

# **International Research Ethics**

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# Disclaimer

- The opinions expressed are the author's own. They do not reflect any position or policy of the U.S. Government, the National Institutes of Health, the Henry Jackson Foundation, the Public Health Service, or the Department of Health and Human Services.

# Background: Ethics of Multinational Research

- Multinational research is essential to understanding and ultimately controlling diseases of global importance.
- It necessarily involves many complex ethical issues.

# Multinational collaborative research

- Research study that involves at least two countries:
  - Sponsor country pays, but research goes on in host country,  
or
  - Research is conducted at multiple sites.

# Why multinational research?

- To study diseases that are more prevalent in host country, such as HIV prevention research
- To study health problems in host country, such as malaria or sleeping sickness
- Because more participants are available
- It may be less expensive to do the research in another country

# Outsourcing

- What are the ethical implications of “outsourcing”?
  - Trial of expensive blood pressure medication in India, but company does not intend to market the drug anywhere except the US

# General concerns

- **Exploitation of vulnerable populations**
  - Is everyone in developing countries vulnerable?
- **Power differentials**
  - It may be hard for developing countries to negotiate with more powerful, wealthy, and knowledgeable parties
  - Lack of capacity to review research
- **Language, cultural, and educational barriers**
- **Context of historical injustice**
- **Current injustice**

# Current injustice related to research: The 10/90 gap

- 90% of the global funds for research related to healthcare are spent on 10% of the global disease burden.
- Research on many important diseases that disproportionately affect developing countries is neglected.
- Some, seeking to address this problem, would like to put ethical limits on the research that can be conducted in developing countries.

# Overview

## I. Obligations to individuals

### A. During the trial

#### i. Standard-of-care

#### ii. Ancillary care

### B. After the trial

#### i. Post-trial benefits

## II. Obligations to communities

### A. Responsiveness to health needs

### B. Reasonable availability of the trial intervention

### C. The Fair Benefits Framework

# I. Obligations to individual subjects

During the trial:

- Standard of care/placebos
- Ancillary care

# Standard of care

- What do you test a new intervention in comparison to during the trial?
  - Placebo
  - What is locally available to most people
  - What is locally available to some
  - The best drugs in the world

# Preliminary distinction

- Difference between standard of care as what clinicians think is the best, and
- Standard of care that has an evidence base.
- If the former, it may be important to conduct research.
  - E.g., 41,000 patients underwent high-dose chemotherapy + autologous bone marrow transplant
  - At least 5 major RCTs showed no advantage over the alternative lower dose chemotherapy

**What do the guidelines say about standard  
of care?**

# International guidelines

World Medical Association

*Declaration of Helsinki (2008):*

“The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention” with two exceptions.



# With exceptions...

Possible exceptions:

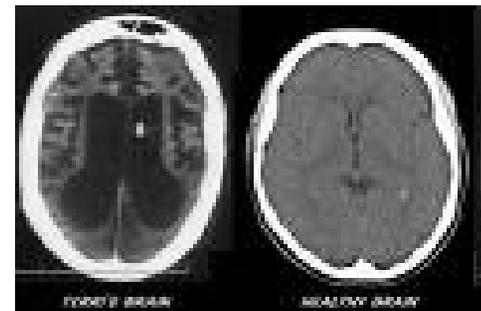
- Where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons, use of placebo is necessary and poses no risks of serious/irreversible harm. “Extreme care must be taken to avoid abuse of this option.”

# More nuanced approaches

- Other policies require scientific justification for the trial design and something less than the best proven standard of care:
  - “Standard of care country endeavors to provide nationally” (UK’s Nuffield Council)
  - “Highest level of care obtainable in the host country” (UNAIDS)
  - “Risks and benefits to subjects reasonably balanced, risks minimized” (NBAC)

# Ancillary care

- Treatment that is provided for study participants that is NOT part of the design of the study
  - Identification of conditions that need treatment during screening and study visits
  - E.g., subjects getting research MRIs that reveal incidental findings



# Guidelines about Ancillary Care During Trials

Council for International Organizations of  
Medical Sciences (CIOMS):

“Although sponsors are, in general, not obliged to provide health care services beyond that which is necessary to conduct research, it is morally praiseworthy to do so.”



# Ancillary care: current status

- No obligation to provide ancillary care during trial.
- In practice, many researchers do provide some amount of ancillary care.
- The issue is not settled.

