Research is urgently needed on diseases such as malaria and HIV infection, which are ravaging resource-poor countries. Medical interventions commonly used in developed nations may not be feasible in settings that lack refrigeration, clean water, or medical infrastructure. In addition, pharmaceutical manufacturers are increasingly carrying out clinical trials in resource-poor countries, where costs are lower and a large number of patients have not received previous treatment. Clinical trials sponsored by pharmaceutical companies often involve drugs for diseases such as hypertension and diabetes, whose primary market will be in developed countries. As illustrated in Table 22.1, research in resource-poor countries raises numerous ethical concerns at each step of a project.

HOW IS RESEARCH IN RESOURCE-POOR COUNTRIES DIFFERENT?

In resource-poor countries, the two primary means of protecting participants—IRB review and informed consent—may be inadequate. IRBs in developing countries may lack training, experience, and resources. IRBs in the United States are unlikely to be familiar with conditions in the host country (1). Informed consent may be problematic in a country where people are poorly educated and lack health literacy, and where physicians in clinical practice usually do not tell patients their diagnosis, admit uncertainty, or obtain consent. Participants may not accept Western models of disease. Furthermore, participants might hear rumors and other misinformation about a research study.

In several highly publicized cases, researchers from developed countries have been harshly criticized for allegedly carrying out inappropriately risky studies in resource-poor countries without adequate consent (3). Allegations of exploitation are complicated by the history of colonialism and the vast economic discrepancies between the North and South. For these reasons, researchers conducting international studies need to be particularly sensitive to ethical concerns. Randomized trials to prevent mother-to-child transmission of HIV infection dramatized these ethical issues (4,5).

STUDY 22.1 Prevention of mother-to-child transmission of HIV infection.

The vast majority of perinatal HIV infections occur in resource-poor countries. In 1994, a placebo-controlled randomized controlled trial (RCT) showed that zidovudine reduced the rate of transmission of HIV from infected pregnant women to their children from 25% to 7%. The treatment regimen was oral zidovudine starting in the second trimester plus intravenous zidovudine during labor plus oral administration to children for 6 weeks after birth. Although this treatment was quickly adopted in the United States and other developed countries, it...
DOES THE RESEARCH ADDRESS A HEALTH PRIORITY?

It would be an imprudent use of limited health care resources in a developing country to conduct human-participants research that does not address a health or public health priority in the host country. In light of the dire health care problems in resource-poor countries, there is little benefit from gaining knowledge about low-priority issues. Furthermore, research projects often pay higher salaries to health care workers than are available in clinical practice, eroding the medical and public health infrastructure. Because the ratio of benefits to burdens in such research would be inappropriate, the study would be unethical unless fair benefits could be negotiated with the communities in which the study is carried out. Since the results would not be relevant in the host country, the participants and their communities would bear the risks of research without the prospect of benefiting from the findings of the study. In particular, it is ethically problematic for researchers and sponsors from developed countries to carry out clinical trials to evaluate drugs that will be marketed exclusively or predominantly in developed countries.

ARE STUDY INTERVENTIONS APPROPRIATE?

Because of scarce resources and logistical constraints, medical interventions that are standard in developed countries may not be available or feasible in resource-poor countries where the trial is conducted. This creates an ethical tension between providing a benefit to research participants and obtaining generalizable scientific knowledge.

TABLE 22-1 Questions About Clinical Trials in Resource-Poor Countries

1. Does the research address a health or public health priority in the host country?
2. Are study interventions provided to participants appropriate?
   - Is a placebo control proposed?
   - Is background care for the condition under study appropriate?
   - Is ancillary care for other conditions appropriate?
   - If the control intervention would not be acceptable in the researchers’ own country, special justification is needed.
3. Are there barriers to informed consent, and how can they be overcome?
4. Will participants and their communities receive fair benefits?
5. Is IRB review rigorous?
6. Are stakeholders in the host country partners in the study?
USE OF PLACEBOS IN CLINICAL TRIALS IN DEVELOPING COUNTRIES

As discussed in Chapter 26, although placebo controls enhance the scientific rigor of a clinical trial, they may also raise ethical concerns. It is unethical for researchers to withhold a therapy that is known to be effective for the condition being studied if the subjects will suffer significant harm as a result of their participation.

