CASE STUDIES

Note to the Facilitator
The Case Studies section provides 10 health-research case studies to prompt discussion about the material presented in the curriculum.

Case Studies in the Curriculum
Case Study 1: Principles of Research Ethics (slide 13)
Case Study 2: Informed Consent (slide 46)
Case Study 3: Research Ethics Committee Considerations (slide 57)
Case Study 4: Community Participation (slide 77)

Additional Case Studies
Case Study 5: Inducement/Compensation
Case Study 6: Social Risks
Case Study 7: Respect for Persons
Case Study 8: Beneficence and Justice
Case Study 9: Individual versus Community Consent
Case Study 10: Research Involving Minors

The case studies are based on real-life research studies conducted throughout the world. They illustrate the complexity of human research and how cultural, social, and gender issues impact the ethics of a research study. The issues that are raised transcend any specific category of research and were selected to elicit a variety of reactions. This type of discussion will enrich the training group and should be pursued. The facilitator might find that discussion becomes so absorbing that he or she will need to curtail it in the interest of time.

We believe that these case studies are applicable to most geographic settings, but discussions of characteristics that are unique to a particular country are encouraged.

Discussing the Case Studies
• The ideal way to discuss the case studies is to divide the participants into groups of eight and have them sit around group tables, round tables being preferred. Ask the groups to pretend to be formally established Research Ethics Committees.

• Each participant should receive a copy of the case study. Inform the participants that the discussions are to be based only on the information provided. Ask the groups to focus on ethical dilemmas rather than scientific design issues. Ask each group to designate a chairperson and a reporter.

• Allow five minutes for individual reading, followed by 15 minutes of group discussion. Have each reporter present the small-group findings to the entire group. Allow 20 to 25 minutes for discussion with the entire group.
• Each case study will take approximately 45 minutes. Adjust the number of case studies or groups presenting to fit into the time allowed for the entire workshop.

**Resource for More Case Studies**
The Research Policy and Cooperation Department of the World Health Organization published in 2009 the *Casebook on Ethical Issues in International Health Research*. The publication is available online at: [http://www.who.int/rpc/research_ethics](http://www.who.int/rpc/research_ethics).

This casebook contains 63 case studies, each of which raises an important and difficult ethical issue connected with planning, reviewing, or conducting health-related research. The purpose of the book is to encourage thoughtful analysis of these issues by researchers and members of research ethics committees, particularly those involved with studies that are conducted or sponsored internationally. The case studies have been kept short and include only those descriptive, background details that are relevant to the case. Case studies in this publication were drawn from one or more actual research projects.

Readers and facilitators of this curriculum are encouraged to review the casebook as an alternative or addition to the case studies included in this curriculum.
Case Study 1. Principles of Research Ethics  
Developing a Vaccine for Malaria

Source: *Casebook on Ethical Issues in International Health Research*, World Health Organization

A North American university is planning to test a multistage, DNA malaria vaccine. Preliminary studies in North America have been encouraging; immunization of human subjects shows evidence of a strong immune response. Experimental challenge studies in North American volunteers will begin soon. Larger field studies, both Phase II and III, are being planned. A country in sub-Saharan Africa where malaria is endemic has expressed interest in participating in the vaccine research effort. The African and North American researchers begin working together to design a study protocol to assess the vaccine’s efficacy in reducing deaths due to malaria in children under five years of age, particularly infants.

A district in the country with a population of approximately 150,000 has developed an effective epidemiologic surveillance system. Trained community health workers (CHWs) visit all homes in each village in the district every three months to record all births, deaths, major illnesses, marriages, and migrations. A centralized, computerized record-keeping system was created and is regularly updated with data from the CHWs reports. Nevertheless, most of the villages are remote, and there are only four health posts to serve the entire population. Furthermore, in addition to the high malaria burden (18 percent of annual income lost due to the disease), trained health care workers, laboratory facilities, and medicines are in short supply. Children under five years of age in the study area suffer an average of six bouts of malaria a year. Fatally afflicted children and infants often die less than seventy-two hours after developing symptoms.

The researchers will randomly select potential participants (infants) for the vaccine trial from the database gathered by the CHWs. A study vaccination team will visit each home, explain the study, and obtain informed consent from the appropriate caregiver. Researchers will administer the vaccine or placebo in double-blind fashion to those who agree to participate. Although many children will experience some soreness at the injection site, the risks of vaccination are minor. Once all participants receive the vaccine, the team will leave the village without implementing any other interventions. Using the system already in place—that is, monitoring patients who come to the clinic or hospital with symptoms of malaria, as well as the active surveillance regularly conducted by the CHWs—researchers can collect data on subsequent illness and death due to malaria. If the vaccine is found to be effective, the benefit is prevention of morbidity or mortality due to malaria.

