Informed Consent, Fair Benefits, and Post-trial Considerations in International Research

Seema Shah, J.D.
Department of Clinical Bioethics, Division of AIDS
The National Institutes of Health (NIH), USA

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 Public Health Service, or the Department of Health and Human Services.

Ethics of Multinational Research

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

Multinational collaborative research

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

- On health problems:
  - In host country, such as malaria, sleeping sickness, OR
  - Increasingly,
    - More participants may be available, or
    - It may be less expensive to do the research in another country.

Overview

1. Informed consent
2. Post-trial benefits to individual participants
3. Benefits to communities
    a. Reasonable availability of the trial intervention
    b. Responsiveness to health needs
4. An alternative: Fair Benefits Framework
5. Challenges to Fair Benefits Framework

1. Informed Consent in Research in the Developing World

Overview:

- Respecting individual autonomy in varying cultural contexts
- Practical considerations:
  - Signature requirement
  - Obtaining informed consent in countries with low literacy levels

Informed Consent

- Obtaining informed consent in research demonstrates respect for individual autonomy.
- In some cultures, individual autonomy must be balanced against community interests.
- Some have argued that in more community-centered societies, obtaining individual informed consent may lead to conflict or be disrespectful.

Informed Consent

In Mali, researchers have taken approaches where, instead of approaching individuals first, a tiered model of consent was used.

Tiered Consent

- A stepwise process:
  1. Approached the leaders of the community.
  2. Conducted group discussions with the heads of extended families.
  3. Then led group discussions with mothers of children who would be involved in the study.
  4. Finally, obtained consent from individual families.
     - Also approached mothers-in-law of pregnant women before obtaining consent from the women themselves.

Tiered Consent Model: Who decides?

- Cultural claims are notoriously difficult to evaluate:
  - Culture is not monolithic.
  - People in power in a culture may have skewed or biased perspectives, but may be the ones who control information about the culture.
  - People outside a culture may not be sure how to determine whether a particular claim about a culture is true, or may not know whom to ask.

Empirical Data Relevant to Community Consent

One solution: Look to empirical data for the relevant community.

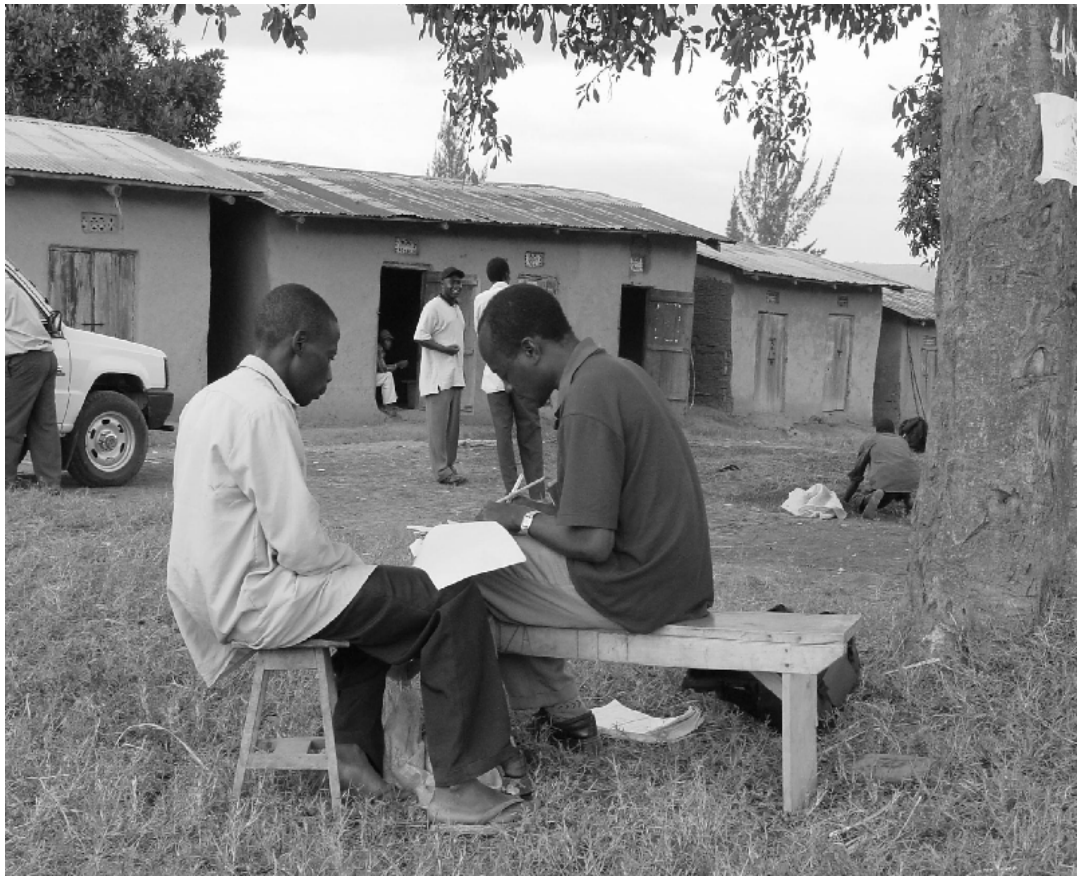
- In a randomized study of anti-malarial treatments, 347 mothers giving parental consent were asked about the informed consent process.