# Ancillary care: A framework

- Belsky & Richardson have attempted to derive a limited obligation based on an entrustment model
- In some cases, researchers may be obligated simply to inform and refer subjects
- Factors that affect whether and how much ancillary care should be provided may include:
  - How much permission to perform interventions granted
  - The nature of the study
  - Confidential nature of the information revealed
  - Length of involvement in the study

Belsky L, Richardson H. Medical Researchers' Ancillary Clinical-Care Responsibilities. *BMJ* 2004;328:1494-1496.

**After the trial**

# After the trial

- Researchers develop relationships with research subjects, who take on risks to contribute to generalizable knowledge.
- When the research comes to an end, the participants' need for treatment may persist.
- Researchers may not want to abandon study participants altogether, or make them worse off after the research is over.

# What are we worried about?

The worry is:

- Potential research subjects are in great need and vulnerable to exploitation—may not be able to get a fair level of benefits from their research participation.

One qualification: obligations may fall on parties other than researchers instead, or as well.

**What Do the Guidelines Say?**

# Guidelines about Post-Trial Intervention Access

Declaration of Helsinki (2000):

“At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by that study.”



# Declaration of Helsinki (2008)

- “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.”

# National Bioethics Advisory Commission

- Report on Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries:
  - “Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants.”



# National Bioethics Advisory Commission

- Also noted that:
  - Research protocols should typically describe the duration, extent, and financing of such continued access.
  - The results of the trial are relevant.
  - If no arrangements made, “the researcher should justify to the ethics review committee why this is the case.”

# Limitations of the guidelines

- Should we handle acute and chronic conditions differently?
- Acute vs. Chronic conditions:
  - **Acute** conditions: Providing effective malaria vaccine to the control group?
  - **Chronic** conditions: Providing access to ART for the rest of the participants' lives?



# Limitations of the guidelines

- They provide little guidance regarding long-term, resource-intensive, post-trial obligations.
- They do not address uncertainty inherent in post-trial planning:
  - Funding source changes
  - Political changes
  - Related scientific developments.

# Limitations of the Available Guidance

- Even if there is provision for referral to host country's system of treatment, the system may not be prepared for it:
  - May not be able to provide the same standard of care available in the trial, or
  - May be overwhelmed when large studies finish and many people need care.
- Could these guidelines create a disincentive to do research in very resource-poor settings?

# How does this work in practice?

- The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment.
- Plans for post-trial access can be taken into account during funding decisions.
- Conducted a study of the NIH guidance on post-trial access for antiretroviral treatment trials.

# Study of the Implementation of the NIH Guidance

- 18 studies conducted from July 2005-July 2007.
- Most plans did not guarantee access, but referred subjects to existing structures
  - Local governments
  - President's Emergency Plan for AIDS Relief (PEPFAR)
  - The Global Fund
  - Employer plans
- Unusual steps:
  - Soliciting charitable donations.
  - One plan guaranteed transitional access.

# Extrapolating to other diseases

- Post-trial access for HIV/AIDS antiretroviral trials in developing countries is:
  - More challenging in some respects—requires expensive, life-long, and potentially life-saving treatment in contexts that may lack the necessary health care infrastructure.
  - But increasing number of funding mechanisms available.
- Treatment of acute illness or prevention modalities may be more feasible.

# Obligations to communities

# Post-trial Community Benefits

- Many have expressed concerns that research in developing countries may involve exploitation by developed countries who take unfair advantage of developing countries.
- As a consequence, some ethics guidelines focus on the benefits to the host community.

# Post-trial Benefits to Communities

- Two related protections to prevent exploitation of communities have been suggested:
  - Responsiveness of the research question to health needs in the host country, and
  - Reasonable availability of a successful intervention in the host country after the trial.

# CIOMS: Responsiveness to Health Needs

- “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 the health needs and the priorities of the population or community in which it is to be carried out...”

# Responsiveness to Health Needs

- Declaration of Helsinki (2008):

“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.  
...”

# What does it mean for a study to be responsive?

- Responsive research is likely to include:
  - HIV/AIDS, malaria, or tuberculosis in Sub-Saharan Africa
- But what is unresponsive research?

