The Ethics of Clinical Research in the Third World

An essential ethical condition for a randomized clinical trial comparing two treatments for a disease is that there be no good reason for thinking one is better than the other. Usually, investigators hope and even expect that the new treatment will be better, but there should not be solid evidence one way or the other. If there is, not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial. The necessity for investigators to be in this state of equipoise applies to placebo-controlled trials, as well. Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment.

Investigators are responsible for all subjects enrolled in a trial, not just some of them, and the goals of the research are always secondary to the well-being of the participants. Those requirements are made clear in the Declaration of Helsinki of the World Health Organization (WHO), which is widely regarded as providing the fundamental guiding principles of research involving human subjects. It states, "In research on man [sic], the interest of science and society should never take precedence over considerations related to the wellbeing of the subject," and "In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method."

One reason ethical codes are unequivocal about investigators' primary obligation to care for the human subjects of their research is the strong temptation to subordinate the subjects' welfare to the objectives of the study. That is particularly likely when the research question is extremely important and the answer would probably improve the care of future patients substantially. In those circumstances, it is sometimes argued explicitly that obtaining a rapid, unambiguous answer to the research question is the primary ethical obligation. With the most altruistic of motives, then, researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end. When that line is crossed, there is very little left to the value of the intervention being studied compared to the harms inflicted.

A textbook example of unethical research is the Tuskegee Study of Untreated Syphilis. In that study, which was sponsored by the U.S. Public Health Service and lasted from 1932 to 1972, 412 poor African-American men with untreated syphilis were followed and compared with 204 men free of the disease to determine the natural history of syphilis. Although there was no very good treatment available at the time the study began (heavy metals were the standard treatment), the research continued even after penicillin became widely available and was known to be highly effective against syphilis. The study was not terminated until it came to the attention of a reporter and the outrage provoked by front-page stories in the Washington Star and New York Times embarrassed the Nixon administration into calling a halt to it. The ethical violations were multiple: Subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best known treatment; and the study was continued even after highly effective treatment became available. And what were the arguments in favor of the Tuskegee study? That these poor African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if there were no study; and that the study was important (a "never-to-be-repeated opportunity," said one physician after penicillin became available). Ethical concern was even stood on its head when it was suggested that not only was the information valuable, but it was especially so for people like the subjects — an impoverished rural population with a very high rate of untreated syphilis. The only lament seemed to be that many of the subjects inadvertently received treatment by other doctors.

Some of these issues are raised by Lurie and Wolfe elsewhere in this issue of the Journal. They discuss the ethics of ongoing trials in the Third World of regimens to prevent the vertical transmission of human immunodeficiency virus (HIV) infection. All except one of the trials employ placebo-treated control groups, despite the fact that zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the United States for all HIV-infected pregnant women. The justifications are reminiscent of those for the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World. Thus, in response to protests from Wolfe and others to the secretary of Health and Human Services, the directors of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) — the organizations sponsoring the studies — argued, "It is an unfortunate fact that the current standard of perinatal care for the HIV-infected pregnant women in the sites of the studies does not include any HIV prophylactic intervention at all," and the inclusion of placebo controls "will result in the most rapid, accurate, and reliable answer to the question of the value of the intervention being studied compared to the local
Also in this issue of the *Journal*, Whalen et al. report the results of a clinical trial in Uganda of various regimens of prophylaxis against tuberculosis in HIV-infected adults, most of whom had positive tuberculin skin tests. This study, too, employed a placebo-controlled group, and in some ways it is analogous to the studies criticized by Lurie and Wolfe. In the United States it would probably be impossible to carry out such a study, because of long-standing official recommendations that HIV-infected persons with positive tuberculin skin tests receive prophylaxis against tuberculosis. The first was issued in 1990 by the CDC's Advisory Committee for Elimination of Tuberculosis. It stated that tuberculosis-test-positive persons with HIV infection "should be considered candidates for preventive therapy." Three years later, the recommendation was reiterated more strongly in a joint statement by the American Thoracic Society and the CDC, in collaboration with the Infectious Diseases Society of America and the American Academy of Pediatrics. According to this statement, "... the identification of persons with dual infection and the administration of preventive therapy to these persons is of great importance." However, some believe that these recommendations were premature, since they were based largely on the success of prophylaxis in HIV-negative persons.