Critics sharply attacked the use of placebos in Study 22.1 because an effective drug regimen was available in developed countries. It would be unethical to carry out a placebo-controlled trial for this condition in the developed world, and critics argued that a double standard that allowed a placebo control in developing countries would also be unethical. One critic wrote, “Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research” (6). From this viewpoint, an appropriate study design would be an equivalency trial comparing the short-course regimen with the standard treatment offered in the United States. The deputy editor of the New England Journal of Medicine attacked these placebo-controlled studies because they “subordinate the subjects’ welfare to the objectives of the study” (7). She compared these studies with the infamous Tuskegee study, which withheld effective treatment from poor, uneducated black research participants.

The 2000 revisions to the Declaration of Helsinki declared that new interventions “should be tested against . . . the best current prophylactic, diagnostic, and therapeutic methods” (8). Hence, the control group should receive the standard of care that is available in developed countries. In its deliberations, the World Medical Association rejected an alternative standard, that the control group should receive the “highest attainable and sustainable” level of care in the host country.

Others defended these mother-to-child transmission trials because placebo controls were necessary to address the health priorities of the host country (1). In a resource-poor country, the pertinent research, clinical, and public health question is whether short-course antiretroviral therapy (ART) would be more effective than what is currently available in the country, not how it compares with care that is unaffordable and impossible to implement. An equivalency trial would not address the former question. In this view, an equivalency trial would indeed be unethical because the results would not be relevant in the host country, and therefore the country would bear the risks of research without benefiting from its findings.

As a result of these debates, a “clarification” to the Helsinki Declaration was issued in 2002: “a placebo controlled trial may be ethically acceptable, even if proven therapy is available . . . [if] for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method” (8). In 2007, the World Health Organization declared: “The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations” (9). For example, if HIV prevention trials in the developed world are carried out with participants who are injection drug users or men having sex with other men, the results will not be applicable to populations in developing countries where HIV is predominantly transmitted through heterosexual intercourse.

The issue is commonly framed as the “standard of care” that must be provided to all study participants. However, in this chapter we avoid this term because it suggests that certain interventions are required or obligatory. It is contested whether researchers must provide to study participants all interventions that are “standard” in developed countries.

Study 22.1 is permissible under current international ethical guidelines. Without a placebo-controlled trial, it would be impossible to address a pressing public health question in the host country.

In these perinatal HIV trials, the placebo group had a lower transmission rate compared to historical rates. Thus, an equivalency trial would have overestimated the absolute benefit of the short-course intervention.

These clinical trials established proof of principle that antiretrovirals are feasible in developing countries. Subsequently, billions of dollars were made available through United Nations Joint
Programme on HIV/AIDS (UNAIDS), the President’s Emergency Plan for AIDS Relief (PEPFAR), and the Gates Foundation to provide antiretroviral therapy in resource-poor countries. Additional clinical trials were funded to test even simpler regimens and address transmission through breastfeeding. In these later trials, the control arm received the regimen that previous trials had shown to be the most effective in resource-poor settings.

**WHAT IS THE RESEARCHER’S OBLIGATION TO PROVIDE BACKGROUND CARE?**

What obligations do researchers have to provide to participants in a clinical trial interventions in addition to the study intervention? As the following case illustrates, there are two distinct questions: what background care researchers should provide for the condition being studied, and what ancillary care should they provide for other conditions they identify? This section deals with the former question, and the latter question is analyzed in the next section.

**STUDY 22.2**  
HIV prevention trial.

Researchers are carrying out a randomized controlled trial of a new microbicide for HIV prevention. Participants will return for follow-up evaluations 1 month after receiving the study or control intervention and every 6 months thereafter for 2 years. What obligations do researchers have to provide other HIV prevention measures, such as counseling and condoms?

According to the ethical obligation to minimize harm to participants, researchers should provide interventions that are known to be effective and feasible to prevent or treat the condition addressed in the clinical trial. In HIV prevention studies, researchers have a strong obligation to provide counseling for risk reduction and condoms (9). As discussed in Chapter 6, participants in clinical trials commonly have a therapeutic misconception; for example, in Study 22.2 they might mistakenly believe that they will receive an intervention that effectively prevents HIV infections. If researchers do not recommend and provide condoms, participants might mistakenly believe that they no longer need to use them. They might even increase risky behaviors as a result of this misunderstanding. Thus, to prevent harm to participants, HIV prevention researchers should provide standard, proven prevention measures (9). Such background care must be provided even though it will tend to reduce the number of study endpoints and thus lower the power of the trial. To avoid conflicts of interest, researchers could train persons who are independent of the study to provide high-quality counseling.