There is no clearly defined immunological marker to measure protective immunity against malaria. As mortality is the most important outcome variable that can be measured, the researchers will look at deaths as a study endpoint. To the extent that health records and verbal autopsies allow, the researchers are specifically interested in those deaths known to be caused by malaria. If all cases of malaria in the study...
population were identified and treated, researchers could not measure the efficacy of the vaccine in preventing deaths. In the absence of a surrogate marker for mortality, the study researchers do not want to interfere with the “natural” consequences of malaria transmission in the study villages.

Questions
1. Is the use of a placebo appropriate in this context?
2. Is the study design appropriate to demonstrate the efficacy of the vaccine?
3. Should the researchers provide treatment for malaria cases in the community?
4. Should the researchers provide information on how to prevent illness?
5. The case study does not indicate that any provision has been made for an ethical review by the country where the research is being conducted. If the North American partners insist that the review conducted in North America is adequate, what should the host country do? If the host country does not have the capacity to provide ethical oversight, what options are available?
Case Study 2. Informed Consent
Development of a New Microbicide

Source: FHI 360

A randomized, placebo-controlled trial of a vaginal microbicide product is under way in a resource-poor country. The purpose of this trial is to look at the effectiveness of a topically applied microbicide on heterosexual acquisition of HIV. Half of the women enrolled will receive the test product and condoms and the other half will receive a placebo and condoms. Both the local Research Ethics Committee (REC) and sponsor’s REC have approved this research and the consent process.

During a routine monitoring visit for this trial, the monitor observes the consent process for several study participants. The monitor finds that the study counselors administering the informed consent do not explain all of the information on the consent form, as was planned at the staff training. Most of the consent form is paraphrased and several essential elements are omitted. All participants sign the consent form.

When the counselors are questioned about this, they state that the women at this site are not capable of understanding everything in the consent form, so the site counselors and the study investigator agreed on emphasizing only the most important aspects of the consent form.

The monitor speaks to the investigator about this issue. She is told that investigators are encouraged to review and modify consent forms as necessary to account for local conditions. The investigator feels that the study counselors were correctly following the informed consent process. The monitor reports her findings to the REC.

Question
In this case the REC should:
1. Recommend that the study be terminated (not allowed to continue).
2. Retrain the site investigator and the study staff in the informed consent process.
3. Rely on the site investigator’s knowledge of the study population.
4. Take no action. Signed consent forms for each participant are on file.
Case Study 3. Research Ethics Committee Considerations
Testing a New Vaccine for Malaria

Source: Faculty of Health Sciences, University del Valle, Cali, Colombia

To test a human vaccine against malaria caused by *Plasmodium vivax*, a research group submits a three-phase protocol to the Research Ethics Committee (REC) of the local university. Differing from other protocols, a “challenge” methodology is proposed; researchers plan to infect research participants with malaria to evaluate the effectiveness of the vaccine the following way:

**Phase Ia**
The objective is to evaluate the model and the effectiveness of the infection (this model has not been implemented with *P. vivax* in any part of the world). Twenty-five volunteers will be exposed to five, four, or three bites in the left forearm by *Anopheles* mosquitoes infected with known and studied varieties of *P. vivax*. The participants will be monitored, and when they present malaria symptoms, they will be treated with conventional therapy.

**Phase Ib**
The objective is to correct possible problems occurring during the conduct of Phase Ia in 25 participants. The same methodology will be followed, with modifications made according to the results of the previous study.

**Phase Ic**
The objective is to establish the effectiveness of the vaccine. Two groups of 25 participants each will be established, with one group receiving the test vaccine and the other receiving a placebo. Both groups will be exposed to bites of the infected mosquitoes and will be followed for one year. If they present malaria symptoms, they will be evaluated and treated with conventional therapy.

The city where the study will be conducted does not have endemic malaria. Study participants will not be paid, as it is forbidden by national norms. However, they will be covered with insurance for standard medical care as available elsewhere in the country. Adverse events will be evaluated, and compensation for treatment, transportation, and missed working days will be provided as necessary.

