Post-trial Obligations & Reasonable Availability

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Case 1: Prevention of HIV transmission from mother to child

- Goal: how best to prevent transmission of HIV during labor/delivery
- Intervention: Antiretroviral therapy (ART) to mother during pregnancy, through labor
- After delivery: Study stops ART for mothers, refers to national program
Case 1

• Is it ethical for researchers and sponsors to stop providing ART at delivery?

• If not, what should they do instead?
In Venezuela, American scientists conducted a landmark genetic study nearly three decades ago. The subjects of the study are still waiting to benefit from that research.
Case 2

• Research conducted in poor rural community in low income country on Huntington Disease

• HD has adult onset, is uniformly fatal, 50% chance of passing on to offspring
Case 2

Goal:
Find a cure

Research results:
Genetic test
Ethical criticism

• Villagers have no access to the test
• Ruth Macklin: “The international guidelines that exist, such as the Declaration of Helsinki, all mandate...that the products of research, in this case the diagnostic test, be made available to the population that has been [the] subject of study....”
Questions from the cases

• Should researchers and sponsors have to ensure post-trial access to research subjects?

• Should researchers and sponsors have to ensure products are available to communities?
Overview

• Background on international research
• Post-trial Obligations
• Reasonable Availability
• Conclusions and directions for future research
Why conduct international research?

– To study diseases more prevalent in host country
  • E.g., HIV prevention research
– To study health problems in low- and middle-income countries (LMICs)
  • E.g., malaria, sleeping sickness
– More participants are available
– Less expensive
Ethical concerns about research in LMICs

• Language, cultural, and educational barriers
• Power differentials
• Exploitation
• The 10/90 gap
Exploitation of individuals

• Exploitation: benefits and burdens of transaction distributed unfairly

• Researchers from developed countries may be able to take advantage of individuals from less developed countries

• People in LMICs lack adequate health care and resources, may accept unfair risks/burdens, receive insufficient benefit
Exploitation of communities

• Different from exploitation of individuals

• Resource-poor communities need benefits from research, might agree to unfair share of benefits and burdens
Current injustice related to research: The 10/90 gap

Deprivation...creates fortuitous opportunities for researchers.
There is a moral imperative to assist LMICs in the process of developing the capabilities necessary to effectively address their most urgent, unmet health needs.
Research that violates these criteria creates a division of labour that is at least prima facie unfair, because it enlists those who suffer the heaviest health burdens to advance the science that will create the greatest social value for people living in high-income countries.

Much of the debate about the conduct of clinical trials involving participants from the developing world has centred on ethical issues that apply most directly to large-scale, late-phase research. As clinical research becomes increasingly global, however, individuals from low-income and middle-income countries (LMICs) have been recruited into small-scale, translational trials of novel technologies such as gene transfer. The distinctive ethical concerns that have arisen from such practices have received almost no attention. We consider four rationales for recruiting participants from LMICs into translational trials.

First, is the idea that LMICs occasionally present investigators with a research opportunity that would otherwise be unavailable if they used volunteers from high-income countries. Thus, an Italian gene transfer study of severe combined immunodeficiency disease associated with adenosine deaminase deficiency (ADA-SCID) would not have been ethically permissible in high-income countries.
POST-TRIAL OBLIGATIONS TO INDIVIDUALS
What do researchers owe participants after research?

• Terms: “post-trial access” & “aftercare”

• Central, unanswered questions
  – If need for care persists after research, but is likely to go unmet, what obligations do stakeholders have?
  – Are there limits on these obligations?

• No clear consensus
### Categories of regulatory approaches to post-trial access

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<th>Requirement: Researchers/sponsors should</th>
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“Even after completion of the clinical study, the principal investigator should make an effort to ensure that the subjects have access to the best preventive, diagnostic, and therapeutic methods identified by the clinical study concerned.”

“The protocol must include provisions for aftercare, including closure activities and a proper referral mechanism to deal with the health needs of participants and members of the research team.”

National Ethical Guidelines for Health Research (2006),
Inform: India

• Favorably cites 2004 Declaration of Helsinki and requires that researchers:
  – Identify and describe in protocol “post-trial access by study participants to . . . procedures identified as beneficial in the study or access to other appropriate care....”