Specifying what interventions are standard or proven in resource-poor countries is often controversial. The general rule is that researchers should do what a reasonable physician in the host country would do under the circumstances. However, the interpretation of this general maxim depends on the specific circumstance. Condoms and counseling are affordable, feasible, and included in international guidelines for HIV prevention. A more controversial issue is whether researchers are obligated to provide all “state of the art” prevention services regardless of cost and sustainability. If the sponsor provides as background care intravenous medicines that are not feasible outside a research setting for the foreseeable future because of a lack of clean water and electricity, the results of the trial will not be applicable in the host country. Similarly, in a HIV prevention trial in injection drug users, it would make little sense for researchers to provide preventive measures that would not otherwise be permitted or available in the host country. For example, if methadone and needle exchange for injection drug users are illegal in the host country, researchers should respect such prohibitions. Furthermore, even if the researchers could persuade government officials to allow these measures for the duration of the trial, providing them to study participants would make the results of the trial inapplicable to other persons in the host country. Participants in the host country would therefore undergo risks and inconvenience to gain knowledge that would not benefit their countrymen. Arguably, the ratio of benefits to risks would then be unacceptable.
WHAT IS THE RESEARCHER’S OBLIGATION TO PROVIDE ANCILLARY CARE?
During a clinical trial, researchers might discover that participants have other illnesses or conditions that can be readily treated. What ancillary care should investigators provide during the study for these other conditions?

STUDY 22.2 (Continued).

During a trial of a new microbicide to prevent HIV infection in high-risk seronegative women in a sub-Saharan country, researchers identify some participants with the following conditions:

• Sexually transmitted infections, which could be treated with a short course of antibiotics.
• Pulmonary tuberculosis (TB), which would require an extended course of several months.
• New HIV infection in participants who were seronegative upon entry to the study.
• Children of participants are at risk for malaria, which could be prevented by mosquito nets.

What responsibility do the investigators have for providing care to prevent or treat these other medical conditions during the study?

By ancillary care, we mean interventions for other conditions that are not required to make a clinical trial scientifically rigorous or minimize risks caused by study procedures. Some claim that researchers have no responsibility to provide ancillary care during a clinical trial because the role of the researcher differs from that of the treating physician. In this view, the only interventions that researchers must provide are those needed to carry out the study in a safe and scientifically valid manner. Researchers cannot be expected to address all the medical problems that participants have or develop. An open-ended obligation to provide ancillary care in a resource-poor setting with limited basic health care might keep researchers from fulfilling their primary and unique goal of obtaining generalizable knowledge. However, this position has been criticized as treating participants merely as a means to achieve the ends of research. To critics, it seems inhumane for researchers not to alleviate suffering if they can readily do so at little burden to themselves.

One approach to ancillary care is based on reciprocity (10). In this view, participants in a clinical trial give permission for researchers to collect personal health information and carry out interventions. As a matter of reciprocity, researchers have limited obligations to respond to aspects of the participant’s health that are related to those interventions or to the information they need to conduct the trial. An alternative view of ancillary care is that participants entrust certain aspects of their health to the researcher (11,12). Such partial entrustment creates certain reciprocal obligations for researchers to respond to those aspects of health that were entrusted to them. However, it is questionable whether the researcher-participant relationship can be properly characterized as entrustment.

The extent of the researcher’s obligation to provide ancillary care during a clinical trial therefore will depend on several factors (10). There must be some limit to a researcher’s obligation to provide ancillary care, to ensure that there will be adequate resources to carry out the study protocol.

The Connection Between the Participant’s Condition and the Research Topic and Interventions
The more closely the condition is related to the research question and study design, the greater is the researcher’s responsibility to provide ancillary care.

STUDY 22.2 (Continued).

It is expected that some participants will develop HIV infection in the course of the trial; indeed, this is the primary endpoint of the study. Thus, identifying women with new infections is integral to the study design and researchers have a strong obligation to provide ancillary care, such as ART.
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STUDY 22.2 (Continued).

In Study 22.2, during follow-up evaluations, some participants can be expected to have sexually transmitted diseases (STDs). Researchers should be testing for STDs as part of the protocol because STDs may be a confounder or an adverse effect of the study intervention. Treatment for STDs is simple, and it would be convenient for the study participants to receive it from the researchers rather than a local source of medical care. It also would strengthen the validity of the study to document exactly what treatment was given.

In contrast, although TB and malaria are common in the host country, they are not as tightly linked to the study topic. Hence the obligation of researchers to provide care is weaker for the latter conditions.

The intensity and duration of the researcher-participant relationship

The stronger the researcher-participant relationship, arguably the stronger is the researcher’s responsibility to participants. And the more that a participant has done for a study, the stronger is the reciprocal obligation of the researchers to provide ancillary care.

