Ethical Issues in International Research: Post-study Obligations

Joseph Millum, Ph.D.

Clinical Center Department of Bioethics/Fogarty International Center

9 November 2016

The views expressed are my own and do not represent the views of the NIH, PHS, or DHHS

Case 1: Access to antiretrovirals

- Improved access to antiretroviral therapy (ART) in many low- and middle-income countries (LMICs)
- Many patients are now failing second-line ART regimens due to resistant HIV strains

Trial design

- Open-label phase IV, prospective interventional study
- Enrolling 500 HIV-1-infected adults currently failing a second-line regimen containing a protease inhibitor
- Testing novel method for assessing resistance and assignment to new treatment regimen
- Sites in Brazil, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda

Treatment after the trial

- Some of the therapeutic agents being evaluated in the study were not available outside the trial in host countries
- Participants who needed them would leave the trial without access to these life-saving drugs

Case 2: Huntington's test

- Huntington's disease is a hereditary brain disease
- Caused by an autosomal dominant mutation – children have a 50% chance of inheriting Huntington's
- Symptoms usually start between ages 30 – 50
- Most Huntington's patients die within 20 years of onset

Research in Venezuela

- A rural community on Lake Maracaibo, Venezuela has the highest concentration of Huntington's carriers in the world
- In 1993, U.S. researchers used blood and semen samples from the community to identify the gene causing Huntington's
- A genetic test was developed
- No one in the community has access to the test

- “In the U.S. or Europe whoever has the disease in their family has the option to decide. I want to get the test, or I don't want to know. The people of Maracaibo don't have that option, even after they collaborated in the research.”

  (Ernesto Solis, Maracaibo physician)

Two ethical issues

1. Post-trial access: What care should participants receive after a study?
2. Reasonable availability: Should host communities have access to study interventions after a successful study?

1. Post-trial access

International guidelines

- “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 trial.”

  (World Medical Association, Declaration of Helsinki, 2013)

International guidelines

- “If an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority.”

(Council for International Organizations of Medical Sciences, Guideline 10)

National regulations and guidelines

- Most human subjects regulations silent or do not require provision of interventions post-trial
- Legal requirement in Argentina and Brazil
- Recommended by national guidelines in some LMICs, e.g. India, South Africa, Uganda.

NIH guidance

Applies only to:

- Provision of antiretroviral treatment
- HIV antiretroviral treatment trials
- Developing countries

NIH guidance

- The “NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment.”
- “Priority may be given to sites where sources are identified for the provision of antiretroviral treatment following the completion of the trial.”

Ethical analysis

Possible grounds for ethical obligations

- Harm to participants
- Special relationships
- Reciprocity
- Duty of rescue

Challenge

- In many cases, trial participation leaves participants better off than they would be otherwise

 Participation without post-trial access would not harm them

Special relationships

- During the research a relationship develops between researchers and their participants
- It is analogous to the doctor-patient relationship
- Participants entrust aspects of their health to the researchers

Challenges

- Role morality of researcher may be different than role morality of clinician
- In any case, clinicians do not have open-ended obligations to their patients

⇒ At most a duty not to abandon them

Reciprocation

- Research participants contribute to medical knowledge
- They deserve reward in return for this contribution
- Additional medical care might be an appropriate way to reward them

Challenge

- Extent of the obligation depends on extent of the participant's contribution
  - e.g. burden of participation, risks taken on
- Multiple parties have duties to reciprocate

Duty of rescue

- “If it is in our power to prevent something bad from happening, without thereby sacrificing anything morally significant, we ought, morally, to do it” (Peter Singer)
- Researchers may be able to give urgently needed treatment
- Participants may not have other sources of treatment

Challenges

- Applies only to low-cost, high-benefit interventions
- Not specific to research participants or to researchers

Justification	Interpretation	Application to post-trial access
Harm	Compensate all harms caused by research	Usually not applicable
Relationship	Provide care that reflects relationship	Researchers may have limited obligations
Reciprocity	Provide reward proportional to contribution	Researchers and sponsors may have limited obligations
Rescue	Meet urgent medical needs, if low cost	Obligations not limited to participants

Conclusions: the ethics of post-trial access

- None of the justifications imply an open-ended obligation for researchers
- None of the justifications imply that access to the study intervention is always the way to discharge the obligation
- We need to consider the duties of multiple parties
  - e.g. researchers, sponsors, national governments

Practice

Current practice for effective products

- Highly variable
- Focus on transitioning participants to other care
- Occasional use of open-label extension studies for serious conditions
- Some trials only conducted where the national health system can provide post-trial care

Case 1: Access to antiretrovirals

- Manufacturers agreed to provide drugs for free
- Trial sponsor designed an extension study to test whether participants would remain virally suppressed two years after return to clinical care
- Two years provided time for countries to license the drugs and provide them through national programs

2. Reasonable availability

International guidelines

- “Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.”

  (WMA, Declaration of Helsinki, Paragraph 20)

International guidelines

- “Before undertaking research in a population or community with limited resources, the sponsor and the investigator 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.”

(CIOMS, Guideline 10)

Ethical analysis

Exploitation

- X exploits Y when X takes unfair advantage of Y's situation

The nature of exploitation

- Does it have to be harmful?
  - No
- Does it involve a problem with consent?
  - No
- It is possible to have mutually advantageous consensual exploitation

Burdens to host communities

- Using scarce clinical facilities
- Attracting physicians, nurses, and other clinicians away from the public health system
- Crowding out more valuable research

Benefits to host communities

- Answer questions about local health problems
- Develop new interventions for the population
- Expand and improve health care and research facilities
- Train health care workers

Criticisms of reasonable availability

- Not relevant to some research, e.g. Phase 1 trials, epidemiology studies
- Sometimes provides no benefits, e.g. interventions not shown effective
- Excessive burden on researchers and sponsors
- Exploitation is about the *amount*, not the *type* of benefits

“Fair Benefits” framework

- Wide range of benefits count, e.g. additional clinical care, clean water
- Communities must agree that the level of benefits is fair
- Transparency about benefit agreements to allow comparisons

Criticisms of “Fair Benefits”

- Lacks a theory of fair transactions
- Possible “race to the bottom” in practice

An interpretation of “responsiveness”

- *Responsive* research is research that has sufficient *local social value*
- The expected benefits of the knowledge to the host community prevent it from being exploitative

Conclusions: reasonable availability

- Hard to justify requirement of reasonable availability of study product
- But, also hard to justify research that is not relevant to the health of host communities in LMICs

Case 2: Huntington's test

- Most people in Maracaibo do not know about the test and none have access to it
- The original goal of finding a cure has not been achieved
- But the researcher who led the project has raised more than $6 million for a Huntington's disease clinic in Maracaibo

Conclusions

- Agreement that participants in clinical trials and communities that host clinical trials should benefit from research participation
- Disagreement about
  - Type and extent of benefit
  - Who has the duty to provide the benefit

Conclusions: a cautionary note

- Conducting research in environments where many people lack access to affordable quality care is ethically challenging
- It is also vitally important for the health of people in LMICs
- This is a challenge that should be met, not avoided