Researchers operate at the interface of multiple obligations and interests:
  - Undertake research, acquire funding, further careers, protect human subjects
  - Can potentially bias how researchers perceive their research designs and conduct research
  - Therefore review by committee “at arms length”
  - To ensure that participants are protected and welfare promoted (1, 2, 3, 4, 6, 7)

What makes research ethical?
6. Informed consent

- Informed consent:
  - The right to choose freely whether or not to participate based on an understanding of all relevant information
  - Ensures that participants will only take part if the research is consistent with their interests, values and preferences (autonomy)
- See Emmanuel, Z, Wendler, D and Grady, C (2000) "What makes clinical research ethical?" JAMA, 283, 2701 – 2711

What makes research ethical? 6. Informed consent cont'd

Components:

- 1 Disclosure of information
- 2 Comprehension or understanding
- 3 Voluntariness or freedom
- 4 Capacity to consent
- 5 Explicit formal consent

In HIV vaccine trials, consent is also staged:

- Screening
- Enrollment
- HIV testing

What makes research ethical? 6. Informed consent cont'd

- 1 Information
- Participants must be informed of the following:
  - Aims, duration
  - Methods (e.g. randomization, placebo, blinding)
  - Practical aspects (VCT, tests, visits etc)
  - Potential risks (e.g. trial related stigma)
  - Expected benefits (e.g. counselling)
  - Right to withdraw
  - Confidentiality (and limits if any)
  - Personal implications

What makes research ethical? 6. Informed consent cont'd

- What complexities exist?
  - Transmission of complex information, compounded by language differences, translation
  - Information transmission typically viewed as a one way process
  - Determinations of "what" must be transmitted?

See Lindegger, G & Richter, L (2000) HIV vaccine trials: Critical issues in informed consent. SAJS, 96, 313-318

What makes research ethical? 6. Informed consent cont'd

- 2 Comprehension
  - Disclosure is not sufficient
  - Understanding must be ensured and tested
- What complexities exist?
  - Social desirability: Tendency to act to avoid disapproval - impacts on reported understanding
  - Over-emphasis on understanding of technical aspects (e.g. placebo)
  - Understanding of personal implications ?
  - "Tests of understanding": May emphasize technical aspects, may rely on ST memory

What makes research ethical? 6. Informed consent cont'd

- Researchers and counsellors can enhance comprehension by:
  - Creating an optimal environment for decision making ("consent counselling")
  - Ensuring use of counsellors with "values match" to potential participants
  - Encouraging dialogue; discussion with family
  - Allowing time to reflect
  - Sensitivity to process aspects of counselling (e.g. social desirability, non-verbal cues)
  - Multiple methods of assessing comprehension

What makes research ethical? 6. Informed consent cont'd

- 3 Voluntariness

- Participants must be free to choose whether or not to participate:
  - Free of coercion (threat of negative sanction)
  - Undue influence (incentives that are so large that cause prospective participants:
    - To expose themselves to risks they would otherwise consider unacceptable; or
    - To ignore or devalue concerns about risks
- Complexities? Vulnerability of potential participants

What makes research ethical? 6. Informed consent cont'd

- Researchers can promote participant's freedom by:
  - Adequate assessment of specific vulnerability factors
  - Commitment to offsetting these, e.g:
    - Education to offset lack of familiarity with research
    - Avoiding excessive payment to offset impoverishment
  - Providing participants with ways to voice concerns and monitor the impact of participation
    - CABs; trial site counsellors

Debate: Informed consent & culture

- Is it appropriate to secure first person informed consent (IC) in some cultural contexts?
  - –Can legitimate parties (husbands/ traditional leaders) give proxy consent?
- First person IC = best safeguard against exploitation
  - –Therefore substantive principle must apply
- Demonstrate respect for multi-person involvement
  - –In procedural implementation of consent
    - •Endorsement of community leader to enter community;
    - •Respect participant's choice to involve others

Ijsselumuiden, C & Faden, R (1992). Research and informed consent in Africa: Another look. N Engl Jnl Med, 326, 830-834, Also Lindegger & Richter (2000) SAJS, 96, 313-8

What makes research ethical? 7. Respect for dignity

- Once enrolled, researchers should respect the dignity of participants in an ongoing manner by:

  –Respecting their right to withdraw at any time (consent is “revocable”)

  –Monitoring their welfare throughout the research (ongoing “social harm” monitoring)

  –Informing volunteers of research results

  –Respecting confidentiality of freely volunteered data

  Allen, M et al (2002). Trial related discrimination in HIV vaccine clinical trials. AIDS research and human retroviruses, 17, 667-674

What makes research ethical? 8. Community participation

- Why community participation?
  - Right and responsibility to participate in HIV vaccine development activities
  - Can offset potential vulnerabilities
- What are the mechanisms?
  - Include the formation of a Community Advisory Board (CAB)
- What possible roles?
  - Includes inputs to design (e.g. IC)
  - Advising on cultural conventions, expectations;
  - Evaluating impact of the research

Community participation cont'd

- What are the benefits of community participation?
  - Enhanced cultural appropriateness
  - Increased acceptability of the research to the participating community
  - Fairness regarding important decisions (e.g. adequate incentives)
  - Sound bi-directional information exchange
- In preparation for HIV vaccine trials in South Africa community structures are being formed at sites

Community participation cont'd

- What are the complexities?
  - Defining community: which stakeholders and interest groups must be represented?
  - Difficulties in ensuring representation of such groups
  - Defining "participation" (Recipients of education full and equal partners)
  - Determining what "participation point" on the research continuum? (Protocol development dissemination of results)

Summary: Ethical issues in HIV vaccine research

- The ethical considerations in HIV vaccine research apply to other research with human subjects, especially:
  - International collaborative research
  - HIV prevention research
  - Research with potentially vulnerable participants
- Complex risk-benefit determinations & potentially vulnerable participants require careful review, involved comunities and sound consent procedures

HIV AIDS Vaccines Ethics Group

- To raise awareness and build the ethical capacity of various stakeholders
- To research ethical aspects of clinical trials, with specific attention to informed consent
- To co-ordinate the development of ethical guidelines in collaboration with national ethics structures
- To examine behavioural aspects of HIV vaccine trials
- To support ethical trials in Africa through the African AIDS Vaccine Program

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