Chapter III – Ethical Conduct and the Role of Community in TB Drug Research

CORE INFORMATION

Brief History of Research Ethics
Research is an organized process of searching for an answer to a question; or testing a hypothesis or educated guess based on observation. Through the process of testing a hypothesis, information (or data) is produced and collected, and then analyzed and used as evidence to evaluate whether the original hypothesis has been proven true, or false.

Research is conducted in a variety of different settings, and with a variety of different subjects; laboratories, communities, hospitals, test tubes, animals, and in humans. (See Chapter I for further information.)

Today, clinical research on humans is highly regulated and reviewed, all over the world, to ensure the safety and protection of trial participants. This, however, was not always the case. Ethical principles for clinical research have developed over time; in part due to several past cases of severe human exploitation in clinical research (see Research Fundamentals for Activists (TAG), Module 2).

In 1947 the United Nations developed the Nuremberg Code, which set out 10 ethical points to be followed when conducting human research. The Belmont Report, another document outlining ethical standards for clinical trials, was written in 1979. Today, any clinical trial conducted anywhere in the world is strictly reviewed to ensure it follows the principles outlined in these two documents.

Principles of Research Ethics
Researchers and ethical authorities work to ensure that research is conducted according to high ethical standards. The following principles form a basis for ethical conduct of all clinical trials.

- Value – the trial should answer a question that will enhance health or provide useful knowledge in the health field.
- Validity – the trial should have an appropriate, careful and practical design and methodology.
- Beneficence/favorable risk-to-benefit ratio – investigators are to do no harm by ensuring there is a fair risk-to-benefit ratio for participating in a trial (see below for further explanation).
- Respect for persons – all research volunteers must be treated as free human beings with the right to choose whether or not to participate in the study, selected for participation in a fair matter, aware of risks involved, able to give voluntary, informed consent, and protected throughout the entire research process from recruitment to follow-up and results dissemination.
- Justice –investigators must choose study participants fairly and to distribute risks and benefits equally among volunteers.
• Independent review – ethical and regulatory committees that are independent of the research team must review and give approval for the study prior to patient enrollment.

Risks versus benefits of participation
Participating in any clinical trial involves both risks and benefits. When someone is deciding whether or not to participate in a trial, that person must fully understand the risks and benefits involved in order to make an informed decision as to whether the benefits outweigh the risks of participation for him or herself personally.

When researchers plan a study, they must make sure that the risks and benefits of participation are balanced. If the relative balance of risks and benefits is not reasonable, the trial will not be considered fair or ethical. If there are too many risks, it is unfair to ask people to participate. If there are too many benefits, people may participate for the wrong reasons, and the study could be considered coercive.

Review of Clinical Trials
Many different groups have a responsibility for ensuring the ethical conduct of clinical trials. All clinical trials, no matter where in the world they are conducted, must be reviewed by external groups. It is important for all review groups to be independent from researchers to guard against bias and conflicts of interest.

Ethical Review Committees/Institutional Review Boards
To ensure that trials are conducted according to ethical standards, a locally based ethics committee must review and approve the proposed protocol, informed consent document and other study-related materials before clinical trials can begin. These committees are generally referred to as ethical review committees (ERC) or, institutional review boards (IRB). The main concerns of the ERC or IRB are the safety and respect of human rights of trial participants and the ethical conduct of the trial. The Committee or Board must approve the study processes before the study can start, and will follow the study as it is conducted.

Committees are made up of scientists, ethicists, community members and other experts who are independent of the trial sponsors and investigators and who are trained in evaluating research proposals. This combination of people provides an unbiased, fair and well-rounded evaluation of the study proposal. In addition to the ethics review, the ERC, IRB, or related committee usually also conducts a regulatory or scientific review.

Regulatory or Scientific Review
Regulatory/scientific review ensures that the trial is asking valid scientific questions and that the study is well-designed to answer these questions.

A national regulatory authority (NRA) generally reviews the technical and scientific information about the experimental product (e.g., candidate drug) or regimen and the trial protocol that gives detailed
information about how the study will be conducted. The NRA, therefore, is responsible to approve both the experimental product being tested and the specific study before it starts. Every six months or year, a report on the progress and results of the trial is sent to the NRA.

Regulatory approval must be obtained from authorities in each country where a study is conducted. Each country has different regulatory procedures. For example, in Europe, a body known as the European Medicines Agency (EMA) establishes overall regulations for NRAs and reviews products at the time of licensure; in South Africa this body is called the Medical Control Council (MCC), and in the United States it is the Food and Drug Administration (FDA).

