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Science at the heart of medicine

Post-trial Access to Beneficial Products of Research

An ethical obligation

Ruth Macklin, PhD

Distributive Justice

- "Distributive justice" requires a fair distribution of the benefits and burdens of research.
  - Risks of research should not be borne by groups or populations that will not receive the benefits of the research.
  - Those who share in the benefits of research should also share in the risks.

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International research ethics guidelines

- World Medical Association. *Declaration of Helsinki* (2000-2008)
  - > Currently under revision (again)
- CIOMS *International Guidelines for Biomedical Research Involving Human Subjects* (2002)
  - > Currently under revision (again)
- UNAIDS/WHO *Ethical Considerations in Biomedical HIV Prevention Trials* (2007)

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2008 Declaration of Helsinki: Study Participants

- At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits (Para. 33)
  - No clear obligation to provide beneficial interventions
  - What other care is appropriate?
  - What other benefits are appropriate?
  - Who is under an obligation to share the benefits?
  - Who should decide?

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Proposed New DoH Paragaph on Post-trial Access: Study Participants

- In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the study. This information should also be disclosed to participants during the informed consent process. All study participants should be informed about the outcome of the study.

2008 Declaration of Helsinki: Population or Community

- Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
    - No mention of who has responsibility to provide benefits to the population
    - Limited to disadvantaged or vulnerable populations
    - Which populations are vulnerable?

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Proposed New DoH Paragaph on Post-trial Access: Population or Community

- Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and the research cannot be carried out in a non-vulnerable population. In addition, this population or community should stand to benefit from the knowledge, practices or interventions that result from the research.
- Consideration should also be given to ensuring that the community receives a fair level of additional benefits.

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CIOMS: post-trial obligations to population

- CIOMS 2002 Guideline 10
  - > Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that:
    - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
    - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

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Responsiveness

- CIOMS Commentary on Guideline 10
  - It is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population
    - Responsiveness is thus tied to "reasonable availability" of products developed or knowledge generated

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US Code of Federal Regulations

- Says nothing about post-trial obligations to research subjects or to the community or country where research is conducted

Code of Federal Regulations

- **TITLE 45**
  PUBLIC WELFARE

> **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

- **PART 46**
  PROTECTION OF HUMAN SUBJECTS
- **Revised January 15, 2009**
  Effective July 14, 2009

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UNAIDS/WHO Ethics Guidance Document for Biomedical HIV Prevention Trials

- …trial sponsors and countries should agree on responsibilities and plans to make available as soon as possible any biomedical HIV preventive intervention demonstrated to be safe and effective…to all participants in the trials in which it was tested, as well as to other populations at higher risk of HIV exposure in the country.
  - Identifies the responsible agents
  - Requires a process of negotiation
  - Addresses both the research participants and the population where the trial is conducted
  - What if these parties don't agree?

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Criticisms

- Numerous criticisms in the bioethics literature of the "responsiveness" requirement
  - Critiques range over views that the requirement is
    - Unnecessary
    - Too burdensome
    - Impossible to fulfill
    - It has some merit but is too vague to understand how to implement it

Requirement Unnecessary

- Objection
  - As long as an investigation is carried out in compliance with the basic rules requiring a favorable benefit-risk ratio, properly obtained informed consent, and other protections of the rights and welfare of human subjects, there is no further need to ensure responsiveness to the health needs in the place where the research is being conducted.
- Reply
  - This is a minimalist view of ethics. “What was good enough in the past is good enough in the present and future.”

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Too burdensome

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Too burdensome

- Objection
  - If “responsiveness” requires sponsors of research to provide or pay for success products of research in developing countries
    - It is unrealistic to impose this financial burden
  - If “responsiveness” requires host country governments to provide successful products after a trial is completed
    - They will be unable to afford it
- Reply
  - No single institution, organization, or government should be responsible for fulfilling the requirement
  - Shared responsibility is necessary

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Precludes rare disease research

- Objection
  - Responsiveness requirement refers to “health needs and priorities” of developing countries. But a country may have a small number of people suffering from a rare disease, which would then not be a “health priority” because of its rarity.
- Reply
  - The number of people suffering from a disease is only one way of determining health priorities. A health priority may also stem from the severity of a disease, its disabling or stigmatizing features. These may be other reasons a country may invoke to determine priority.
    - Examples: lymphatic filariasis, guinea worm disease