Whether the study by Whalen et al. was ethical depends, in my view, entirely on the strength of the preexisting evidence. Only if there was genuine doubt about the benefits of prophylaxis would a placebo group be ethically justified. This is not the place to review the scientific evidence, some of which is discussed in the editorial of Msamanga and Fawzi elsewhere in this issue. Suffice it to say that the case is debatable. Msamanga and Fawzi conclude that "future studies should not include a placebo group, since preventive therapy should be considered the standard of care." I agree. The difficult question is whether there should have been a placebo group in the first place.

Although I believe an argument can be made that a placebo-controlled trial was ethically justifiable because it was still uncertain whether prophylaxis would work, it should not be argued that it was ethical because no prophylaxis is the "local standard of care" in sub-Saharan Africa. For reasons discussed by Lurie and Wolfe, that reasoning is badly flawed. As mentioned earlier, the Declaration of Helsinki requires control groups to receive the "best" current treatment, not the local one. The shift in wording between "best" and "local" may be slight, but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsoring country. Furthermore, it directly contradicts the Department of Health and Human Services' own regulations governing U.S.-sponsored research in foreign countries, as well as joint guidelines for research in the Third World issued by WHO and the Council for International Organizations of Medical Sciences, which require that human subjects receive protection at least equivalent to that in the sponsoring country. The fact that Whalen et al. offered isoniazid to the placebo group when it was found superior to placebo indicates that they were aware of their responsibility to all the subjects in the trial.

The *Journal* has taken the position that it will not publish reports of unethical research, regardless of their scientific merit. After deliberating at length about the study by Whalen at al., the editors concluded that publication was ethically justified, although there remain differences among us. The fact that the subjects gave informed consent and the study was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee certainly supported our decision but did not allay all our misgivings. It is still important to determine whether clinical studies are consistent with preexisting, widely accepted ethical guidelines, such as the Declaration of Helsinki, and with federal regulations, since they cannot be influenced by pressures specific to a particular study.

Quite apart from the merits of the study by Whalen et al., there is a larger issue. There appears to be a general retreat from the clear principles enunciated in the Nuremberg Code and the Declaration of Helsinki as applied to research in the Third World. Why is that? Is it because the "local standard of care" is different? I don't think so. In my view, that is merely a self-serving justification after the fact. Is it because diseases and their treatments are very different in the Third World, so that information gained in the industrialized world has no relevance and we have to start from scratch? That, too, seems an unlikely explanation, although here again it is often offered as a justification. Sometimes there may be relevant differences between populations, but that cannot be assumed. Unless there are specific indications to the contrary, the safest and most reasonable position is that people everywhere are likely to respond similarly to the same treatment.

I think we have to look elsewhere for the real reasons. One of them may be a slavish adherence to the tenets of clinical trials. According to these, all trials should be randomized, double-blind, and placebo-controlled, if at all possible. That rigidity may explain the NIHs' pressure on Marc Lallemant to include a placebo group in his study, as described by Lurie and Wolfe. Sometimes journals are blamed for the problem, because they are thought to demand strict conformity to the standard methods. That is not true, at least not at this journal. We do not want a scientifically neat study if it is ethically flawed, but like Lurie and Wolfe we believe that in many cases it is possible, with a little ingenuity, to have both scientific and ethical rigor.

The retreat from ethical principles may also be explained by some of the exigencies of doing clinical research in an increasingly regulated and competitive environment. Research in the Third World looks relatively attractive as it becomes better funded and regulations at home become more restrictive. Despite the existence of codes requiring that human subjects receive at least the same protection abroad as at home, they are still honored partly in the breach. The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives. To survive, it is necessary to get the work done as quickly as possible, with a minimum of obstacles. When these considerations prevail, it seems as if we have not come very far from Tuskegee after all. Those of us in the research community need to redouble our commitment to the highest ethical standards, no matter where the research is conducted, and sponsoring agencies need to enforce those standards, not undercut them.

Marcia Angell, M.D.
References


Related Letters:

Questions about a Placebo-Controlled Trial of Preventive Therapy for Tuberculosis in HIV-Infected Ugandans

Desvarieux M., Turner M. T., Whalen C. C., Johnson J. L., Mugerwa R. D., Ellner J. J., Msamanga G., Angell M.


