Ethical Issues in International Research: Post-study Obligations

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