• Exceptions: Indirect community benefit, small scale/student projects

Indian Council of Medical Research 2006
## Ethical guidance

<table>
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<th>Year</th>
<th>Issuing Authority</th>
<th>Target</th>
<th>Nature of Obligation</th>
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<tr>
<td>2001</td>
<td>U.S. NBAC</td>
<td>Researchers and sponsors</td>
<td>Good faith efforts to “secure” post-trial access to beneficial interventions</td>
</tr>
<tr>
<td>2002</td>
<td>CIOMS</td>
<td>Sponsors</td>
<td>“Continue to provide” access to beneficial intervention pending regulatory approval</td>
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<tr>
<td>2005</td>
<td>Nuffield Council on Bioethics</td>
<td>Stakeholders</td>
<td>“Begin negotiations...at an early stage.” Funding treatment “may be unrealistic and lead to sponsors curtailing other research.”</td>
</tr>
<tr>
<td>2012</td>
<td>UNAIDS</td>
<td>Stakeholders</td>
<td>Participants infected during prevention trials should “be provided access to treatment.”</td>
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<tr>
<td>2013</td>
<td>WMA Declaration of Helsinki</td>
<td>Stakeholders</td>
<td>“[M]ake provisions...for all participants who still need an intervention identified as beneficial.”</td>
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Evolving ethical guidance: Declaration of Helsinki

2000
Patients should be “assured of access” to best proven intervention

2004
“Identify” post-trial access to beneficial interventions during study planning process

2008
Participants should be “informed” about the study outcome, “entitled” to share in benefits

“[M]ake provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.” (2013)
Funding policies

• U.K. Wellcome Trust: funding post-trial provisions outside remit
• But may consider post-trial provisions when deciding whether to award grants
• And may require post-trial access for chronic or progressive conditions
Funding policies

• French Agence Nationale de Recherche sur le Sida et le Hépatites Virales (ANRS) restricts HIV prevention research to areas where public ART programs exist

• Presumably to ensure post-trial access
NIH Guidance (2005)

“For antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial.”

http://grants.nih.gov/grants/policy/antiretroviral/
NIH Guidance

- However, “NIH’s authority to ‘encourage and support research’ does not extend to providing treatment following the completion of that research.”
- Therefore, recommends “investigators/contractors work with. . .stakeholders to identify available sources of antiretroviral treatment.”
- NIH may give preference to sites where access to ART has been identified.
Concern about diversion effects

- Policies could divert beneficial research to places where infrastructure already exists and away from some of the worst-off
- E.g., Ebola research

Empirical data

• Few guarantees to provide care (whether research product or other care) after a study is over

• Focus on short-term provision, transitioning participants to other sources of care

  • S. Shah, S. Elmer, C. Grady, American Journal of Public Health (September 2009).
  • Ciaranello A, Walensky RP, Sax PE, Chang Y, Freedberg KA, Weissman JS., HIV Clinical Trials (Jan./Feb. 2009).
Regulations vs. ethical guidance

• Some similarities
  – No clear consensus
  – Plan in advance, inform participants
  – Important that intervention is beneficial

• Some differences
  – No regulations seem to require provision, more caveats/nuance in some regulations
  – Ethics guidance more stringent, but obligations spread across stakeholders
Ethical justifications for post-trial obligations

- Exploitation
- Participants’ needs, avoiding harm
- Reciprocity
- Duty of rescue
- Beneficence and global justice
- Researcher-participant relationship
Exploitation

• Claim: Without post-trial access, participants will be exploited
• Exploitation occurs when burdens and benefits shared unfairly, relative to contribution
• But post-trial access usually only arises if participants benefit
Participants needs/avoiding harm

• Claim: Harm from no post-trial access
• But harm has to be relative to baseline before research, not much data
• One study of ART suggests harm in not planning for transition
• Participants more likely to experience virologic failure if unprepared for end

Reciprocity

• Claim: If participants take on risks/burdens of research for benefit to others, entitled to something in return
  – How much?
  – Norms of reciprocity are unclear
  – What if participants have net benefit?
Duty of rescue

- Claim: researchers have duties to rescue when they can help participants greatly and at little cost to themselves

- Limited duties, dependent on cost of rescue → only will generate limited post-trial obligations for a short time
Beneficence

• Claim: we all have more general duties to help others and rectify global injustice; post-trial access is one way to do that

• However, duty may be satisfied in many different ways
Researcher-participant relationship

• Claim: researchers have a special duty as researchers to provide post-trial access

• Why?

• Access to what?

• For how long?
Researcher-participant relationship

• Claim: researchers have a special duty as researchers to provide post-trial access

• Why?
  • Access to what?
  • For how long?
Researcher-participant relationship

• Analogy to discharge planning→ obligations of transition?

  – Researchers and sponsors should try to identify long term, sustainable external access

  – Should minimize gaps in care triggered by research
Many different justifications….