STUDY 22.2 (Continued).

Researchers will have a strong relationship with participants. They will spend considerable time educating women about the proper use of the microbicide and answering their questions about this intimate intervention. This close relationship creates greater responsibilities to provide ancillary care.

The relative cost of ancillary care relative to the study budget

Researchers should try to write into their budget the costs of justified ancillary care. However, it would be unreasonable to expect researchers to spend so much time and study resources on ancillary care that they compromise the goal of obtaining generalizable knowledge.

STUDY 22.2 (Continued).

Treating STDs does not require follow-up visits or high costs. Although some study sponsors (such as the NIH) do not allow funds to be used for clinical care, a strong argument can be made that treating STDs is justified for research purposes as well as clinical purposes. In contrast, treating a chronic illness such as TB is more complicated and costly, requiring many follow-up visits.

The Extent of Ancillary Care Obligations

Researchers should first inform participants of other conditions they discover, explain what further care would be desirable, and arrange for additional care. In general, it is desirable to have participants receive ancillary care from providers outside the study site to prevent confusion over the researcher’s role. If the host country has a functioning health care system for the problem, referral would be sufficient. Dilemmas arise when, as often occurs in resource-poor countries, this is not the case. One option is for researchers to collaborate with a local hospital, for example, by establishing a research or demonstration project for conditions that would be unfeasible to treat at the research site, such as TB. Alternatively, the investigators could volunteer to serve as physicians or teachers at the hospital or clinic to improve the quality of care there.

Providing ancillary care only to trial participants but not to others in the community where the trial is conducted will widen health disparities in the resource-poor host country. Exacerbating health
disparities violates the principles of justice (13). Thus, researchers who provide ancillary care should do so in a way that ameliorates rather than worsens health disparities within the host country (13).

**STUDY 22.2** (Continued).

Researchers should provide ART to trial participants who develop incident HIV infection in a manner that would ameliorate health disparities. If researchers provide ART to participants at the research site, women in the trial who seroconvert will have much better care than women in the community who also develop HIV infection. Instead, it would be preferable for researchers to arrange to have research participants receive care through the country’s national HIV program and provide funds to do so if necessary. If the country does not need additional funding, researchers should provide an amount equivalent to the cost of antiretrovirals to improve the quality of care, for example, by reducing waiting times or improving transportation to national clinics.

Even in situations where researchers have no ethical obligation to provide ancillary care, it is praiseworthy for them to do so. Many researchers carrying out studies in resource-poor countries have devoted considerable time and energy to raising the standard of clinical care in the community where they conduct their research; this is to be commended and encouraged.

**STUDY 22.2** (Continued).

Although a researcher has only weak obligations to persons who are not study participants, there are humanitarian reasons to prevent serious disease in children, which would be more severe in the context of concomitant HIV infection acquired through mother-to-child transmission. Researchers could partner with charitable agencies that provide children with insecticide-treated mosquito nets to prevent malaria.

**WILL PARTICIPANTS AND COMMUNITIES RECEIVE FAIR BENEFITS?**

Because participants in a research study help researchers, sponsors, and society at large, they should receive some benefit in return as a matter of reciprocity. Advocates contend that researchers and sponsors must avoid taking unfair advantage of participants and their communities by providing those who bear the risks of research appropriate benefits, in addition to the long-term benefit of generalizable knowledge.

**AVAILABILITY OF THE STUDY INTERVENTION AFTER THE TRIAL**

Researchers and sponsors need to consider whether the study intervention will be available in the host country if it is shown to be effective and safe.

**STUDY 22.3** Recombinant surfactant in infants with respiratory distress syndrome (RDS).

In 2001, the manufacturer of a new recombinant surfactant proposed a randomized placebo-controlled trial in infants with RDS, a common life-threatening condition in premature infants. The study would be conducted in Latin America. In a three-arm trial, the other groups would receive placebo and an approved surfactant drug. In the developed world, natural surfactants are the standard of care for this condition, and a placebo-controlled trial would be considered unethical. Critics condemned the study as “exploitative” and charged that developing countries would not be able to afford the drug after the trial.
Study 22.3 raised several ethical concerns. Similarly to Study 22.1, the placebo arm of the trial was sharply attacked. Critics argued that better prenatal and obstetrical care is a much higher priority in resource-poor countries than neonatal intensive care. Thus, the placebo arm could not be justified (unlike Study 22.1) on the grounds that it was required to address a pressing public health priority in the host country.