# Unresponsive research

- Very few examples in the literature
- Nuffield Council says further justification is needed to conduct research on Burkitt's Lymphoma
  - Endemic to Kenya and Uganda
  - Accounts for half of all childhood cancers in Africa
  - Almost no cases in developed countries
  - But poses a much lower disease burden than HIV/AIDS, malaria, and TB

# Criticisms of Responsiveness Requirement

- Lack of data: No way to know if this is the best policy
- May lead to undesirable outcomes for developing countries
  - It merely *prohibits* unresponsive research
  - We need to generate research options that study neglected diseases
  - In the meantime, if there are no other options, does that mean a developing country should not permit any research?

# Criticisms of Responsiveness Requirement

- Developing countries may have good reasons to conduct research that is not responsive to their health needs.
  - Policy choice to decide to do a trial to build capacity:
    - Hepatitis A vs. HIV vaccine trials in Thailand.

# Reasonable Availability

## Council for International Organizations of Medical Science (CIOMS):

“As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made *reasonably available* to the inhabitants of the underdeveloped community in which the research was carried out.”

CIOMS



# Guidelines: Post-trial Availability to General Community

Declaration of Helsinki (2008):

“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.”

(Links responsiveness and reasonable availability)

# Challenges to “Reasonable Availability”

- Who is the “community” receiving access?
- Narrow view of benefits
- Not applicable to much research
  - Phase I trials
  - Observational studies

# Fair Benefits Framework Proposal

- ALL potential benefits and risks need to be evaluated
  - to research participants, during and after trial.
  - to general community, during and after trial.
- Improving community risks/benefits ratio through community involvement
  - Involvement at all level of decision-making.
  - Uncoerced participation.
  - Transparency in decision-making.

# Fair Benefits Framework Proposal

- Fair benefits framework has been criticized for requiring “too little” of researchers.
- Other factors may influence the distributive fairness of an outcome:
  - Disproportionately weak bargaining power of developing countries
  - Lack of available alternatives

# Fair Benefits Framework

- It may be helpful to supplement the framework with attempts to build the bargaining power of developing countries
- Importantly, it was intended to get away from the narrow view of “reasonable availability”
  - There are many types of benefits of research that can be valuable

Emanuel EJ, Grady C, Lie R, Wendler D, Participants in the 2001 Conference of Ethical Aspects of Research in Developing Countries. Fair Benefits for Research in Developing Countries. *Science* 2002;298:2133-2134.

# Our outsourcing example

- What ethical considerations arise for the trial of an expensive blood pressure medication in India?
  - Standard of care
  - Ancillary care
  - Post-trial access
  - Responsiveness
  - Reasonable availability
  - Fair Benefits

# Consequences of community obligations?

- The greater the obligation to interact with the community, the more time researchers must invest in community engagement
- The more time researchers spend with a particular community, the more they are vulnerable to charges of creating an overresearched community.
- What is an overresearched community?

# Overresearched communities

- Potential harms of overresearched communities:
  - Skewed scientific data.
  - Benefits of research do not go to other communities.
  - Burdens are unfairly borne by the overresearched community.
    - May be a particular concern in South Africa with vaccine and microbicide trials in which subjects are being warned that they may have a higher risk of HIV infection because of the trial interventions.

# Overresearched communities

- Potential benefits of overresearched communities:
  - Members of one overresearched community in Rakai describe their experience with research as generally positive.
  - Through true community engagement, researchers can help a community based on what they really need (e.g., orphan problem in Vulindlela).

# Overresearched communities



# Conclusion

- Ethical considerations regarding research in the developing world operate in contexts with complex political, cultural, and practical dimensions.
- Although there are no easy answers, it is critical to think carefully about study design, the benefits and burdens for research subjects, and community participation in developing and evaluating research.

Questions?

# Guidance for HIV Vaccine Trials

- **UNAIDS Guidance Point 16 (2000):**
  - Care and treatment for HIV/AIDS should be provided for participants in HIV vaccine trials who become infected in the course of the trial



# Guidance for HIV Vaccine Trials

- **UNAIDS Guidance Point 16 (2000):**
  - **At a maximum: The best available therapy**
  - **At a minimum: Should take into consideration**
    - **Standard of care (sponsor country)**
    - **Highest level of care (host country)**
    - **Infrastructure in host country**
    - **Duration and sustainability of care for trial participants**

# Other Funder Policies

- **Medical Research Council (MRC), United Kingdom**
  - Refer participants who become infected with HIV to local sources of care, and
  - Encourages partnership with host country officials.
- **Agence Nationale de Recherche sur le Sida (ANRS), France**
  - Must have a commitment to providing care,
  - Or trial will not be funded.