- Justifications imply limited post-trial obligations to participants
- Not limited to international research
- Strongest arguments suggest that focus should be on:
  - Avoiding harm caused by research
  - Emergencies that arise at end
  - Transitioning participants
REASONABLE AVAILABILITY TO COMMUNITIES
International ethical requirements

- Two related protections to prevent exploitation are required by international guidance documents (and supported by prominent bioethicists):
  - Responsiveness
  - Reasonable availability
Before undertaking research in a population with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is **responsive** to [local] health needs and the priorities of the population...
- any intervention or product developed, or knowledge generated, will be made **reasonably available** for the benefit of that 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.”
“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.”
More on Responsiveness

**Justice in translation: from bench to bedside in the developing world**

John Lennox, Jonathan Emmerman

A recent challenge in the conduct of clinical trials involving participants from the developing world has centered on ethical issues that apply most directly to large-scale, long-term research. As clinical research becomes increasingly global, however, individuals from low-income and middle-income countries (LMICs) are becoming less represented in clinical research, and the accountability of research decisions to those communities is being called into question. This viewpoint examines the ethical implications of research in LMICs, considering the role of LMICs in, and the accountability of LMICs to, the development of global health policy.

**Virtual Mentor**

**Ethics of International Research: What Does Responsiveness Mean?**

Christine Grady, RN, PhD

Policy Forum

April 2006, Volume 8, Number 4: 235-240.

**Rethinking the responsiveness requirement for international research**

Rebecca Wolitz, Ezekiel Emanuel, Seema Shah

Burkitt’s lymphoma is endemic in Kenya and Uganda. It accounts for more than half of all childhood cancers in Africa but almost no malignant disease in developed countries.1 Yet, other diseases in sub-Saharan Africa, such as malaria, cause much greater mortality.2 For this reason, the Taskforce on Ethical Issues in Global Health and Development (2000) recommended that global health research be focused on the health needs of LMICs.

**Sharing the benefits of research fairly: two approaches**

Joseph Millum

**EXPLOITATION AND FAIRNESS**

Exploitation occurs when one party takes ‘unfair advantage’ of another. Consequently, one party can exploit another if both benefit from their interaction. Indeed, such ‘mutually advantageous exploitation’ has been the focus of discussion about exploitation in research.2 The problem explored in this paper arises because of the vulnerability of some of the parties affected by research. Whether this vulnerability is a consequence of poverty, illness, ignorance, or a lack of alternatives, it means that these parties have much less power, and so are liable to agree to unfair distributions of the benefits and burdens of research. For example, an HIV-
Vulnerable populations?
Critiques of Reasonable Availability (RA)

• What does it mean?
  – By when should products be made available?
  – What counts as available?

• Doesn’t always get it right
  – Sometimes could require too little
  – Other times, could require too much
More critiques

• Who is the “community” receiving access?
• Narrow view of benefits
• Not applicable to much research
Fair Benefits Framework

- 2001: conference on ethical aspects of research in developing countries by members of NIH Department of Bioethics
- Identified problems with reasonable availability
- Proposed alternative: Fair Benefits Framework
Fair Benefits

• Meant to address concerns about exploiting individuals and communities

• Requires that risks, burdens, and benefits of research be distributed fairly amongst the various parties (sponsors, researchers, communities, and participants)

Fair Benefits Framework

• All potential benefits and risks need to be evaluated
  – Reasonable availability could be one, but is not mandated
  – Benefits do not have to relate to health
  – Expertise, health care, infrastructure, etc. all could count

Fair Benefits

- Has been criticized:
  - Devolves into community consent?
  - What is fair?
  - How to implement?
  - Race to the bottom?

→ Need for more research on how to operationalize Fair Benefits Framework
Conclusions on post-trial access for individuals

- Regulations tend to focus on two poles: ensuring or describing
- Stronger obligations in guidance and policies, but spread across stakeholders
- In practice, researchers focus on referral
- Need more work to frame obligation correctly, provide guidance
Conclusions on reasonable availability for communities

• Reasonable availability is problematic

• Need more research on how to translate Fair Benefits into practice, and how to conceptualize global justice obligations of researchers
Case 1: Prevention of HIV transmission from mother to child

• Goal: how best to prevent transmission of HIV during labor/delivery

• Intervention: ART to mother during pregnancy, through labor

• After delivery: Study stops ART for mothers, refers to national program
Case 1

• Researchers who stop providing ART during delivery may increase the chances that women don’t stay in care; difficult time to transition

• Short term provision of ART, efforts to ease transition may be warranted
In Venezuela, American scientists conducted a landmark genetic study nearly three decades ago. The subjects of the study are still waiting to benefit from that research.
Response to criticism

• Unclear that test results would help
  – Some would commit suicide if positive
  – Some have children post-diagnosis
  – No cure

• The villagers would need genetic counseling

• Other benefits are more pressing

• Significant political hurdles to surmount
Counter to response to criticism

• Macklin’s response: “It is unacceptably paternalistic for researchers to claim this is bad news we should not visit on people. That is really a form of intellectual colonialism that we know what’s better for those people, and it’s better for them not to have a test.”

• Note: Then the remedy is to ask the villagers what benefits they value, not to mandate that they get the test.