HIV Clinical trials: ethics, human rights and social challenges

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Acknowledgement

- This presentation is based partly on that on research ethics which was originally prepared by Ms C. Slack of the HIV AIDS Vaccines Ethics Group at University of KwaZulu-Natal, Pietermaritzburg and was used for training of fieldworkers during the Nelson Mandela/HSRC Study of HIV/AIDS: *South African National HIV Prevalence, Behavioural Risks and Mass Media Household Survey* in 2002. Her e-mail address is slackca@ukzn.ac.za

- Ms Slack's original presentation was largely based on the following article:

  - Emmanuel, Z., Wendler, D., & Grady, C. (2000). What makes clinical research ethical. *Journal of the American Medical Association,* 283, 2701 – 2711.

- Another useful resource that was used in preparing this presentation is:

  - Department of Health (2000). *Ethical Considerations for HIV and AIDS Clinical and Epidemiological Research.* HIV and AIDS/STD Directorate, Department of Health, Pretoria.

Outline of presentation

- What is the role of ethics in research with human subjects?
- Why is there a need for research ethics?
- What are the key principles in research ethics?
- What makes research ethical?
- Ethical challenges in clinical trials
- Conclusions

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

- Research aims to develop knowledge
- Aims of research are a recognized good, but are not superior to the welfare of humans who participate
- Participants should not be used as just "means to an end"; they have dignity
- Research participants should be protected from exploitation / harm and their welfare should be promoted
- Ethics provide a framework to do this

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What is the role of ethics in research? (contd)

- Ethics promote the rights and welfare of participants in research
- Ethics also promote good science as participants who feel respected may:
  - Follow research requests
  - Answer truthfully
  - Return for follow up
  - Therefore, increasing the quality of the data

Why is there a need for research ethics?

- History of abusive research on Jews by Nazi doctors in World War II and African-Americans by the USA research establishment in the Tuskegee Syphilis study

- Led to first code of ethics such as the 1947 Nuremberg Code, the 1964/2000 World Medical Association's Declaration of Helsinki and the USA's 1979 Belmont Report *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* which highlighted the need to protect research subjects from risks, harm and exploitation

- There have been several codes since then that describe how researchers should respect the dignity and welfare of human subjects

What are the key principles in research ethics?

1. Avoid harm to volunteers (non-maleficence)
2. Promote the welfare of volunteers (beneficence)
3. Respect volunteers' freedom of choice (autonomy: "self – rule")
4. Promote fairness (justice)

Key principles in research ethics (contd)

1. **Non-maleficence**: Do no harm

- **There should be no injury or harm to participants as a result of participation**
- **Researchers cannot intentionally harm participants**
- **Researchers also have to consider harms that could result unintentionally**

Key principles in research ethics (contd)

2. Beneficence: Do good

- Researchers should take active and positive steps to maximize the possible benefits for research participants
- Researchers should take active steps to reduce possible harms to a minimum
- Sometimes benefits are for society or future generations

Key principles in research ethics (contd)

3. Respect for individual autonomy: "self-rule"

- A person's freedom of thought and action should be respected
- Researchers must respect rights of participants who can make decisions to do so
- Researchers must take special measures to protect vulnerable participants whose freedom to make choices is limited, or those with no capacity to choose

Key principles in research ethics (contd)

4. **Justice**: persons should receive what is owed them

- **There should be a balance of risks and benefits**
- **Those who carry the risks should have access to the benefits (and visa versa)**
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- **Researchers must make sure that research participants do not carry risks without a proportionate share of the benefits**

Ethical principles in context: The role of culture

- Ethical principles govern the activity of research, regardless of where it occurs (Queens in New York or Soweto in South Africa or Matero in Lusaka)
- Ethical principles are therefore universal
- But they must be applied in a manner that takes into account the context (social or cultural factors)
  - For example, some people have argued that in some cultures husbands and traditional leaders can give substitute consent for others (e.g. women).

Ethical principles in context: The role of culture (contd)

- However, this might lead to exploitation

- Researchers should therefore always get first person informed consent from the individual

- They should do this in a sensitive way that allows the person to involve others if they wish to do so

Ethical principles in context: The role of culture (contd)

- Richter et al. (1999) developed a very useful practical guide for obtaining both informed consent and recruitment for participation by community members which is culturally sensitive.

- The guideline takes into account the differences between those who are from collectivistic societies found in developing countries especially in Africa and those which are more individualistic in orientations which are found in the developed world.

Ethical principles in context: The role of culture (contd)

- Participants are active rather than passive and use of research counsellors as well as support/advocacy counsellors to help with both informed consent and recruitment.

- The Community Advisory Board is a critical element of the process as it represents the interests of the community and advise the research team on cultural matters and local issues.
  - It also helps with among others preparation of the informed consent form and also advise on appropriate incentives for participants.

What makes research ethical?

