

Post-trial Obligations in International Research

Seema Shah, J.D.

Department of Bioethics, NIH Clinical Center

Division of AIDS, NIAID

Post-trial access for HIV/AIDS

- In the 1990s, a drug company wanted to test antiretroviral treatment (ART) regimens on people infected with HIV/AIDS in South Africa.
- ART was not available to most people in South Africa at that time.
- The ethics committee required that the drug company provide ART regimens after the study.
- The sponsors refused—they were unwilling to purchase another company's drugs in order to provide combination therapy.

Disclaimer

The opinions expressed are my 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.

Recap: why might researchers have post-trial obligations?

1. Compensation for harm: danger of taking participants off treatment
2. Duty of rescue: researchers are in a special position to help participants
3. Reciprocation for the participants' contribution or the risks they've taken
4. Relationship between researchers and participants

International research ethics

- Post-trial obligations are one important component of international research ethics.
- This issue arose largely because of concerns about exploitation of subjects in developing countries.
- Many of the topics explored in this talk, like many components of international research ethics, could also apply to research conducted domestically.
- But they take on a special salience for international research.

The importance of data

- Discussion about international research ethics has not relied much on data.
- If ethical guidelines are to accomplish their goals effectively, it is important to know:
 - How well they relate to the public's views
 - What is feasible in practice
 - How the guidelines are being implemented
 - What they leave unresolved

Overview

- Data on subjects' views about post-trial obligations
- Data on post-trial planning
- What the data suggest about unresolved issues related to post-trial obligations

What do subjects think about post-trial access?

Caveat about the data

- These data are tricky to interpret, both for views on and availability of post-trial access, because they are not always referring to the same thing.
 - Some studies focus on access to investigational drug, others focus on access to needed care, and others ask about information given to participants after the trial.

Studies of subjects' views

- Nearly all Kenyan subjects receiving care for HIV or for other conditions thought researchers should provide post-trial access to ART if it benefited the subjects and they needed the treatment.

Shaffer DN, *et al*, Journal of Medical Ethics (2006).

Subjects' views

- In an international HIV trial, US subjects were less likely than European and Latin American subjects to state that the trial drug should be free to participants (if proven safe and effective).

Pace C, *et al.*, *AIDS Res Hum Retroviruses* (2006).

Subjects' views

- A study of 93 U.S. research subjects in non-HIV trials (10 focus groups) found divergent views about obligations to provide treatment.
- But there was near-consensus about obligations to provide information.

N. Sofaer, et al., J. Med. Ethics (2009).

Why did subjects think researchers do have obligations?

- Subjects' health need
- Respect for subjects
- Reciprocity
- Researcher-subject relationship continues after the trial stops

Researcher/subject relationship leads to an obligation

- “I knew it was a study, and I knew I had signed papers and I knew all that. But, at the end...I’ve developed a relationship with the doctor and coordinator and all, and I liked the doctor. And I want[ed] to continue to go there and I want[ed] to get the medication that I was given, but I couldn’t.”

Obligations based on causing harm

- Researchers should inform subjects of harm:
 - E.g., participants who had been in Vioxx trials thought they should have been told about the adverse events.
 - One person said , “Our cars get recalled.”
- Some participants thought that researchers should pay for the full cost of care if the study drug caused harm:
 - “I’d sue their butts off....”

Pragmatic reasons to provide post-trial access

- Sponsors should collect data on former subjects, who are “assets” in whom they had “invested all this medication, all this time, all this note-taking.”

Why do subjects think researchers don't have obligations?

- Consent form is a contract
- Subjects assume the risk
- Requiring access would have the negative effect of decreasing research
- Researcher-subject relationship ends when the trial stops

Researcher/subject relationship leads to no obligation

- “I thought that was the nature of a trial. That there’s a beginning and an ending point.”

No obligations even if the drug caused harm

- Several uninsured participants who believed their health suffered from not receiving the study drug after the trial thought that sponsors had no obligations to provide post-trial access to the drug.

What do researchers have obligations to do after the trial?