- 94% reported making the decision about enrolling their child on their own.

Individual v. community consent

- Another model frequently used:
  - Have community discussions about the study.
  - Engage with disenfranchised subgroups directly.
    - Sex worker advisory boards in Vulindlela, South Africa.
  - But only require individual consent for research participation.

Photo courtesy of Ezekiel Emanuel.



Practical Issues: Informed Consent and the Signature Requirement

- The Federal Regulations require that research subjects sign informed consent documents.
- Requirement can only be waived when:
  - There is no other record of the subject's participation, and there is a risk to subjects regarding confidentiality, or
  - Research is minimal risk, and does not involve procedures for which you would need written consent if done outside of research.

Distrust/Fear of Providing Signatures

- In Uganda, up to 25% of research subjects have documented reluctance to sign informed consent forms.
  - May come from the fact that under Idi Amin's reign, being identified in documents sometimes led to punishment by the government.
- Waiver may be permitted if breaching confidentiality poses risks.

Cultural Views on Signatures

- Some cultures have differing views of signatures:
  - Once you have signed, you cannot withdraw from research, or
  - Verbal agreements are binding—requiring more, like a signature, is insulting and suggests that the subject's word cannot be trusted.
- Probably cannot obtain waiver of the requirements for these types of concerns.

Signature Requirement

- Perhaps the Federal Regulations should permit waiver of the requirement and oral consent in particular cultural contexts.
- Could have the investigator document the consent process and have an independent witness sign.
- Should be very clear that the oral consent process precedes enrollment in the study.

Informed Consent in Low-literacy Populations

- In some populations, many individuals may not be able to read or sign informed consent documents.
  - Signature can be an "X" or a thumbprint.
  - Researchers may need to use creative ways of disseminating information.

Creative Ways of Sharing Information

- Vulindlela, South Africa
  - Community information-sharing meetings, &
  - Flip chart with pictures following a particular woman from initial consent discussion all the way through trial participation.
- Rakai, Uganda:
  - Communicating through theater, &
  - Giving subjects tours of the lab to explain the research process.

2. Post-trial Access to Benefits

- 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.

Post-trial Access to Benefits

- Researchers may not want to abandon study participants altogether, or make them worse off after the research is over.
- What do researchers owe their participants after their participation in the study has ended?
  - The intervention given to them during the trial, if it is beneficial?
  - Any desired ancillary care provided during the trial?

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: 2004 Clarification

- Unclear clarification:
  - Reaffirmed its prior position.
  - But only required that researchers *identify* arrangements or mechanisms for post-trial access in the protocol that can be reviewed by ethics committees.