When the REC asks researchers about alternatives to the proposed methodology, the research team mentions that this type of study has been conducted in rural, malaria-endemic sites with 300 volunteers receiving the vaccine and 300 volunteers receiving the placebo. The follow-up period was longer than that proposed for this study. The researchers justify the methodology because they feel they will have better control of the participants and will be able to provide better treatment in case of adverse events.

**Questions**
1. Is the study methodology appropriate?
2. Should the study be reviewed and approved phase by phase?
3. Are the protections for participants sufficient?
4. Should Phase Ib be eliminated?
Case Study 4. Community Participation
HIV Vaccine Study with At-Risk Groups

Source: FHI 360

An HIV vaccine trial is proposed in three large cities in Asia. The study will target previously identified at-risk groups, including injecting-drug users.

The research team plans to enroll injecting drug users at government-run rehabilitation centers and on the street. Most injecting-drug users in the rehabilitation centers have been sent there by the local legal system. Individuals who agree to participate in the research will receive an identification card with a participant number and contact information for questions or problems.

In preparation for the study, the researcher meets with rehabilitation center management and police staff to discuss the study and ask for their cooperation. The authorities who run the rehabilitation centers are optimistic that most of the injecting-drug users will agree to participate. In addition, the police request that participant identification cards include the police department’s official seal and that the names of participants recruited on the street be provided to police so that they are not arrested and prevented access to the study. Community representatives are asked for input on the recruitment process.

Questions
1. Can this injecting-drug user population (community) be included in this study? Why or why not?
2. What measures can the research staff take to ensure that informed consent is given freely by all participants?
3. If you believe that the potential participants will not be able to give voluntary informed consent, what could be done to change the informed consent process?
ADDITIONAL CASE STUDIES

Case Study 5. Inducement/Compensation
A Trial for Malaria Prophylaxis

Source: National Institute of Health Research and Development, Jakarta, Indonesia

A study in rural West Papua, Indonesia, is planned to determine the safety and prophylactic efficacy of Malarone for prevention of malaria among Indonesian transmigrants. The study will be placebo-controlled, randomized, and double-blinded in three phases: I) a 17-day radical cure with Malarone; II) a 20-week administration of Malarone versus placebo; and III) a four-week post-prophylaxis follow-up, for a total duration of 27 weeks. Participants will be transmigrants who are at least 12 years old and have been residents of West Papua for three to 20 months.

Four hundred subjects are expected to successfully complete Phase I of the study. Volunteers will be randomized to continue or discontinue the trial after Phase I. Those randomized to continue will be further randomized to receive either Malarone or placebo. Those randomized to discontinue will be asked to enroll in an open-label study of pimaquine as a prophylactic. Malaria smears will be done at screening, at the end of the radical cure, once weekly during Phase II, and at any time that malaria-like illness develops.

As medications should be taken with food, both will be provided free of charge to participants. There will be 24-hour coverage by an on-site physician and transportation to the Jayapura General Hospital in case of emergencies. A medical monitor will assure patient well-being and compliance with all safeguards as described in the protocol.

If a participant develops malaria during the prophylaxis phase of the study, he or she will be treated with a three-day course of Malarone. If a participant develops a complication during any phase, he or she will receive prompt medical care free of charge (including transportation to and the costs of hospitalization in Jayapura, if referral is medically indicated according to the local standard of care). Prompt diagnosis, treatment, and follow-up will be provided to volunteers for non-malarial illnesses or injuries that develop during their participation in the study.

Questions
1. Is there undue inducement in the study?
2. Is the use of placebo justified?
3. Are the safeguards adequate?
4. Do the benefits justify the study?
5. What information should be provided to participants before enrollment?
6. Is the selection of the study site at a transmigrant settlement appropriate?
Case Study 6. Social Risks
Comparison of Female and Male Condoms

Source: FHI 360

A cluster-randomized trial is being conducted at rural plantations in a developing country. The study sites, rather than the individual study participants, are randomly selected to receive the intervention or not. Intervention sites introduce female condoms along with continued distribution of male condoms, while the control sites receive male condoms only. All adult male and female residents of the sites are exposed to the intervention by means of large entertainment events featuring music, dance, and puppetry.

The participants are women, who undergo screening and informed consent and are then interviewed and tested for sexually transmitted infections (STIs) at each of three follow-up visits over the course of 12 months. The informed consent form mentions the strain and distress that can accompany a diagnosis of STI, with no reference to the possibility of more serious, perhaps violent repercussions. Despite the informational program, 1 percent of the women report trauma as a result of abusive behavior by their sexual partners. As documented on Serious Adverse Event forms, women are assaulted for:

- Informing partners of study participation
- Suggesting condom use to partners
- Notifying partners of their STI-positive status and asking partners to seek treatment

It is understood that this partner violence is a direct result of participating in this study. Violent incidents are reported to researchers at both intervention and control sites. This is the only problem reported in the research study thus far.