An additional concern was access to the study intervention after the trial if it proved to be effective. The costs of the recombinant surfactant and ICUs would be prohibitive except for wealthy persons. Furthermore, the market for the drug would be much larger in developed countries than in the poor country where the trial was carried out. Thus, although the participants in Latin America would bear the risks of the trial, wealthier nations would obtain most of the benefits of the knowledge gained. This discrepancy violates the principle of justice.

To avoid such unfairness, some have proposed that if a trial shows that the study intervention is effective and safe, it should be made reasonably available in the host country. In this view, because the participants helped the researchers, sponsor, and society at large, they should receive some benefit in return. One proposed standard is reasonable access after the conclusion of the trial to treatments proven to be effective in the host country.

A number of practical and conceptual issues need to be worked out regarding reasonable availability or fair benefits.

**When is an Intervention Proven to be Effective?**

Usually the results of a single clinical trial do not change clinical practice. In general, favorable results from a clinical trial need to be replicated or confirmed in other research. Thus, it may be premature to introduce an intervention as a new standard of care on the basis of a single clinical trial.

**To Whom Should an Effective Intervention be Made Accessible?**

For participants in the active arm of a trial, the case for continued access would be particularly strong if the drug improved clinical symptoms in a chronic illness; it would be callous to withdraw the drug and allow relapse to occur. However, approval of a new drug in the host country is beyond the sponsor’s control and may require additional clinical trials. Thus sponsors are not in a position to guarantee post-trial access—they can only make good-faith efforts to provide it.

Participants in the control group, who have provided crucial outcomes data for the trial, have a strong reason to receive the investigational agent after the termination of the trial if it is medically appropriate. The argument again is based on reciprocity: all participants in a clinical trial deserve some personal benefit in return for their contributions. In Study 22.3, however, infants in the control group would not be eligible for surfactant at the conclusion of the trial.

Other persons in the community where a trial is carried out, who did not participate in the trial, have weaker claims to access to the investigational agent. Their contributions were substantially less than those of the participants. Furthermore, it would require a much greater commitment of resources to provide the study agent to such a large number of people.
What Constitutes Reasonable Access to the Study Intervention?

The term “reasonable access” is ambiguous. Must the new drug be free to host country citizens, or may the sponsor make it available at its cost? In Study 22.3, the cost to the manufacturer for the recombinant surfactant would still be prohibitive in an impoverished country. In addition, the cost of ICU equipment and staffing is considerable. Yet another question to be addressed is, how long after the conclusion of the trial should the researcher and sponsor make the intervention accessible?

Many discussions regarding reasonable access fail to take into account that rigorous evidence of the efficacy and safety of an intervention often set in motion forces that result in lower prices and new resources to provide the intervention. The hepatitis B vaccine and ART to prevent mother-to-child transmission of HIV infection are widely available today in developing countries because costs dropped sharply after pivotal trials were published and more resources became available to purchase them, not because they were guaranteed at the onset of the trial.

Who is Responsible for Ensuring Reasonable Access?

No single stakeholder has both the means and the resources to guarantee reasonable access (13). Although researchers are the public face of the trial, they do not have the long-term financial resources to guarantee access. Some sponsors, particularly large multinational drug companies, may be able to afford to pay for access to the intervention. However, small biotechnology startup companies may not be able to do so. The NIH cannot ensure post-trial access because it is forbidden by law to pay for the costs of clinical care. Finally, the host-country government plays a crucial role because only it has the authority to approve a new drug and provide the medical infrastructure to deliver it. In some cases, an argument could be made that the government’s responsibility to basic provide health care to its population should include covering a new drug in its national health program or trying to obtain external funds to cover it.

Overly high expectations to ensure reasonable availability of the study drug during the planning of a clinical trial will be counterproductive if they delay well-designed and ethically responsible clinical trials to evaluate a promising intervention.

In summary, none of these questions regarding post-trial access to a study drug have a definitive answer. Reasonable arguments can be made on both sides. The appropriate resolution will depend on the specifics of the situation and will need to be negotiated by the stakeholders.

FAIR BENEFITS

Some ethics experts point out that providing reasonable access to study interventions after a trial may be an inadequate reciprocation for participation in research. First, it is too limited and weak an obligation. If the study is something other than a pivotal clinical trial (for example, an epidemiological study), no additional benefits will be required. Even if the study is a clinical trial, it might be a negative study. Second, other benefits might be more useful to participants or their communities than the trial drug. For example, they might benefit more from better primary care or better education for host country health care workers. Third, the appropriate target group for benefits may be all persons in the community where the study is carried out, not just trial participants. Providing benefits only to trial participants will widen health disparities in the resource-poor host country and therefore raise concerns about causing injustice (13). Thus, providing benefits to the host country should be done in a way that ameliorates rather than worsens health disparities.