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:
  - "Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access.
  - When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case."

Post-Trial Intervention Access

- **Acute vs. Chronic conditions for post-trial access to experimental interventions:**
  - **Acute** conditions → short-term treatment → relatively small expenditure of time and resources.
    - One-shot deal to provide an effective malaria vaccine to the control group.

Post-Trial Intervention Access

- **Chronic** conditions → long-term treatment → can add up to huge, long-term financial and logistical commitment

  - Providing HIV care for the rest of all participants' lives?

Post-trial Ancillary Care

- Issues with post-trial supplementary care:
  - Potentially huge use of resources (money, personnel, infrastructure).
  - Necessary care may be unrelated to researcher's training and focus.
  - Others may have an obligation to provide care.
    - There may be a joint obligation requiring partnership between researchers and the local health care delivery system and the Ministry of Health

What are the 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.

What are the limitations of the guidelines?

- Even if there is provision for referral to host country's system of treatment, the system may not be able to provide the same standard of care available in the trial.
  - Is there is an obligation to ensure *state-of-the-art* care?
- Could they create a disincentive to do research in resource-poor settings?
- If research is conducted only in places where post-trial care is available, this deprives poorest countries opportunities to host research.

NIH Guidance: Access to Antiretrovirals

- For NIH-funded studies, a more practical guidance document was issued in March, 2005.
- The guidance document only applies to antiretroviral treatment (ART) trials in developing countries, and addresses the provision of ART after the study.

NIH Guidance

- "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."

Implementation

- The guidance notes that NIH's authority is limited to supporting research, and does not extend to providing post-trial treatment.
- Thus, applicants are expected to provide NIH Program Staff with identification of other sources for ART provision.
- Priority may be given to sites where sources are identified for provision of ART.

Competing Considerations

- This guidance attempts to strike a delicate balance between
  - Creating stringent requirements for researchers to ensure post-trial access, and
  - Encouraging researchers to continue performing trials in countries with non-existent, ineffective, or poorly-funded ART programs.

Study of the Implementation of the NIH Guidance

- Many plans have built on existing structures, such as programs funded by local governments, the President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund, or some combination thereof.
- Creative solutions
  - Creation of a non-profit organization.
  - Solicitation of charitable donations.

3. Post-trial Community Benefits

- Many have expressed concerns that research in developing countries may result in unfair advantage for the developed world.
- 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.

  → Is post-trial access for the participant community a necessary ethical requirement?

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:

  "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research."

Criticisms of Responsiveness Requirement

- May be paternalistic.
- Developing countries may have good reasons to conduct research that is not responsive to their health needs.
  - Altruism: Are we saying that developing countries are not allowed to be altruistic to other nations?
  - It may be an explicit policy choice to decide to do a trial that will provide needed expertise to do future, more relevant trials:
    - 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

Challenges to "Reasonable Availability"

- What is the relevant time frame?
- Who is the "community" receiving access?
- Narrow view of benefits.
- Not applicable to some research:
  - Phase I trials, or
  - Observational studies.

Addressing Worries of Exploitation

- In developed countries, research generally aims to benefit the population in which it occurs.
- Transplanting this idea to the developing world may have some value in minimizing exploitation.
- Yet, there may be valid reasons that countries in the developing world have to conduct research that it does not benefit them in this particular way, but that benefits them in other ways.

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.
- Others argue that some developing countries may not be in a good position to negotiate for a reasonable allocation of benefits.
- But, it was intended to get away from the narrow view of "reasonable availability."

  →There are many types of benefits of research that can be important.

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.

Challenges to the Fair Benefits Framework

- What counts as the "community"?
  - How do you engage and incorporate minority or disenfranchised members of the community?
- To truly engage in community benefits, researchers may have to commit to long-term work in one community
  - This leads to concerns about overresearched communities.

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.
- As such, it is critical to the ethical conduct of multinational research to think about benefits and burdens of research in a comprehensive fashion, and to have community participation in developing and evaluating research.