- The requirements for ethical research:
  - The research has social value
  - It is properly designed and conducted
  - The participants/site/community are chosen fairly (justice)
  - The risk – benefit ratio is favourable (beneficence)
  - The research has been reviewed
  - Adequate informed consent is secured (autonomy)
  - There is respect for the dignity of participants (e.g. confidentiality)

Ethical challenges in HIV clinical trials

- **Appropriateness to host country's health needs must be ascertained by both local ethics committees and communities in which the trials are conducted.**
- **Good research and ethical standards be applied equally in vulnerable and non-vulnerable communities.**
- **Researchers must ensure that patients in trials provide informed consent and understand the implications of the trial rather than merely seeing the project as a way to access to HIV-related medication especially when treatment is not widely available.**

Ethical challenges in HIV clinical trials (Contd)

- **The use of placebos after an intervention has been shown to be effective is unethical even in poor countries.**
  - **Any treatment offered should conform at least to the local standard of care.**
    - **For example, if an HIV prevention intervention has been shown to effectively reduce HIV transmission it should not be withheld from research subjects. All subjects must be given information and the means to prevent HIV transmission by means of practising safer sex and effective treatment for sexually transmitted diseases.**
- **Any adverse drug effects experienced as a result of participating in the trial should be managed at no cost to participants and/or referred to appropriate health services.**

Ethical challenges in HIV clinical trials (Contd)

- **Similarly patients who withdraw from trials should be advised about ongoing management of their condition especially through provision of the local standard of care.**

- **When patients who participate in HIV trials have no alternative access to drug therapy after a therapeutic response or after the completion of clinical trials, continued access to study medications should be considered.**

Ethical challenges in HIV clinical trials (Contd)

- **HIV testing as part of a trial is a complex issue with important implications and consequences to the individual. In particular, informing a person that they are HIV positive impacts on their quality of life and should be considered to be a major intervention.**

- **Therefore, the advantages and disadvantages of HIV testing should be carefully considered and included in informed consent forms.**

Ethical challenges in HIV clinical trials (Contd)

- **Informed consent may be difficult to achieve, especially when engaging people from disadvantaged and vulnerable communities where literacy and education opportunities are inadequate and where there are language barriers.**

- **Incentives should not be so excessive so as unfairly influence the patients to submit themselves to the trial. Incentives such as financial, transport, and food should be fair and reasonable without "making the patient an offer they cannot refuse" and thereby influence the patient to overlook other important consideration.**

Ethical challenges in HIV clinical trials (Contd)

- **Pharmaceutical companies doing research on their products frequently offer researchers incentives and the researchers should guard against these 'incentives' promoting excessive allegiance with a pharmaceutical company, which may adversely affect their objectivity and neutrality.**

- **Researchers and members of ethical committees should disclose their financial interests relating to proposed research projects**

Ethical challenges in HIV clinical trials (Contd)

In order not to create unrealistic or misleading expectations the following must be carefully considered:

- **Researchers should not communicate the results of clinical trials to the public without first subjecting the study to peer review and to the normal rigorous scientific scrutiny needed for therapeutic and vaccine trials.**

- **Phase I and II trials should be published in scientifically refereed journals or presented to scientific forums where the results can be openly viewed and scrutinised.**

Ethical challenges in HIV clinical trials (Contd)

- These results should not be released to the mass media before peer review because they may be misinterpreted, misunderstood, sensationalised and result in serious public misunderstanding.

- Important findings, which need to be urgently released, should be done via the 'fast track' system employed by most reputable scientific journals.

  - Most medical journals have now developed this system to fast track review and publish important research findings.

Ethical challenges in HIV clinical trials (Contd)

- **Some of the important ethical considerations in HIV vaccine research include:**
  - **The implications of wide spread HIV testing on high-risk populations;**
  - **The impact of local HIV prevention initiatives on research outcomes;**
  - **The possible influence of the vaccine candidates to offer a disincentive for people to take necessary precautions to prevent HIV transmission.**
  - **The implications of 'false positive' HIV tests in patients who agree to vaccine trials; and,**
  - **The appropriateness of the vaccine clade to the local population.**

Conclusions

- **Ethics promote the rights and welfare of participants in research including in clinical trials which involve complex research designs and science that most vulnerable communities do not understand.**

- **Ways need to be found to involve the communities at all stages of conducting a clinical trial to ensure that participation is not coerced and also takes into account their culture where appropriate.**

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Resource documents

- **Other two useful resources are:**

  - **Richter,L.M., Lindegger, G.C., Abdool Karim, Q. & Gasa, N. (1999). *Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials. Discussion document.* Report commissioned by UNAIDS. School of Psychology, University of (KwaZulu-)Natal, South Africa.**

  - **Patterson, D. (2000). *Resolving legal, ethical and human rights challenges in HIV vaccine research. A discussion paper.* Prepared for Putting Third First –Critical Legal Issues and HIV/AIDS.A satellite meeting by the Canadian HIV/AIDS Legal Network and the AIDS Law Project, South Africa and co-hosted by UNAIDS. Durban, South Africa, 7 July 2000.**