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Guinea worm disease

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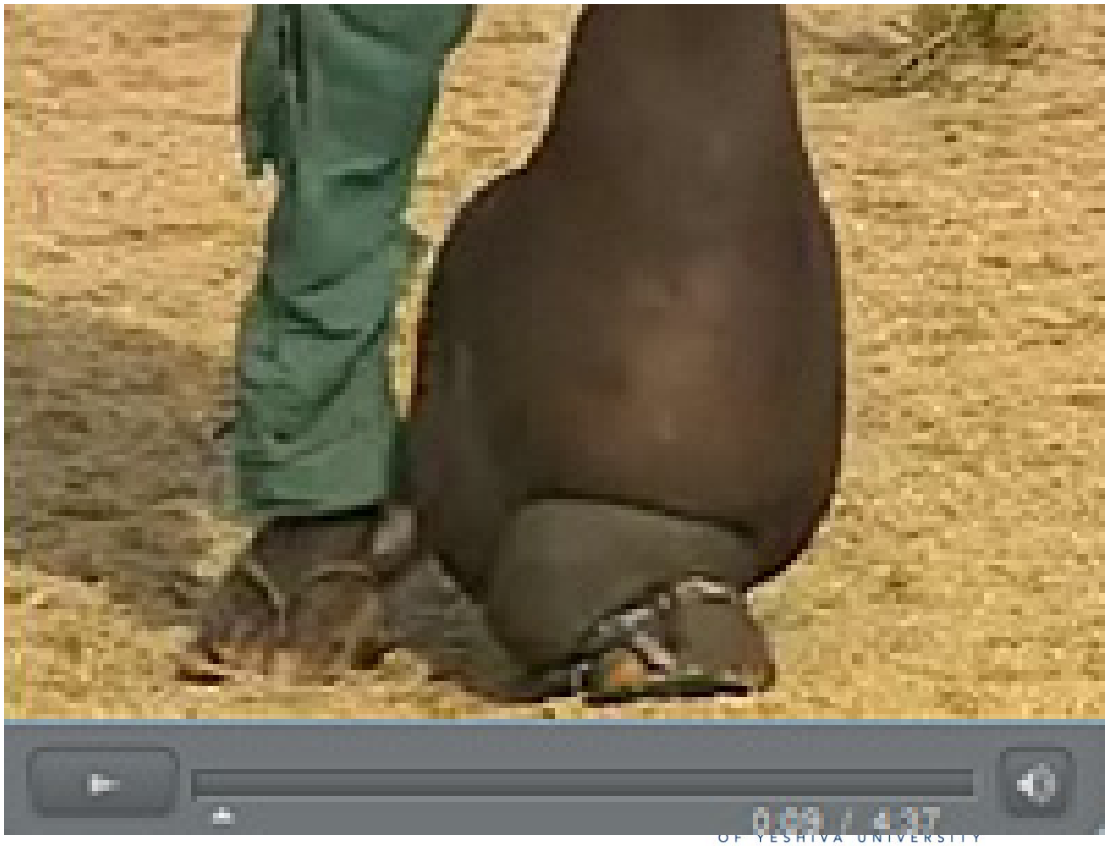
Lymphatic filariasis



Free riders

“Free rider” problem

- Objection
  - The responsiveness requirement does not have legal enforceability.
    - Therefore, the requirement could privilege those communities who choose not to abide by it and penalize those who hold fast by refusing to host unresponsive research
  - Reply
    - Most international ethical guidance lacks legal enforceability. The requirement imposes a *moral* obligation on sponsors regarding what research to conduct and where to conduct it.

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Requirement insufficient

Objection

- Responsiveness alone cannot systematically prevent exploitation of developing countries, promote their interests and preferences, and meet their most pressing and unmet health needs.

Reply

- This is obviously true. It shows only that the responsiveness requirement is not an *ethically sufficient* condition for multinational research. It does not show that the requirement is not *ethically necessary*.

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Early phases of research

- Objection
  - The early phases of research do not yield a product. Therefore, the “reasonable availability” requirement is inapplicable.
- Reply
  - This simply underscores the importance of the “responsiveness” requirement. When early phases of research are conducted in developing countries, they must be responsive to the health needs of the population as a precursor to later research that may yield successful products.

Conclusions

- Existing international ethics guidelines vary in strength of requirement for post-trial access
- Controversy exists regarding who has responsibility to ensure access
- Justice in global health requires collaboration among all stakeholders
- Ensuring access to the products of successful research is a human rights obligation

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Human Rights

- 1. The States Parties to the present Covenant recognize the right of everyone:
  - (b) To enjoy the benefits of scientific progress and its applications
    - Article 15
    - International Covenant on Economic, Social and Cultural Rights

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- Thank you!!!

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