Education and debate

Establishing ethical trials for treatment and prevention of AIDS in developing countries

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Developing countries have been hardest hit by HIV but often cannot afford the expensive drugs or high tech health care used in Western countries. How can researchers and sponsors of trials investigating treatment and prevention of HIV in developing countries make sure they take proper account of local conditions?

As the HIV epidemic continues to spread, clinical and prevention trials are needed in developing nations to learn how best to alleviate suffering. Such international trials, however, raise ethical concerns because of great disparities in wealth, power, and medical infrastructure and a history of exploitation. Several reports suggest broad ethical and policy guidelines for trials in developing countries (box 1).¹⁻⁵ However, such guidelines may be too general to resolve many controversies that arise in the context of specific trials.⁴ Because of substantive disagreements regarding such international trials, measures that assure procedural fairness are vital. We argue that partnerships between developed and developing countries are essential to working out ethical problems that arise in particular trials and propose steps to ensure that such partnerships are effective.

Partnerships with stakeholders

For research to be effective, partnerships must be established with researchers, government agencies,

Street theatre can improve community knowledge and enable informed consent

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Box 1: Guidelines for clinical and prevention trials in developing nations¹⁻⁵

- Research must be responsive to the needs of host nations and consistent with their priorities for health care
- Although it may sometimes be ethically appropriate to provide participants in the control group with a lower standard of care than in developed countries, such discrepancies need to be approved by the ethics review committee in the host country
- Researchers and sponsors need to make reasonable efforts to secure access after the trial to experimental interventions that were proved effective
- Informed consent must be obtained from participants, although the documentation of consent may vary
- Sponsors and researchers from developed countries need to help build capacity for clinical trials and ethical review of research in developing countries

and community leaders in host countries at the planning stage of trials. It is all too common for host country partners to be presented with detailed protocols developed primarily by investigators and sponsors from developed nations and then given the opportunity to comment.⁶ This is too little, too late.

Partnerships between researchers in host and sponsoring nations will ensure that the proposed research meets the needs of the host country and can be carried out successfully. As the number of researchers in host countries and their skills are often limited, sponsors and researchers may have to invest in a host nation's infrastructure. Partnerships are also important with government agencies, such as ministries of health, which have political authority.⁷ Ideally, such cooperation will assure that a proposed project fits the host nation's health priorities and that interventions that are proved effective will become available.

Partnerships with community leaders and with people who might be eligible for the clinical trial are more challenging but essential. Researchers and government officials in the host country may have very different social and educational backgrounds from

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participants and thus not appreciate participants' views or how their concerns might be met.² Risks that are considered minimal in the United States, such as from drawing blood, may be regarded as serious in cultures with a different explanatory model of illness.^{2 4}

Community based partners can help identify issues that complicate the informed consent process, such as customs of deference to husbands, other relatives, or community leaders.^{2 4} They can also suggest how to strengthen the informed consent process—for example, using street theatre to educate the community before seeking consent from individual participants.² In some instances, government agencies are uninterested in, or even hostile to, research that host nation researchers and community partners strongly support. When legal, such research may go forward without government approval. Finally, partners who have been active in the design of the project might also suggest how to improve recruitment and follow up.⁸

Establishing community partnerships

Community partnership could be implemented through community advisory boards, comprised of leaders of non-governmental organisations and patient advocacy groups, healthcare workers providing services to people eligible for the trial, and those who have or are at risk of HIV and their relatives.^{6 8} Concerns have been raised about how to identify people who can legitimately represent or speak for a heterogeneous community that has diverse interests, viewpoints, and cultures.^{7 10 11} Indeed, there may be disagreements among people claiming to speak for a community. However, what is important is not that community advisory boards have power to approve or veto protocols, but that they have the opportunity to voice concerns and persuade other stakeholders to modify the clinical trial.^{8 9}

In our experience, it is important to consult widely within the community, asking who is influential in the community, held in high esteem, or heavily involved in grassroots projects. These discussions make the process of selecting an advisory board more transparent and help assure that the board is representative and respected. It is true that unscrupulous researchers could abuse partnerships by selecting boards that can be expected to approve ethically problematic trials. However, the possibility of abuse should not prevent well intentioned researchers from using community advisory boards to strengthen clinical trials.