- Continue to provide treatment to participants until marketed or for the rest of their lives
- “Bridge” the gap to post-trial care
- Offer the drug to subjects at a fair price
- Conduct limited post-trial surveillance of subjects
- Provide information to subjects about their research participation (e.g., placebo or drug?)
- Disseminate information about the trial

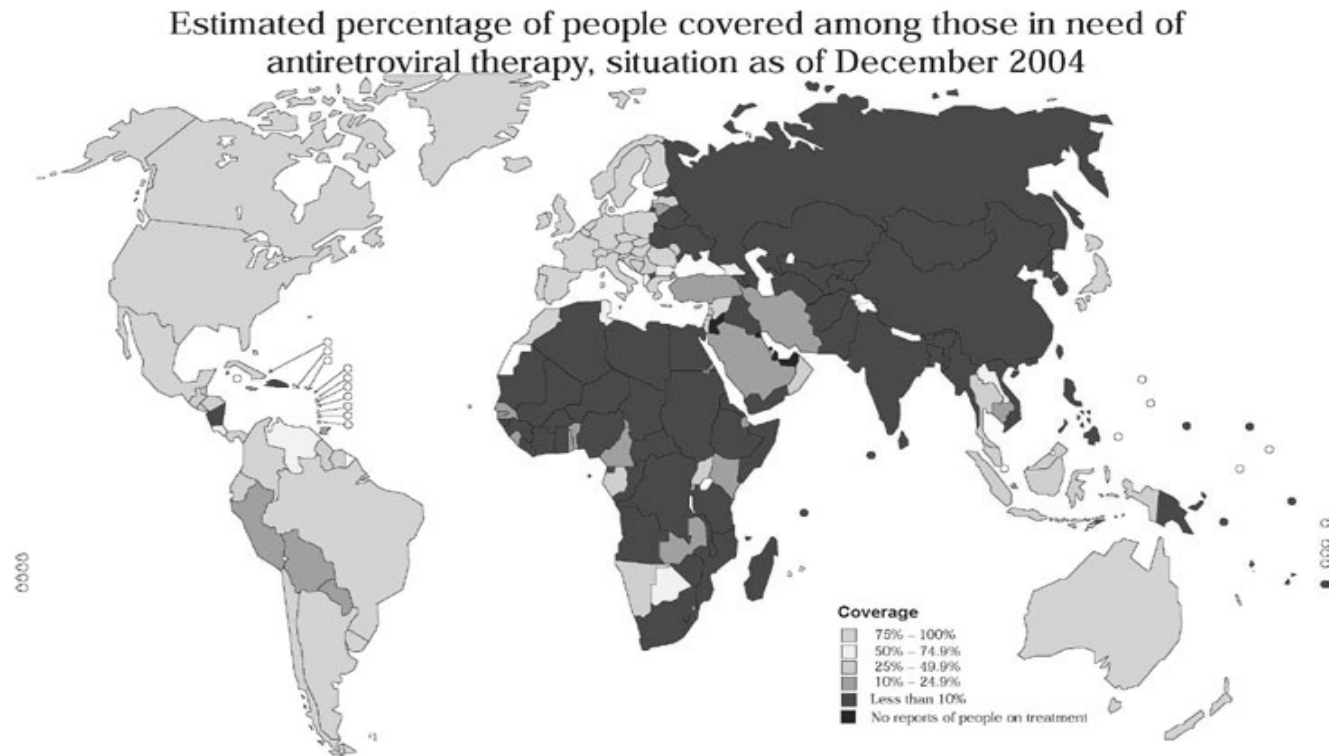
How does post-trial access work in practice?

Data from HIV/AIDS Clinical Trials

- 2 studies in published literature
- 1 study looked at 31 trials conducted by a variety of sponsors from 1987-2006, majority of trials were in U.S. only.
- 1 study looked at 18 NIH-sponsored trials from 2005-2008 subject to NIH policy on post-trial access, all trials had sites in developing countries.

Background

As of December 2004, the World Health Organization documented that in many countries, less than 10% of those who needed antiretroviral therapy had access to it.



The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dashed lines represent approximate border lines for which there may not yet be full agreement.

Data on post-trial access in HIV clinical trials

- Study reviewing phase 3 and phase 4 antiretroviral trials from 1987-2006 from clinicaltrials.gov, FDA records, and AIDS Clinical Trials Group registry.
- Obtained and examined informed consent documents and protocols for 31 trials (half of sample that met inclusion criteria).
- 58% of trials in sample were conducted entirely in U.S.

Ciaranello A, Walensky RP, Sax PE, Chang Y, Freedberg KA, Weissman JS.,
HIV Clinical Trials (Jan./Feb. 2009).