**Question**
How should the REC advise the researchers?
1. Stop the research to protect the women.
2. Amend the informed consent form and re-consent all participants.
3. Continue the study, but orally inform participants of the risks.
4. Continue the study as designed.
5. Add messages about domestic violence to the intervention and report the violent episodes to management at the plantations.
Case Study 7. Respect for Persons
Sexually Transmitted Infections among Commercial Sex Workers

Source: FHI 360

A Ministry of Health has requested a prevalence/behavioral surveillance study for sexually transmitted infection (STI) among commercial sex workers. Participants in this study will be tested for three common STIs and will participate in an interview. Participants will receive a card with a number linking them to their blood sample and will have the option of presenting their cards to get the results of the STI tests. Those with positive results for any of the three infections will be offered free treatment. In addition, all participants will receive a small gift in return for their participation.

The target population consists of brothel-based sex workers who are strictly controlled by the brothel managers. Prior to initiating the research, a researcher meets with the brothel manager to ask permission to conduct the study. During the meeting, the manager states that all of the women working in the brothel will participate in the study.

Questions
1. What steps can the researchers take to ensure that informed consent is freely given by all participants?
2. If a woman chooses not to participate in the study, what can be done to protect her from retaliation by the manager?
3. If you believe that the women will not be able to give voluntary informed consent, what alternatives could you suggest to the Ministry of Health?
Case Study 8. Beneficence and Justice
Study on Condom Use

Source: FHI 360

A time-series intervention trial is being conducted with commercial sex workers. The goal of the trial is to assess the impact of adding the female condom to a male condom distribution system, measured in terms of a change in the proportion of sex acts protected by condoms. Condom use is estimated by interviewing study participants about their use of protection in their last 10 sex acts. These measurements are to be made at five points: twice following exposure to promotion and distribution activities for the male condom, and three times following exposure to promotion and distribution of both the male and female condom.

The local principal investigator, a highly respected advocate for the sex workers, explains that women are very enthusiastic about participating in the female condom trial, as it would provide them free access to this innovative method of dual protection.

The first round of condom-use measurement was completed as planned. Preliminary data analysis revealed that study participants were reporting male condom use in over 95 percent of sex acts. Following verification of the interviewers’ techniques, a second round of interviews was completed. It yielded a similar, exceptionally high level of male condom use. There is concern that introducing a new product will have a negative effect on the use of male condoms. In addition, there are questions about the availability and affordability of the female condoms after the conclusion of the study, even if the study is successful.

Question
What is the best way to proceed?
1. Continue the study as designed.
2. Terminate the study at this point.
3. Suspend the study. Seek assurance that female condoms will be made available if proved successful.
Case Study 9. Individual versus Community Consent
The Impact of Vitamin A on Diarrhea in Children

Source: Harvard School of Public Health, USA

A U.S. university gives a grant to conduct a study to evaluate the impact of periodic doses of high-dose vitamin A on the incidence of diarrhea and acute respiratory infection (ARI) in children less than five years of age.

High-dose vitamin A capsules or placebo would be administered in a double-blind fashion every four months for one year to children from six months to five years of age. A record of morbidity (diarrhea and ARI) and mortality data would be measured weekly, and blood samples for vitamin A status would be drawn at zero, six, and 12 months.

To inform the community of the impending study, the local chief and council of elders called the villagers together. In a festive environment, the researchers described the study and answered questions from community members and the council. Later, the village chief and council met briefly and gave their approval.

Shortly thereafter, in accordance with the guidelines of the funding university’s Institutional Review Board* (IRB), the field staff began going house to house to obtain signed parental informed consent for children to participate in the study. The mothers (usually the parent at home during the visit) said that they did not need to sign anything as the chief had already approved the study and they could not sign anything because they could not read what they would be signing. On the second day, the field staff were summoned to the chief’s house and politely informed that since the chief and council had given approval for the study, it was both unnecessary and unacceptable to seek individual signatures. The staff said the grant agreement required them to obtain signed informed consent forms. They were told that if they insisted on doing so, they would have to leave the community.