For these reasons, some writers argue that researchers and sponsors from the developed world should provide fair benefits to the research participants and their communities in reciprocity for what they contribute to the research (14). Otherwise, researchers and sponsors would be taking unfair advantage of them. “Fair benefits” is a broader and more flexible concept than reasonable access to the study intervention. Researchers could provide benefits to research participants in a number of ways, such as by providing health education or some basic health services; training local health care workers, researchers, and IRBs; donating equipment at the end of the study; and giving local inves-
Investigators a key role in analyzing data and writing papers. Such contributions ensure that the community where the research is carried out will receive benefits in reciprocity for participating in the research. By building infrastructure, researchers can help provide sustainable improvements that will help to narrow health disparities between rich and poor nations.

The type and amount of such collateral benefits to participants and communities should be negotiated among the sponsor, investigators, and host-country stakeholders before the study is launched. To overcome disparities in negotiating power, agreements should be made public so that other communities and countries will know what benefits might be achieved.

**STUDY 22.3 (Continued).**

Because of concerns about fairness, this trial was not carried out as proposed. Instead, an international multicenter RCT was conducted at sites in developed as well as developing nations. The control group in all countries received a currently approved form of surfactant.

Conducting the trial in both developed and developing countries resolved concerns about exploitation of vulnerable participants and communities, because participants in developed countries that would benefit from the intervention also assumed the risks of the clinical trial.

Under a framework of fair benefits rather than reasonable access, investigators could provide benefits to the communities where the trial was conducted by building pediatric ICUs and clinical laboratories, improving prenatal care, and training health care workers. Arguably, these measures will provide a broader-based and more durable benefit to the community than promising access to the study drug.

**ARE THERE BARRIERS TO INFORMED CONSENT?**

Investigators in developing countries can overcome the challenges of obtaining informed consent, as the following study illustrates (2,15).

**STUDY 22.4 Prevention of postpartum hemorrhage.**

Worldwide, more than 150,000 women die each year from postpartum hemorrhage. The majority of these deaths occur in developing countries, almost exclusively in women who give birth outside of hospitals. An RCT was conducted to compare oral misoprostol, a prostaglandin analogue, with placebo in postpartum hemorrhage in women in rural India. In this setting, most pregnant women have no access to physicians and hospital facilities. Auxiliary nurse midwives perform deliveries at home or at village centers, but are not permitted to give injections. Oxytocin, the standard of care in the developed world for postpartum hemorrhage, requires refrigeration and injection, and therefore is not feasible in resource-poor countries. Previous clinical trials in developed countries showed that misoprostol is safe and effective, though somewhat less effective than injectable oxytocin. Because the drug costs about $1 a dose and does not require refrigeration, it can be used in resource-poor countries.

Several ethical concerns were raised about this trial. First, was a placebo ethically appropriate in light of the known effectiveness of oxytocin? Second, were the risks to participants acceptable? All participants with severe hemorrhage were provided access to a hospital, where transfusion, surgical procedures, and ICUs were available. Third, could informed consent be obtained in this setting from illiterate women who traditionally defer to their husbands and mothers-in-law? The study was approved by the Ministry of Health in India and the ethics board of a local medical school.
In this clinical trial, the use of placebo in a resource-poor country was ethically justified even though an effective treatment was available in developed countries. A comparison between oxytocin and misoprostol was not relevant to the clinical and public health question posed in this study: Is an oral drug more effective than no treatment at all (the currently available level of care in this setting)?

Study 22.4 illustrates the challenges of obtaining informed consent in resource-poor countries (15). A purely individual approach to informed consent is not appropriate in many cultures. In some cultures, people regard themselves primarily as members of a family or community, rather than as autonomous individuals. People might not make important decisions by themselves, and instead consult with others or defer to their opinion. In such cultures, participants should be offered the options of consulting with others about the decision to participate in research or allowing others to make the decision. In Study 22.4, researchers needed the approval of village elders and leaders to carry out the study. Furthermore, in rural India, women traditionally defer to their husband or mother-in-law and do not make decisions independently of their families. Researchers should allow participants to choose whether to involve these family members in the consent process. Ultimately, however, a woman must have the right to refuse to participate in research, even if others want her to participate (1). Researchers should devise a consent process that protects participants from undue influence or coercion and protects women who disagree with their family against reprisal. In some cases, a woman might want to participate in research despite the objection of others. Researchers need to ascertain that she understands the psychosocial risks in this situation and take steps to minimize those risks, for example, by heightening confidentiality protections. However, as with any informed adult, she should be allowed to enroll in the study if she wishes.