Articles cited in this paper:

- Wendler, D., Emanuel, E. J., Lie, R. K. (2004). The Standard of Care Debate: Can Research in Developing Countries Be Both Ethical and Responsive...
to Those Countries' Health Needs?. Am. J. Public Health 94: 923-928 [Abstract] [Full Text]


- (1997). Tuberculosis Prophylaxis in Africa and Clinical Trials in Developing Countries. AIDS Clin Care 1997: 5-5 [Full Text]

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NIMH Project Accept  
Baseline Behavioral Assessment  
Incident Report

Site: 3 – Tanzania  
Principal Investigator: Dr. Jessie Mbwambo  
Date of Report: 24 June, 2005  
Date of Incident: 10-16 June, 2005

Community: 1  
Type of Report: Initial Report

Description of Incident:

An unexpected incident happened concerning the behavior of one of the Baseline Assessment Interviewers. Interviewer 06 completed two major infractions. Evidence exists confirming that the dates of the misconduct range from 10-16 June, 2005.

The first major infraction involves falsification of study documents. Interviewer 06 completed three CRF’s without having contacted and interviewed the selected participants. # and # were fabricated on Friday, 10 June. # was fabricated on Tuesday, 14 June. Two of these CRF’s, # and # had already been DataFaxed to Thailand before we became aware of their fabrication.

The second major infraction involves forging signatures of the sub-village leaders whose job it is to guide the interviewers around the sub-villages for Tsh3,000 per day. Interviewer 06 did not pay four different sub-village leaders – from Bepere, Bondeni, Vihingo, and Mtukula – for a day of work, yet received money from the Baseline Assessment Coordinator, amounting to a total of Tsh12,000. In addition to not paying the sub-village leaders their wage, Interviewer 06 did not return the money to the Baseline Assessment Coordinator at the end of the day. He forged the signatures of the four leaders on the log form that the leaders fill out to confirm they have received the money. Also, to cover up the money he stole, on a subsequent day Interviewer 06 asked one sub-village leader to print his own name to resemble the forgery Interviewer 06 had made the previous day.

Additionally, minor occurrences of Interviewer 06’s misconduct have come to our attention. He has accrued numerous debts from local businesses in Kisarawe and Community 1 (Mzenga) amounting to over Tsh70,000.

Action Taken:

1. Suspicion around Interviewer 06’s behavior first arose on Monday, 13 June when he returned from the field with 5 completed interviews while reporting that he had visited 3 different sub-villages. The time needed to travel between the sub-
villages and conduct the interviews did not seem adequate to accomplish the task.

2. On Tuesday, 14 June, another interviewer reported that a sub-village leader complained that Interviewer 06 had not paid the leader for guiding Interviewer 06 around the sub-village.

3. On Wednesday, 15 June, the Baseline Coordinator and Research Coordinator investigated the rumor that Interviewer 06 had not paid sub-village leaders. Four sub-village leaders – one each from Bepere, Bondeni, Vihingo, and Mtukhula – confirmed and complained about not receiving money from Interviewer 06.

4. On Thursday, 16 June, a study driver confirmed that he did not take Interviewer 06 to a sub-village from which Interviewer 06 turned in a completed CRF on Friday, 10 June. The Baseline Assessment and Research Coordinator verified this by inspecting the driver's log book.

5. On Thursday, 16 June, two pairs of Interviewer 06's HHCF's final code 98 were found to have times that overlapped while conducting the survey,
   - HHID #55 start time: 10:00 am, end time: *11:05 am
   - HHID #51 start time: *10:42 am, end time: 11:20 am.
   *note that #55 ends after #51 starts

6. On Friday, 17 June, the Project Director – together with the Intervention Coordinator, Research Coordinator and Baseline Assessment Coordinator – met with Interviewer 06 to present to him the evidence they had collected.

7. The PI terminated Interviewer 06's employment on Friday, 17 June, effective immediately. Interviewer 06 will receive his salary for the work he did minus the amount he owes to local Kisarawe businesses and the sub-village leaders, but he will not receive fringe benefits normally given for good work performance.

8. The Baseline Coordinator apologized to the sub-village leaders on 15 June. The Field Supervisors reiterated these apologies on 17-18 June. The Project Director will reaffirm these apologies to the sub-village leaders one more time after the conclusion of the investigation into the incident, as well as informing them of the final results of the investigation (e.g. termination of Interviewer 06's employment).