Questions
1. How should the researcher handle this problem?
2. How critical is signed informed consent in this setting?
3. Is it acceptable to obtain consent from the village chief or is individual consent necessary?
4. Is informed consent culturally bound or is it a universal principle?
5. Are there circumstances when informed consent is unnecessary?
6. Does it protect the researcher or the participant?
7. Can the IRB waive informed consent in such instances?

* In this curriculum, Institutional Review Boards are referred to as Research Ethics Committees (RECs). The authors have preserved the terminology used by the contributing institute.
Case Study 10. Research Involving Minors
Comparing Childhood Vaccination Regimens

Source: El Salvador National Ethics Committee, San Salvador, El Salvador

A study is being planned to compare a new childhood vaccine consisting of five components in a single dose with the existing regimen. At present, children in this country receive a vaccine with three components in a single dose, and two additional components in a separate dose, all given during the same visit.

The study group will be boys and girls, 15 months old, who would go to the country’s Health Units for the current vaccination regimen. The plan is to enroll 300 children in three months. After parental informed consent, children will be randomized to receive the current vaccination regimen or the new, one-dose regimen.

The investigation would be conducted in five Health Units of the Ministry of Health, where the application of the current vaccination regimen is mandatory and free of charge. The Ministry of Health has given approval to conduct the study.

The main endpoints are:
- Adverse experiences or reactions to the vaccine.
- Antibodies produced in response to the vaccines. For this purpose, the children will have to provide a blood sample at the time of the injection and one month after.

Blood samples will be taken at each clinic, be sent to a central laboratory, and then be sent out of country for antibody analysis. Private pediatricians will be contracted as investigators to reinforce the pediatricians of the Health Units. In case of adverse events, participants would be referred to the government’s Children’s Hospital.

Observations:
- The parents of children seeking care in the Health Units typically are economically poor.
- Most of the parents do not read and write and have little formal education.
- Children often come to the Health Units with individuals other than parents, who are often working.

Questions
1. Should the sponsor of the study provide the Ministry of Health with the control treatment as well as the study product?
2. Should the study be conducted only in the Health Units and not in private clinics?
3. Is the enrollment plan, to be conducted in very busy clinics, realistic? Will there be enough time to explain and obtain informed consent?
4. Can researchers assure that the individuals accompanying the children have legal responsibility for the child? What should researchers do in cases where legal responsibility is uncertain?
5. Can researchers assure that parents will allow the children to provide blood samples? Can researchers assure that the children return to the clinic for follow-up blood sampling or adverse events?
6. How should researchers ensure the control of the blood samples during transport to the central laboratory and out of the country?
7. Should children with adverse events be referred to the Ministry of Health hospital or a private hospital?
CASE STUDIES—DISCUSSION POINTS

Case Study 1. Principles of Research Ethics
Developing a Vaccine for Malaria

1. **Is the use of a placebo appropriate in this context?**
The Declaration of Helsinki recommends “that a new intervention must be tested against the best current proven intervention.” In this case, if evidence is presented that such an intervention does not exist, the use of a placebo would be justified. CIOMS recommends that “ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.” If this were a non-IND study considered for submission to the U.S. Food and Drug Administration (FDA) as support for an IND, current FDA regulations would require the study to be conducted in accordance with GCP rather than the Declaration of Helsinki.

2. **Is the study design appropriate to demonstrate the efficacy of the vaccine?**
The study design raises several ethical and scientific issues. The statement: “Once all participants receive the vaccine, the team will leave the village without implementing any other interventions,” indicates that the team will leave without further consideration for the protection of the participants. Also, mortality as the endpoint of efficacy could be debated by REC members with expertise in this type of research. In complex studies such as this one, the use of special scientific consultants to assist the REC might be considered.

3. **Should the researchers provide treatment for malaria cases in the community?**
The reviewing REC must carefully assess the level of access research participants have to appropriate health care and whether there is a need to provide malaria treatment for all research participants. If it is decided that treatment will be provided, the design of the study would require major changes, which would have important cost implications, such as changes in the required sample size.

4. **Should the researchers provide information on how to prevent illness?**
The need to provide prevention information requires careful assessment by the REC. The REC should consider the current standard for malaria prevention as a reference. As in the case of treatment, a requirement for prevention information would incur major changes to the study. However, the provision of prevention has been required in comparable studies. The extension of these two benefits (treatment and prevention information) to the entire community, though desirable, is not the direct responsibility of the research study.