Data on post-trial access in HIV clinical trials

- Post-trial services were mentioned in 14/31 trials.
- Documents from 12 trials mentioned post-trial medications. Of these:
 - 2 trials did not provide medications.
 - 10 trials offered to provide medications after the trial was over.

Data on post-trial access in HIV clinical trials

- Of the 10 trials offering to provide post-trial medications:
 - 7 were industry-sponsored
 - 7 offered study drug, 1 offered study drug + background ART, and 2 offered the “best available treatment”

For how long and at whose expense?

- Of the 10 trials, post-trial drugs offered until:
 - Commercial availability in 6 trials
 - Rollover trial stopped in 1 trial
 - Unspecified in 3 trials
- Post-trial drugs offered
 - At sponsor expense in 8 trials
 - At participant expense in 1 trial
 - Unspecified in 1 trial

Conclusions from Study 1

- Evidence that post-trial access was being addressed by some researchers even before the major ethical guidelines were issued.
- Some industry and other sponsors provide and fund post-trial access to study drug for participants, but apparently not beyond commercial availability.

Limitations

- Did not look at documents other than protocols or ICs—could not identify plans that were not captured in this way
- Small sample size
- Had to exclude $\frac{1}{2}$ of relevant studies in sample because of lack of access to documents

NIH Guidance: Access to ART

- In March of 2005, the NIH issued guidance regarding post-trial access to antiretroviral treatment (ART).

<http://grants.nih.gov/grants/policy/antiretroviral/>



Study of the Implementation of the Guidance

- We had heard of one creative approach to complying with the guidance
 - An investigator started a non-profit organization selling artwork from Zimbabwe to raise funds for ART
- We decided to conduct a qualitative study to learn more about its implementation and describe how NIH-funded investigators of ART studies have addressed the guidance.

S. Shah, S. Elmer, C. Grady, American Journal of Public Health (September 2009).

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.”

NIH Guidance

- However, the Guidance document notes that “NIH’s authority to ‘encourage and support research’ does not extend to providing treatment following the completion of that research. 42 USC 284(b)(1)(A).”
- Therefore, the NIH recommends “investigators/contractors work with host countries’ authorities and other stakeholders to identify available sources of antiretroviral treatment.”

Implementation

- Applicants should describe their plans in a manner that identifies available sources, if any, for post-trial access.
- Applies to both NIH-funded grants and contracts.
- Priority in funding decisions may be given to sites with post-trial plans.

Results

- We analyzed what appears to be all Division of AIDS protocols that were subject to the guidance as of July, 2006.
 - 18 protocols
 - 14 developing countries
 - At least 96 sites* in countries such as:
 - South Africa, India, Thailand, Brazil, Malawi, Uganda, Zimbabwe, Haiti, Botswana, Senegal, Cambodia, Peru, Tanzania, Kenya, Zambia.

Results

- Each of the 18 studies (100%) addressed the issue of post-trial access for trial participants.
- All but one of the studies discussed post-trial access in the protocol or the included sample informed consent form.
- For the one study that did not address post-trial access in the protocol, site-specific plans for access were addressed in letters sent to DAIDS.

Results

- 13 studies explicitly identified mechanisms through which post-trial access could be obtained.
- Half of the studies described coordination with external funding sources such as the President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund, or nationwide access programs.
- 1 study simply indicated that participants could purchase their drugs at a clinic for the equivalent of U.S.\$30-150 per month.

Results

- Three studies made mention of other external sources of ART:
 - Employer plans
 - Enrollment in other trials
- Very few investigators gave guarantees of post-trial access.
 - One study promised a two-month supply of ART to ease the transition to the nationwide program

An example

- “At the end of the study, you will qualify for treatment in the XXX Government National Antiretroviral Treatment Program, and your treatment will be transferred to the Government Program. The Government Program currently uses some but not all of the drugs available in the study.”

Results

- NIH-funded HIV investigators studying antiretroviral (ART) drugs in the developing world are addressing the issue of post-trial access.
- There were no NIH-funded guarantees of post-trial access, which was consistent with NIH guidance.
- Efforts typically involve partnership with health ministries and officials in developing countries.

Effects of the guidance

- The Guidance encourages investigators to contact Ministries of Health well in advance of the need for post-trial access.
 - Helps ensure that local officials can anticipate the trial participants' needs at the conclusion of a trial.
 - May promote collaborative partnerships.

