Ethical Issues in International Research

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Ethical Issues

- Determination of Standard of Care
  - Are placebo trials ethical if existing therapy exist?

- Obtaining valid informed consent
  - Illiteracy/Poverty/Lack of access to basic medicines

- Exploitation
  - Who Owes What to Whom
  - How to do research in an unjust world

- Beneficence

- Autonomy

- Justice
Study Design 101

- Experimental Drug (A1) vs. Control Group

- Control Group: Standard of Care (Drug B1) Exists
  - A1 vs. B1

- Control Group: Standard of Care: No Drug
  - A1 vs. Placebo
The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best proven current methods, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no proven current method exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of a method and the patients who receive placebo or no treatment will not be subject to any additional risk of serious or irreversible harm.

Existing therapy exists
AZT Placebo Trial
Background

- Problem: Maternal–fetal transmission of HIV
- Prevention Strategy with drugs
- Clinical trials of Zidovudine (AZT)
  - Prenatal treatment of the mother:
    - oral 16–24 weeks prior to birth
    - Intravenous during labor
  - Oral dosing of newborns for 6 weeks
  - No breastfeeding
- Decreased HIV transmission by 2/3
  - 25.5% to 8.3%
- Long course AZT is the new standard of care
More women infected with HIV in Africa than any other continent in the world

Life-saving potential of AZT would be enormous

Cost of a single treatment of AZT far exceeds the average per capita expenditure on health care

Concern with feasibility of administration
  - Lack of pre-natal services
  - Lack of medical infrastructure to give AZT intravenously
Current Proposed Study

- Short-course AZT trial
  - Develop an affordable and effective treatment
  - Investigators from 11 developing countries and UNAIDS, WHO, CDC and NIH
  - African Country

- Study Design
  - Randomized, controlled, double-blind trial
  - short-course AZT intervention vs. control group

Experimental Therapy
What are the Ethical Issues?

What intervention should be given to those in the control group?

- Placebo?
- Long course AZT?
Standards of Care

- There is an international debate about what “standard of care” should be provided to a control group in research:
  - **Universal** (the best current proven intervention anywhere in the world)
  - **Non-universal** (the treatment available in a defined region or community)
Wherever appropriate, a universal standard of care should be offered to the control group.

Where this is not appropriate, then the best *attainable* standard of care.

At a minimum, the best treatment provided by the national public health system?

Do wealthier countries have an obligation to provide needed medicines to the less fortunate countries?
Informed Consent
Informed Consent: Why is it so Important?

Autonomy:
- Informed consent is giving people the opportunity to decide what will and will not happen to them (Respect for persons).

Protection Mechanism
- Subjects need to know what they are getting themselves into (Research can be risky).
The CIOMS Guidelines have defined informed consent as consent given by a competent individual who:

- **Decision-Making Capacity**
  - Understanding
  - Reasoning
  - Expression of a Choice

- **Information**
- **Voluntary**
Voluntary

- Lack of coercion or coercive setting
  - Saying no will result or is perceived to result in a worst-off situation

- Undue Inducement
  - Monetary or material (e.g., drug) incentive will cause individual to make a decision that he or she would not ordinarily make

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Exploitation

“An exploitative transaction is one in which A takes unfair advantage of B.” Wertheimer, Exploitation. 1999.

Raised as a concern when enrolling vulnerable populations/country into a clinical trial sponsored by international pharmaceutical company.
**Exploitation – two thoughts**

- “use” of someone else for one’s own benefit
  - To exploit a person involves the harmful, merely instrumental utilization of him or his capacities, for one’s own advantage or for the sake of one’s own ends.

- unfair level of benefits of an individual exchange (transaction):
  - Towing Truck Example.
Medical research involving a disadvantaged or vulnerable population or community is only justified if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
As a general rule, the sponsoring agency should agree that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begin.
In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community.
Some problems with Reasonable Availability

- Drug may not be approved by regulatory authorities after some time of the study
- May be necessary to do an additional trial
- Questions about on-going interventions for chronic conditions
- Possibly of interest to continue long term follow up
  - Vaccine study for example, duration of protection
  - Level of viral load in HIV vaccine study
- Phase I and Phase II trials
Fair Benefits Approach (FBA) not Reasonable Availability

- Exploitation is about ‘how much’, not ‘what’
- Community may benefit from general improvements in healthcare and facilities as a result of research
- Sponsors rarely able to make open-ended commitments, but can assist in capacity-building, giving potential for a sustained improvement
FBA Procedural Framework

- Research should have social value
- Subjects should be selected fairly
- Favorable risks–benefits ratio
- Availability of the intervention, if proven effective and relevant
- Capacity development
- Free, uncoerced decisionmaking
  - Can refuse participation
- Transparency in decision making
  - Provide an external check that independently assesses the fairness of agreements
Fair Benefits Approach

- There is no normative principles or account of fair distribution that is applicable to the international research context.
- Rely on procedural approach
A company plans to do Phase I safety study on healthy subjects for a drug designed to reduce the damage from severe frostbite. This study will only assess safety and involves only giving the drug to subjects.

Animal and toxicological studies indicate that the drug has no serious side-effects. The researchers want to work in Sudan because it is far less expensive to run a Phase I study there than in any Western country. Also, in past studies, they have found it easy to recruit and retain subjects in rural areas.

They will offer subjects compensation for any injury that might occur as well as payment that is generous but not extravagant by local standards.

In addition, the company has committed itself to funding a network of badly-needed local health clinics in the areas from which subjects are recruited.
Problems of FBA

- A vulnerable party is forced by unjust social circumstances to transact in order to access “basic goods” while the other party is transacting primarily for economic gain.
- A serious moral asymmetry
- Rawls’ Fairness Approach
  - distribute benefits in a manner that is to the greatest advantage of the worst-off party to the transaction.
Mutually advantageous exploitation

- Treats the victim unfairly but leaves the victim better off than in the absence of the exploitative transaction
- Does not receive fair share of surplus value of the transaction
  - Tow-truck example
- Consent does not prevent exploitation, as vulnerable parties will typically consent to an unfair distribution of benefits so long as the transaction represents the best available option
Justice in the Application of Science

- London, AJ
  - Procedural version of the FBA will lead to highly unequal distributions of the benefits of international research because there is significant imbalance in power between the parties.
  - “transparency” principle does not do the necessary work, as there is no standard to assess outcomes.
  - Any FBA treats research as a commodity to be allocated by market mechanisms and hence, the central issues of fairness hinges on whether bargainers can arrive at fair agreements.
  - Assumption: market transactions devoid of fraud, deception, force, or imperfect information
Research at the Auction Block

Problems for the Fair Benefits Approach to International Research
What is Fair?

- If the **amount** of benefit and not the **kind** of benefit is what matters, then there is no reason to require research to focus on significant or priority health needs of host communities.

- Profit almost completely supplants considerations of public health and how to ensure that research collaborations focus on questions in which new knowledge led to improvements in the health of burdened populations.
Global Justice

- Treat the “distribution of scientific inquiry” as a unique social good and hence, an important issue of social justice.
- Research is a social institution.
- Whose health needs are the focus of scientific inquiry?
- Results of research should lead to an increase in Human Development Index
Social purposes of research and research questions

- Does the research address the health problems and reflect the priorities of the society in which it is being conducted?
- Does it contribute to local capacity and knowledge?
- Will it lead to practical changes at the level of individuals and local communities?
Thank you