5. **The case study does not indicate that any provision has been made for an ethical review by the country where the research is being conducted. If the North American partners insist that the review conducted in North America is adequate, what should the host country do? If the host country does not have the capacity to provide ethical oversight, what options are available?**
The review and approval of the research project by an REC in the country where the
research is conducted must be required. CIOMS specifically recommends that the “U.S. government should not sponsor clinical trials in developing countries unless such trials have received prior approval by an ethics committee in the host country and by a U.S. Institutional Review Board.” The absence of local capacity to provide ethical oversight must be documented clearly. In the proven absence of local capacity, the reviewing REC should require, review, and approve the local mechanisms of ethical oversight that will be set in place.
Case Study 2. Informed Consent
Development of a New Microbicide

In this case the REC should:

1. **Recommend that the study be terminated.**
   This is a drastic option, unless it is clear that the consent process was meaningless and could not be corrected.

2. **Retrain the site investigator and the study staff in the informed consent process.**
   **This is the best answer.** If documented informed consent is available at the site, and the site is able to recruit and follow the necessary number of study participants, retraining is probably the best option. If the study is to continue, the sponsor and site must be in agreement on how the study procedures and processes are to be conducted.

3. **Rely on the site investigator’s knowledge of the study population.**
   This answer, **while not necessarily the best answer**, identifies a choice that happens at many investigative sites. While it might be true that the investigator knows the study population, the approved informed consent form and study procedures were agreed upon prior to initiating the study. To change study procedures that are not urgently needed for the safety of the participants (without notifying the sponsor) could affect the entire study. Look for a better answer.

4. **No action. Signed consent forms for each participant are on file.**
   This is **not** the best answer. Although there is documentation of informed consent in the form of signed documents, this is meaningless and shows a lack of respect for persons. Look for a better answer.
Case Study 3. Research Ethics Committee Considerations
Testing a New Vaccine for Malaria

1. Is the study methodology appropriate?
The development of a new drug or vaccine goes through sequential and progressive phases to ensure the safe development of a new product. Preclinical studies are conducted in basic science laboratories and in animals appropriate for the product under study. These studies are designed to provide preliminary information on the safety and efficacy of the product prior to experimentation in humans. The data obtained at the preclinical level are then submitted to a regulatory agency (e.g., U.S. Food and Drug Administration) to obtain permission to initiate studies in humans (clinical trials).

In addition to the REC approval, the initiation of a study as proposed would also require permission by the national regulatory agency and the regulatory agency in the country of origin of the vaccine.

A challenge study is justified only when the scientific rationale for the study is very clear, the information gained is very important for an outlined development process, appropriate protections for participants are in place, and the study will be conducted by highly experienced investigators in sites with high-quality health care facilities.

2. Should the study be reviewed and approved phase by phase?
Approving study continuation phase by phase, through progress reports, is an acceptable option. In reality, Phase Ic would only be a first, relatively minor step to establish the effectiveness of the vaccine. This study would have to be followed by a number of large and expensive studies. The REC should be informed of the entire plan for the development of the vaccine as a consideration for its approval of the study.

3. Are the protections for participants sufficient?
The assurance that appropriate protections will be provided to the study participants is most important. The informed consent should provide clear and comprehensible information on the study design and its risks and benefits. Rapid access to high-quality care must be confirmed, including possible long-term care for complications related to study participation.

4. Should Phase Ib be eliminated?
The elimination of Phase Ib is a valid consideration. This decision requires important scientific expertise in the area, which might exist within the REC or be obtained through expert advisors.

The reasons for approval given by the local REC were:

- The number of study participants is smaller, which means a lower risk of a serious adverse event for the study population.
• Recruitment in a city allows the researchers to enroll participants with a better understanding of the research and avoids coercion of volunteers from endemic areas.
• The follow-up and staff capacity are better in the city than in a rural, endemic area where health resources, communication, and ability to transfer participants for further care may be limited.
• It allows for open recruitment, with better social vigilance, due to the presence of good communication and the local REC.
Case Study 4. Community Participation
HIV Vaccine Study with At-Risk Groups

1. Can this injecting-drug user population (community) be included in this study? Why or why not?
   It might be possible to include these injecting-drug users, but only with a well-designed informed consent process that includes multiple, advanced meetings with the authorities to ensure that they understand the nature of the study and to reiterate that participation is voluntary. The study should stress that it is acceptable to have a large number of this community refuse participation.

2. What measures can the research staff take to ensure that informed consent is given freely by all participants?
   It will be essential to use a private room for informed consent discussions. Members of the rehabilitation center staff should not be present for the discussions. Participation in the study should not result in an award or favorable treatment of rehabilitation center detainees. Also, informing the injecting-drug user community of the research in advance might mean that some of the detainees are aware of the research before they are sent to the rehabilitation centers.