9. On Thursday, 16 June, sub-village leaders were paid by Project Afiki the amount owed to them on Thursday, 16 June.

10. On 17, 18, 20, and 21 June, the Baseline Assessment Field Supervisors confirmed the information and all preliminary & final codes on Interviewer 06's HHCFs, as well as conducting Quality Assurance Activities on all Code 98 completed surveys that Interviewer 06 had turned in for Batches 3-6. Of the 19 completed Code 98's, 16 were found to be legitimate and 3 were found to be
falsified with none of the participants having ever been interviewed by Interviewer ….

11. On Friday, 17 June, the Project Director warned all the entire Project Afiki staff about the implications and repercussions of forging data to ensure that other team members will not do it. On Monday, 20 June, the Baseline Assessment Coordinator shared the same message again with all the staff on the Baseline Assessment Team.

12. Two out of the three falsified CRF's have already been Datafaxed to Thailand. One falsified CRF, ___, ultimately resulted in a valid code 98. The new CRF for ___ will be re-sent by DataFax. Another falsified CRF, ___, resulted in a valid code 04. The information previously DataFaxed from the falsified CRF ___ will need to be removed from the data set. The third falsified CRF, ___, resulted in a valid code 93. No follow-up will need to be done with Thailand as this CRF had not yet been sent by DataFax. All of the three falsified CRF's will be shredded upon completion of the investigation.

13. The Baseline Assessment Team delayed completion of surveying activities in Community 1 until all of Interviewer ___'s surveys coded 98 were confirmed in order to ensure that all 301 CRF's with code 98 from Community were valid.

14. Systems have been developed to keep better track of the money interviewers pay to the sub-village leaders.

15. Systems are being developed to check the times on a sample of HHCF's to ensure that multiple HHs are not being visited at the same time. It will become a weekly activity as part of the field supervisors' quality assurance responsibilities.

16. Systems have been developed to better monitor the distribution of CRF's and HHCF's every day. Interviewers will be required to sign a log book every time they have one of these forms in their possession.

17. Results of this investigation were shared with the Kisarawe District Commissioner, the District Executive Director, the District Administrative Secretary and the District Medical Officer.

Was this an Adverse Event? ____ (Y) __ (N)

Signature of Reporter: ___________________________ Date of Signature: 24.06.05

__________________
(Print Name)

Signature of PI: ___________________________ Date of Signature: _________
NIMH Project Accept

Incident Report

Site: Tanzania
Principal Investigator: Dr. Jessie Mbwambo

Date Report Completed: 11 August 2009
Date of Incident: June - July 2009
Type of Incident: Conflict between Community Member and PIA Pilot Team

Community: Msimbu – PIA Community
Household ID: 
Participant ID: 
Initials of Head of Household: R.O. (age 55)

Description of Incident:

One household randomly selected for participation in our Post-Intervention Assessment (PIA) Pilot study completed household enumeration without any problems on May 25, 2009. The Head of Household, a female aged 55, assented to the enumeration and provided the ages of the members of her household. She listed multiple children and reported that there were four eligible participants.

When the PIA Pilot team returned to the household on June 17, 2009 to collect data, the same Head of Household told the Pilot Team that the eligible participants no longer lived in the household (either they had gotten married or moved away). Our team got the impression that the head of household was not telling the truth and that she had heard rumors regarding the study. The Head of Household would not listen to any explanations. As the team was preparing to leave, one of the eligible participants approached the team and said she wanted to participate in the surveys. She requested that the team come back the following day.

The PIA Pilot team returned the following day and the participant requested that they return on the following Monday. The Pilot team reported that the Head of Household said, “Why are you coming again? I know this kind of blood draws. It’s mumiani! I don’t want to speak to you because I know what you are doing.” [Mumiani is a Kiswahili term that refers a person who forces people to give blood. There were rumors circulating through Tanzania about twenty years ago that these people would stop people at the road, while they were traveling at night, etc. and draw all of their blood and leave them to die.]

When the team returned the following Monday, the participants were not reached for data collection. The same day, the sub-village leader visited the household alone. He saw a young man by the house who told him that he would beat up anyone who came to their home for pilot data collection.

The team reported the situation to the Pilot Coordinator and meet with the Msimbu/ Homboza village leaders (Thursday, June 25) to discuss how to approach the head of household.
Initial Response to the Incident:

On July 8, the Pilot Team discussed the incident with the Research Coordinator and they decided that they would not return to the household until they received feedback from the Principal Investigator. In a follow-up meeting on July 31, the Tanzania Principal Investigator agreed that the Pilot Team should not return to the household and that these events should be documented as an incident. In a conference call on August, the US PI agreed that the Pilot Team should not return to the household and that an Incident Report be drafted.