Access to effective interventions

The ultimate goal of clinical trials is to improve the quality of medical care and health in the host nations. Practice often falls far short of this principle. Many interventions that were effective in clinical trials have not become available in developing countries where the research was carried out.² Such research is exploitative. Researchers and sponsors from developed countries need to discuss access to successful interventions after the trial with host country partners at the outset and make reasonable, good faith efforts to secure such access.^{2 4}

Because securing access to effective therapies is a complex political process, it is simplistic to assert that

research is unethical if it cannot assure such access. Although researchers can work with host nation partners to make the study intervention widely available, they cannot control the process of drug approval or funding in host nations. Governmental authorities may be reluctant, for political reasons, to approve an effective drug, as in the case of antiretroviral therapy in South Africa. One reason host country researchers and community advisory boards might want to do research when access cannot be assured is to set the stage for advocacy.

Box 2 provides examples of partnerships from scientists in the HIV Prevention Trials Network. In the first and third examples, host country partners in two trials reached different conclusions on whether it was acceptable to carry out a trial in which effective treatment would not be available to participants who were diagnosed as having a condition defined as an end point of the trial.^{8 9}

Specific steps to promote partnerships

Sponsors should fund partnerships as an integral part of clinical trials—If partnerships are to become a reality rather than a slogan, funds must be provided to train host country scientists, research staff, and members of ethics review committees and community advisory boards.^{2 3 4 6} Furthermore, members of ethics review committees and community advisory boards need to be compensated for their time and expenses.

Grant proposals should be reviewed for plans for building partnerships—Such scrutiny will encourage researchers to think creatively about building partnerships. Grant applications should include specific plans for how they will identify partners, organise an

Box 2: Examples of partnerships

Modifying the protocol—In a trial of a vaginal microbicide, abnormal cervical cytology was defined as an adverse outcome. Although long term follow up was available in all study sites for women with abnormal smear test results, follow up for colposcopic abnormalities was not. Host country partners argued persuasively against the use of colposcopy in this study, even though the power to detect adverse effects would be reduced. Colposcopy would be appropriate only for studies in developed countries, where long term follow up is available

Obtaining access to therapies after the trial—After conducting a randomised controlled trial showing that single dose nevirapine reduced mother to child transmission of HIV, US researchers worked with host nation partners to raise funds for pilot dissemination projects and to train healthcare workers to use nevirapine

Standard of care—A proposed randomised controlled trial comparing community and clinic based HIV testing and counselling did not have the funding or infrastructure to provide antiretroviral drugs to those identified as infected with HIV. Host country researchers, government officials, and community advisory boards judged that this trial was relevant to their needs and was ethically acceptable because it would show how best to identify people who could benefit from antiretroviral drugs once they became available

Summary points

In international clinical trials, scientists and sponsors in developed nations need to establish partnerships with stakeholders in developing countries

Partners should include researchers, government organisations, community leaders, and people who might be eligible for the trial

Partnerships must start during the planning stages of trials

Investigators and sponsors should take specific steps to promote partnerships

advisory board, and use partnerships to strengthen informed consent, help characterise the appropriate standard of care for the control group, and seek post-trial access to interventions. Review committees should include individuals who have experience with clinical trials in developing countries and understand the complexity of partnerships in this setting.

Partnerships should be continually strengthened—Just as researchers need to strive to improve recruitment and follow up during a clinical trial, they should also continually try to strengthen partnerships through quality improvement. Specific measures might include educational and outreach programmes to community groups, training for members of advisory boards about the scientific and ethical aspects of clinical trials, as well as attention to the dynamics of research team meetings.

Research team meetings need to promote partnerships—Meetings designed to build and sustain collaboration often subvert these goals because of cultural misunderstandings. Patterns of deference to authority based on age, experience, status, and sex may frustrate efforts to elicit feedback and discussion. As a result, collaborative meetings may actually contribute to or sustain a sense of disempowerment. Those who chair meetings must develop the skills to conduct project meetings in ways that ensure everyone speaks and is heard. For instance, chairs might need to explicitly invite people from developing countries to give their views, ask junior people to speak before more senior people have stated their position, or ask participants about their views in private as well as in meetings. Finally, chairs need to elicit the range of perspectives in communities—for example, by asking advisory board members what other perspectives are important in their communities.

Conclusions

By inclination and training, researchers may want to focus on the technical aspects of designing protocols and analysing data. However, researchers conducting clinical trials in developing countries have ethical obligations beyond those falling on researchers working in the developed world.⁴ No single profession, team, or country has a monopoly on wisdom. Establishing partnerships will assure procedural fairness and promote

the ethical conduct of clinical trials in a world characterised by grave inequities.

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Endpiece

A choice

When you reach your 60s, you have to decide whether you're going to be a sot or an ascetic. In other words, if you want to go on working after you're 60, some degree of asceticism is necessary.

Malcolm Muggeridge (1903-90),
British journalist

Fred Charatan,
retired geriatric physician, Florida