3. If you believe that the potential participants will not be able to give voluntary informed consent, what could be done to change the informed consent process?
   If you believe that they will not be able to give voluntary informed consent, they should not be enrolled. It might be better to recruit only injecting-drug users who are not detained in rehabilitation centers.
Case Study 5. Inducement/Compensation
A Trial for Malaria Prophylaxis

1. Is there undue inducement in the study?
   As indicated in the protocol, one of the main objectives of the study was to determine the safety and efficacy of malaria prevention among Indonesian transmigrants. Particular social and economic situations might apply to this population, and it might be considered a vulnerable population requiring special protections.

2. Is the use of placebo justified?
   The Declaration of Helsinki states: “the use of placebo or no treatment is acceptable where no current proven intervention exists.” The reviewing REC should request documentation from the research team that no current proven intervention exists. Otherwise, the use of Malarone should be tested against the best current proven alternative. The REC may allow placebo use if compelling scientific reasons are presented and there is no risk of serious harm. As in Case Study 1, if this were a non-IND study considered for submission to the U.S. Food and Drug Administration (FDA) as support for an IND, current FDA regulations would require the study to be conducted in accordance with GCP rather than the Declaration of Helsinki.

3. Are the safeguards adequate?
   In addition to the described safeguards, consideration should be given to provide the standard of malaria prevention (other than drugs) to all participants.

4. Do the benefits justify the study?
   In general, the benefit-risk analysis justifies the study. Provision of the standard of malaria prevention should be considered.

5. What information should be provided to participants before enrollment?
   Information on the meaning of placebo-controlled study should be made very understandable to the participants. It must be very clear to them that some of them will not receive any treatment.

6. Is the selection of the study site at a transmigrant settlement appropriate?
   There is no apparent undue influence in the study. The level of health care provided is appropriate for the participants’ protection.
Case Study 6. Social Risks
Comparison of Female and Male Condoms

How should the REC advise the researchers?

1. **Stop the research to protect the women.**
   While this is certainly an option, it is an extreme one. It might be worthwhile to look for a way to continue the study and reduce the possibility of violence.

2. **Amend the informed consent form and re-consent all participants.**
   This is a **better answer**. Research often involves some amount of risk, and participants should be aware of the risk before enrolling in a trial. Knowing of this particular risk, some women might decide to not participate.

3. **Continue the study, but orally inform participants of the risks.**
   A good answer, but others might be better. Implementing this change would take less time than repeating the written consent process, but the quality of the information might be degraded.

4. **Continue the study as designed.**
   This is **not** the best answer. Ignoring the problem altogether is not in the best interest of the participant. Look at the other answers or a combination of the other answers to address the situation.

5. **Add messages about domestic violence to the intervention and report the violent episodes to management at the plantations.**
   This is **not** the best answer. Exposing participants and their partners to retaliation by the plantation managers might cause more violent outbursts. However, it might be advisable to amend the intervention to include information about domestic violence.
Case Study 7. Respect for Persons
Sexually Transmitted Infections among Commercial Sex Workers

1. What steps can the research staff take to ensure that the informed consent is freely given by all participants?
   First, the researcher should work to educate the brothel manager. Informing him that nonparticipation is acceptable might cause him to relax his attitude. In addition, the informed consent process should take place in a private, confidential setting. Women should be reminded repeatedly of the voluntary nature of the research.

2. If a woman chooses not to participate in the study, what can be done to protect her from retaliation by the manager?
   Because the manager might insist that women participate, it will be imperative that nonparticipants are anonymous. Conducting informed consent individually will be important so that peer pressure is reduced. In addition, one might consider treating all of the women as if they had enrolled. (For example, giving nonparticipants thank-you gifts or fake blood sample cards will make it difficult to distinguish the participants from the nonparticipants.)

3. If you believe that the women will not be able to give voluntary informed consent, what alternatives could you suggest to the Ministry of Health?
   If the target population will not be able to consent freely, then you are obligated to change the study or choose a different target population. For example, commercial sex workers who are not brothel-based might not face pressure from a manager that would alter their decision.
Case Study 8. Beneficence and Justice
Study on Condom Use

What is the best way to proceed?

1. **Continue the study as designed.**
   While this is certainly an option, continuing the study might not be in the best interest of the participants. The established high rate of male condom use and the uncertain poststudy availability of the female condom make this a poor choice.