Follow-up Response to the Incident:

The Research Coordinator consulted with the study Assessment Committee on how to code the refusal of the Head of Household. Since the Head of Household initially provided assent and did not refuse enumeration, we did not know how to appropriately document the Head of Household’s actions.

We were advised by [redacted] (August 9, 2009) to change the household result code to H92 (Enumeration Refused by HoH). Even though enumeration was not refused, the head of household in effect reverted the initial assent for enumeration.

Consequences of the Incident:

There were no serious consequences or harm to the project staff. Four potentially eligible participants from one household in the pilot community were not included in the pilot assessment.

Resolution & Measures to Prevent Recurrence:

The Research Coordinator will follow-up with the Pilot Team to discuss this incident. The Team will be instructed to report similar incidents sooner and to respect the Head of Household’s decision to refuse participation in the study, even after he/she has assented to household enumeration.

All field staff will be reminded that their safety is a priority and that they should report any form of harassment or threats to their immediate supervisor as soon as possible.
NIMH Project Accept

Incident Report

Site: Tanzania
Principal Investigator: Dr. Jessie Mbambo

Date Report Completed: 18 March 2010
Date of Incident: 25 February 2010 – 4 March 2010
Type of Incident: Conflict between Head of Household and Sub-Village Leader assisting PIA Team

Community: Vikumburu – PIA Community #7
Household ID: 000
Participant ID: n/a
Initials of Head of Household: E.M.

Description of Incident:

On February 25, 2010, a Project Accept PIA Interviewer along with the Sub-Village Leader approached a household to make contact with the Head of Household (HoH). The HoH quickly got angered and chased the Interviewer and Sub-Village Leader away from the house. While running away from the house, the Head of Household caught up to the Sub-Village Leader and hit him on the face and chest. The Sub-Village Leader was not injured. The HoH did not catch up to the Project Accept Interviewer, who ran to the next household.

This was the third visit to this particular household to try to conduct household enumeration. The enumeration was not completed on the first two visits to the household. During the first visit (Feb 15, 2010), the HoH was not home. During the second visit (Feb 18, 2010), the HoH was home but said he was busy preparing charcoal and did not have time to participate. The Project Accept Interviewer felt as though the HoH was irritated during this second visit, but reported that the HoH did not refuse household enumeration.

Immediately after the incident took place (on Feb 25th), information was circulated to the village leaders. The village leaders used the local security officer in the village to bring the HoH to the office. Project Accept staff were not involved in this meeting as the issue was under the authority of the village leadership. The following week, the Village Leader reported to the PIA Coordinator that the HoH had apologized for his actions and explained that the situation resulted from a miscommunication when the Sub-Village Leader joked to the HoH while approaching the house.

Initial Response to the Incident:

This incident was reported by the PIA Coordinator via e-mail to the Tanzania-based Principle Investigator, Co-Principle Investigators, Research Coordinator, and other key personnel on the evening on February 25th. The group discussed the incident in person on the following day and it was recommended that the Interviewer involved talk about the situation with one of the Co-
Pis on the following working day. This was recommended to make sure the Interviewer was not too distressed by the incident. This discussion took place on Monday, March 1st, 2010.

The incident was reported by the Research Coordinator to the US-based PI and US-based Research Coordinator on February 26th.

**Follow-up Response to the Incident:**

The household result code for this household was marked as a Final Code H92 (Enumeration Refused by HoH). The PIA Coordinator communicated with the Village Leader and Sub-Village Leader about the situation. The PIA Coordinator also discussed this situation with the PIA Team and the staff involved. While the HoH seemed irritated during the 2nd visit, the Interviewer felt that the HoH did not refuse enumeration at this time. The PIA Coordinator emphasized the importance of respecting the HoH's right to refuse enumeration in the future.

**Consequences of the Incident:**

There were no serious consequences or harm to the project staff. The Sub-Village Leader assisting with PIA activities was not injured. The Household was coded as a refusal so any potentially eligible participants from this household were excluded.

**Resolution & Measures to Prevent Recurrence:**

The PIA Coordinator and Research Coordinator will follow-up with the PIA Team to discuss this incident. All field staff will be reminded that their safety is the top priority and that they should report any form of harassment or threats to their immediate supervisor as soon as possible.

__Signature__

__Date__

M. Wondimu

March 19, 2010