Women were allowed to consult with relatives about participating in the trial. If she wished, a woman was permitted to obtain her husband’s approval to participate. However, no one was entered into the study without her individual consent. Consent discussions were carried out in the local language. To protect illiterate women, a relative had to witness the consent procedure.

Detailed consent forms might serve little purpose in low-literacy populations. Although careful translation and back-translation of consent forms are necessary, they are not sufficient to ensure that the consent process is culturally appropriate. Moreover, insisting on signatures or thumbprints may alarm some participants, who fear that the document could be used against them later (for example, if there is a change in the government) (1). Participants may also suspect that they are giving away something. Instead of requiring a signature or fingerprint, researchers could have persons who are independent of the study witness the consent process.

Steps can be taken to enhance informed consent from poorly educated persons in resource-poor countries (16). Stakeholders in the host country, such as community-based organizations, can identify common misconceptions and concerns about the trial and offer suggestions for improving the consent process and explaining difficult terms. For instance, to explain randomization, investigators have used the analogy of testing fertilizers or new seeds on randomized plots.

Innovative means of communicating information, such as street theater and group meetings where people can ask questions, can precede and supplement individual discussions with potential participants (1).

Researchers should administer a questionnaire to participants to ascertain whether they understand key features of the study (16). Although disclosing information about a research study is necessary, the key ethical issue is whether the participants comprehend the disclosed information. If potential participants fail to show adequate comprehension, researchers should hold additional discussions with them until they achieve an acceptable level of understanding.
IS THE IRB REVIEW RIGOROUS?

In some clinical trials in resource-poor countries, the IRB review and approval process may fail to achieve the goal of protecting participants.

STUDY 22.4  (Continued).

This trial showed that misoprostol was effective at reducing the incidence of postpartum hemorrhage (from 12.0% to 6.4%) (2). One case was prevented for every 18 women treated.

STUDY 22.5  Oral antibiotic for meningococcal meningitis.

During a 1996 epidemic of meningococcal meningitis in Nigeria, an RCT was conducted to compare a new oral antibiotic, trovafloxacin, with injections of ceftriaxone, a standard therapy for children with this life-threatening infection. At the time of the study, trovafloxacin was not approved by the FDA and had been given orally to only one child. The study drug was to be given to half the participants as either an oral solution or an intravenous formulation. Due to a shortage of nurses, the control antibiotic was usually given intramuscularly rather than intravenously. Because these intramuscular shots were very painful, children commonly received lower than standard dosages. The protocol did not include a second lumbar puncture to assess response after the antibiotic was started.

Many parents were illiterate. Allegedly, they were told that it was a new medicine and that they could say no, but were not told that the antibiotic was investigational and that standard care was available nearby at a medical camp run by a humanitarian organization.

One 10-year-old girl died after receiving the oral form of the experimental antibiotic. The day after receiving the drug, she developed weakness and cranial nerve palsy. Her treatment was not changed after her symptoms worsened. She died on the third day after starting the intervention. Overall mortality rates in the control and intervention arms were both around 6%, comparable to outcomes in U.S. hospitals and at the local medical facility.

U.S. employees of the pharmaceutical manufacturer who sponsored the study flew into the country to carry out the study and left after 3 weeks, when the treatment phase was concluded. They returned 4–6 weeks later for follow-up visits. Although the company said it was trying to respond quickly to the epidemic, critics said that during the epidemic the country needed more resources for standard care, not a hastily planned research study.

The study files contained a letter of approval from an ethics committee at a local teaching hospital. However, the hospital later said it had no ethics committee at the time the trial was carried out.

An oral antibiotic that is effective against meningococcal meningitis would greatly benefit resource-poor countries, where outbreaks occur but intravenous medications generally are not feasible. Although an oral antibiotic would not be used in the United States to treat meningitis, data from the trial could support FDA approval of the oral form of drug in children with other infections.

Ethical concerns about Study 22.5 included not only the previously discussed issues of unacceptable risks and inadequate informed consent, but also lax oversight and a one-sided relationship between the sponsor and in-country stakeholders.
CHALLENGES IN IRB REVIEW

Review by a panel that is independent of the investigators is a fundamental protection for participants. Careful scientific and ethical reviews should identify problems with risks and consent. However, studies designed by pharmaceutical companies may be reviewed only in house, not by independent experts. FDA reviews for new drugs and new indications for licensed drugs typically focus on design issues rather than ethical concerns.