2. **Terminate the study at this point.**
   This is the *best answer*. The study might have scientific merit, but this is clearly not the best participant population.

3. **Suspend the study. Seek assurance that female condoms will be made reasonably available if proved successful.**
   This is *not* the best answer. However, it would address the issue of justice. Studying female condoms in a population that will not have access to the product following the study is not a fair distribution of the risks and benefits of the research.
Case Study 9. Individual versus Community Consent
The Impact of Vitamin A on Diarrhea in Children

In principle, this potential problem could have been identified in the development phase of the research project. As indicated in the Informed Consent section of this curriculum, the informed consent process begins before the study initiation. At this stage, the investigating team gains knowledge of the local culture and social norms, and the informed process is designed accordingly.

1. How should the researcher handle this problem?
The field investigator should maintain open and collegial communication with the village chief and the university’s Institutional Review Board. His or her goal is to initiate the study with both sides in agreement. The Nuffield Council on Bioethics document, The Ethics of Research Related to Healthcare in Developing Countries, indicates that local practices must be respected, even if they complicate the research.

2. How critical is signed informed consent in this setting?
It is important to distinguish between the waiving of the requirement to obtain informed consent and the waiving of the requirement to obtain a signed informed consent form. A signed informed consent in this setting does not seem to be necessary.

3. Is it acceptable to obtain consent from the village chief or is individual consent necessary?
CIOMS international ethics guidelines (2002) read: “In some cultures an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual consent.”

4. Is informed consent culturally bound or is it a universal principle?
Informed consent is a universal principle for research involving human participants. However, how the informed process is designed and how the information is presented and documented are culturally bound.

5. Are there circumstances when informed consent is unnecessary?
Yes, there are circumstances, clearly delineated in national regulations, when the requirement for informed consent or its signed documentation may be waived by the responsible REC. A useful reference is the U.S. Code of Federal Regulations, included in the Additional Resources section of this curriculum.

6. Does it protect the researcher or the participant?
The basic purpose of informed consent is to protect the research participant. It might also provide some legal protection to the investigator, but this is not its main purpose.
7. **Can the REC waive informed consent in such instances?**
   As indicated in the answer to Question 5, an REC may waive informed consent. Preferably, the waiver should be made by the local reviewing REC.
Case Study 10. Research Involving Minors
Comparing Childhood Vaccination Regimens

Research involving minors, considered a vulnerable population, requires special REC attention. The major national and international regulations include special sections on protections for children. These regulations include assuring that research does not involve greater than minimal risk and requiring permission by parents or guardians. It is essential for a REC to have access to local or national regulations on the subject. One essential REC determination is whether this study involves minimal risk or a greater than minimal risk, and the prospect of direct benefit to the participants. One point to consider might be whether the risk of applying the five components in one single injection is comparable to the risk of applying the same five components in two injections in the same visit.

1. **Should the sponsor of the study provide the Ministry of Health with the control treatment as well as the study product?**
   The study is presented as a comparison of the currently available vaccine provided by the Ministry of Health (MOH) with a new vaccine provided by the sponsor. Whether the sponsor should pay the MOH for the currently used vaccine is a valid consideration. But it could also be a contribution of the MOH.

2. **Should the study be conducted only in the Health Units and not in private clinics?**
   The population selected for the study is children attending government Health Units, not children attending private clinics. This is what the REC is being asked to review.

3. **Is the enrollment plan, to be conducted in very busy clinics, realistic? Will there be enough time to explain and obtain informed consent?**

4. **Can researchers assure that the individuals accompanying the children have legal responsibility for the child? What should researchers do in cases where legal responsibility is uncertain?**

5. **Can researchers assure that parents will allow the children to provide blood samples? Can researchers assure that the children return to the clinic for follow-up blood sampling or adverse events?**

6. **How should researchers ensure the control of the blood samples during transport to the central laboratory and out of the country?**

   Questions 3 to 6 are valid questions, and the REC might rightfully demand a satisfactory response to approve the study. They address mostly administrative procedures related to the study. The investigator should be given the opportunity to address these questions. The presence of the investigator at the time of REC discussions is a practical option. However, the investigator should not be present at the time of deliberation.

7. **Should children with adverse events be referred to the Ministry of Health hospital or a private hospital?**
   This question seems to indicate a concern that the quality of health care might be better at a private hospital than at the government hospitals. The REC should require
the same high-quality level of health care at either site. As in Question 1, whether the sponsor should pay for health care costs at the government hospital is a valid consideration.