Going beyond the guidance

- Some investigators addressed concerns beyond the guidance, such as:
 - Addressing whether drugs available through existing programs complemented the drugs offered on study.
 - Planning an immediate system to provide ART for subjects who withdraw from the study.
- These plans focused on easing the transition for subjects to some other form of care.

One creative solution

- One study planned to explore networking with various organizations, and attempt to raise money from local philanthropists and industrial houses to provide ART.

Variation in Local Contexts

- To some degree, plans reflect variation in available resources and national programs.
 - Studies conducted in Brazil could rely on the Brazilian government's provision of national health care and ART to ensure post-trial access for participants.
 - Researchers conducting studies in countries without a system of access to antiretroviral drugs must work harder to develop plans for post-trial provision of care—e.g., study that indicated where drugs could be purchased.
 - Important to note that there is a trade-off here.

Trade-off

- There is a 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 to address local health concerns and provide fair access to research benefits.

Uncertainty

- Uncertainty was an issue. One site noted that:

“It should be noted that this plan for post-trial care attempts to anticipate situations that will be occurring years in the future. Changes in government and non-governmental funding may affect the treatment options participants will have in the future. Rest assured, XXX will make every effort to secure the best possible care for study participants.”

Limitations

- Some studies may have had post-trial plan details not described in any documents.
- We cannot determine from our data how many research subjects in these studies actually obtained (or will obtain) access to ART.
 - Many studies were ongoing, so we cannot yet assess how post-trial plans for access are implemented.

Unresolved issues regarding post-trial access

Issues in post-trial obligations for HIV/AIDS

- Partnership with others will not solve the problem because there still are gaps in post-trial availability:
 - Many developing countries only provide therapy when CD4+ counts drop below 250
 - Developed countries provide treatment when CD4+ > 350
 - Emerging data suggests that people should be treated even earlier
 - What obligations do researchers have if countries cannot afford to do this?

Post-trial obligations for HIV/AIDS

- And gaps in availability for certain groups:
 - Many adolescents in developing countries are not diagnosed and have poor access to ART.
 - Should researchers focus on developing more feasible approaches to treating adolescents through research studies?
 - Or involving adolescents in trials to get them access to treatment?
 - But what happens afterwards?

Extrapolating to diseases other than HIV

- Post-trial access for HIV/AIDS antiretroviral trials in developing countries is:
 - More challenging than other diseases in some respects—requires expensive, life-long, and potentially life-saving treatment in contexts that may lack the necessary health care infrastructure.
 - But data and increasing number of funding mechanisms are available for HIV/AIDS.

Extrapolating to other diseases

Diseases other than HIV/AIDS:

- Short-term treatment of acute illness or prevention modalities may be more feasible
- But we may need more data on post-trial access here
- Challenges remain for diseases:
 - That are chronic (e.g., diabetes),
 - For which treatment occurs in tertiary care facilities (e.g., surgical interventions for heart disease), or
 - Requiring expensive and complicated treatment regimens for a period of time (e.g., cancer chemotherapy).

Is a lack of post-trial access a reason not to do a study?

- If the justification for post-trial access is to prevent harm caused by the research, maybe so.
 - E.g., if treatment interruption or development of resistance to the study drug outweighs the benefits → research participation could harm participants.
- If the study provides benefit to subjects on balance, could it be acceptable anyway?

Conclusions

- It is important to consider post-trial obligations in advance of conducting international research.
- Some researchers studying HIV/AIDS have attempted to fulfill their obligations by transitioning subjects to local sources of care.

Conclusions

- More data are needed on how post-trial access plans are implemented, and what plans are being developed for diseases other than HIV/AIDS.
- In the meantime, flexible guidance may encourage investigators to coordinate with local officials well in advance of the need for post-trial access, which could increase the chances that plans for post-trial access will endure.

Postscript: What happened with the HIV trial in South Africa?

- Based on the lack of post-trial access, the ethics committee decided not to approve the trial.
- Activists and community members objected because they:
 - Preferred access during the trial to no access at all.
 - Argued that this trial might help them demand access to ART from their government more systematically.
 - Said the trial might help them bide time until ART was more readily available.

Postscript

- The ethics committee approved the trial without a guarantee of post-trial access.
- Today, ART is widely available in South Africa through government programs and donor funding, although there are still gaps to be filled.