A U.S. IRB may not understand conditions in the host country and thus may not appreciate the relevance of the study there, problems with the administration of study medications, the clinical alternatives available at the study site, or the need for a salvage regimen.

IRB review in the host country is intended to address some of these shortcomings of IRB review in the United States. However, in many resource-poor countries, IRBs often lack training in research ethics, experience in reviewing complicated protocols, and resources to carry out their work. For example, photocopying documents or sending them electronically to committee members may not be feasible.

FACILITATING IRB REVIEW

Researchers can facilitate IRB review of international studies if they take the initiative to provide the U.S. IRB with background information they will need to conduct their review. The U.S. IRB needs to understand how the research context in the host country differs from that in the U.S. The IRB must then consider how those differences will affect its judgments about the informed consent process and the risks and benefits of the research. Investigators might provide the following specific information:

1. What are the options for medical care for the condition being studied in the country where the research will be carried out?
2. What increased psychosocial risks do participants in the host country face, compared with risks participants in the U.S. would face if the study were carried out there? For example, risks might be greater because of weaker confidentiality protections or greater stigma. How will the investigators minimize these additional risks?
3. What are barriers to informed and free consent in the host country that are not present in the U.S.? Potential issues include low literacy, non-Western beliefs about illness and health care, attitudes toward written contracts and signatures, and the role of third parties, such as spouses or village elders, in decision-making. There may be sources of undue influence or coercion that would not be present in the U.S. How will the investigators minimize these barriers?
4. If subjects will be paid for participating in the study, what does the amount mean in terms of an average or living wage in the host country? An amount that would not be an undue influence in the U.S. may be so in the host country.

ARE STAKEHOLDERS IN THE HOST COUNTRY PARTNERS?

Research in resource-poor settings is best viewed as a partnership between investigators and sponsors from the developed world and stakeholders in the host country. This would include scientists, clinicians, public and patient representatives, community groups, and government officials (17–19). Ideally, these stakeholders would be involved in the research, beginning with the planning phase. WHO and UNAIDS urge communities to be involved “in an early and sustained manner in the design, development, implementation, and distribution of results” of a trial (9, 20). This should be “an open, iterative, collaborative process that involves a wide variety of participants,” and generally will require “outreach and engagement measures to support participation.” Various terms have been used to refer to this cluster of related ideas, such as community engagement, community participation, and community involvement (18,19,21). Similarly, different models of collaboration have been used, including community advisory boards and working with existing civil society organizations.

Host-country partners can help U.S. researchers understand the needs of the host country, risks associated with conditions in the country that may not be apparent to persons from developed nations, concerns that potential participants might have about the study, and barriers to recruitment, informed consent, and follow-up. In addition, stakeholders might suggest how to overcome these challenges, improve the study design, and help design an ethically appropriate recruitment and consent process.

STUDY 22.5 (Continued).

The researchers were accused of exploiting third-world persons. The protocol was developed in the U.S. and presented to Nigerian authorities for their approval as a finished product. Local physicians said they had no opportunity to suggest changes to address the ethical problems in the protocol.

Research team meetings should be conducted in ways that promote partnerships (17). In many countries, people receive deference based on age, experience, social status, and gender; this might frustrate efforts to elicit feedback and discussion. Those who chair meetings 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 group meetings.

STUDY 22.5 (Continued).

Two years after the trial was conducted, a multisite international clinical trial of trovafloxacin for meningitis was conducted in the U.S. as well as at sites in Latin America, South Africa, and Hungary. All the above ethical problems were corrected. An intravenous formulation was used. The protocol included follow-up lumbar punctures, and nonresponders were switched to another antibiotic. Trovafloxacin was, for a time, widely prescribed in the U.S. However, because it was found to cause fatal liver toxicity, its use was later limited to severe infections caused by multiresistant bacteria.
TAKE HOME POINTS

1. Vast discrepancies in wealth between developed and developing countries raise concerns about research carried out in resource-poor countries by investigators and sponsors from developed countries.
2. To ensure that such trials are ethically sound, researchers must carefully consider the use of placebo, the provision of background and ancillary care, informed consent, access to the study intervention after the trial, and collaboration with host-country stakeholders.

ANNOTATED BIBLIOGRAPHY


Argues that stakeholders in the host country should be involved in the project from the early planning stages.


Analyzes the arguments supporting different theories about what investigators owe research participants as a matter of fairness.


Detailed guidelines for involving community groups in prevention trials.


Researchers should administer a questionnaire to ensure that participants understand the key features of a study.

REFERENCES