Data Safety and Monitoring Board
A Data and Safety Monitoring Board (DSMB) is responsible for monitoring study data and the safety of volunteers in a clinical trial, and serves as a primary reviewer of the study while it is still being conducted. Any adverse events that occur during the trial must be reported to the DSMB, and if the board determines that the study is unsafe if continued, it can stop the study.

Materials reviewed by committees
The Committees detailed above review trial-related materials to make certain that all information, provided to volunteers, including informational materials, can be easily understood and that none could be considered coercive.

The following documents must be submitted to one or more committees for review and approval:

- Trial protocol, which explains in extensive detail every aspect of clinical trial conduct, including:
  - Information about the experimental product being tested (drug, regimen), its safety and efficacy data based on phase I and II studies.
  - Study design and objectives, inclusion and exclusion criteria, details about volunteer participation, information to be collected and how data will be analyzed and detailed instructions for the care if injuries or adverse events occur.
-Advertisements (flyers, newspaper, radio, or television ads) that may be used to recruit volunteers
- Informed consent document
- Any documents given to or seen by potential trial participants, e.g. community outreach strategies, recruitment strategies, informational documents or videos
- Plans for volunteer reimbursement
- Investigator’s brochure (most, but not all, cases)

Review committees may request additional information.
Informed Consent Process

Informed consent is a cornerstone of ethical research. The agreement, between researcher and trial volunteer, indicates that the volunteer fully understands and agrees to all aspects of participating in the clinical trial.

This agreement is documented when a volunteer signs the informed consent form (described below), however researchers cannot rely on this document alone to ensure that the individual truly understands the clinical trial. In most cases, ensuring volunteers’ understanding involves a broader process of education and familiarization with trial participation concepts.

Researchers recognize the importance of obtaining true informed consent. Social and contextual factors must always be considered, such as community members’ familiarity with clinical research, and any social pressure or stigma that may be associated with trial participation or the medical treatment being tested. Research teams must ensure that potential volunteers fully understand key aspects of trial participation, including the potential risks and benefits, before they sign the informed consent form. Thus, the informed consent process ideally involves two levels of outreach, one to the broader community and one to the individual.

Outreach to the individual may begin with community information sessions about the trial where community members learn more specific details about trial participation. Next, when an individual comes into the research center for pre-screening, he or she typically receives one-on-one counseling to learn about the study in more detail. Finally, some studies require that before signing the informed consent, potential volunteers complete an assessment of understanding, which is usually in the form of a questionnaire containing true/false, multiple choice, narrative questions or combination of these, to test their comprehension of the trial and participation.

Although informed consent is not the only factor in ensuring the ethical conduct of a trial, it is an essential factor. Research teams must ensure potential participants understand key factors about the trial, such as:

- Trial purpose
- Details of the candidate drug
- Number and duration of clinic visits required
- Possible benefits and harms
- Right to voluntary participation and to withdraw from the study at any time

While informed consent reflects an individual agreement between the researcher and participant, ethical involvement of community members often begins with a broader process of community engagement in a trial. Outreach to the broader community extends beyond the scope of trial recruitment. It involves engaging leaders and other stakeholders well in advance of the study as an important channel for building understanding and support among the community at large. Having the
support of key leaders and groups also minimizes stigma that may be attached to community members who participate or who even ask for information about the trial.

Many clinical trial centers set up structures called Community Advisory Boards (CABs). A CAB is made up of key members of community stakeholder groups who as a group act as a liaison between the research team and the broader community. See below for further information about the role of the CAB.

While not a requirement, comprehensive community engagement is increasingly becoming a priority in clinical trials worldwide, as reflected by the development of Good Participatory Practice guidelines. See below for further information.

**Informed Consent Document**
The informed consent document is the paper signed by each volunteer for a trial or other clinical study that indicates his or her understanding of, and agreement to the following:

- Why the research is being done
- What researchers want to accomplish and who is responsible for the study
- What will be done during the trial and for how long
- What risks are involved
- What is expected of trial participants
- What, if any, benefits can be expected from participation
- The system in place for care and support of participants
- What other interventions are available
- The participant’s right to leave the trial at any time

**Guidelines for Clinical Trials**
Trial review committees follow internationally agreed-upon guidelines that provide a detailed definition of requirements for ethical research. These guidelines create uniform ethical and scientific standards for all human trials, wherever they take place.

There are several sets of guidelines that outline regulations and recommend policy for conducting clinical trials.

*International Conference on Harmonisation (ICH)*
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project designed to bring together regulatory authorities from a specific group of countries, to create consensus on regulations for conduct of clinical research and for eventual licensure of pharmaceutical products in those countries. By achieving consensus, the project aims to reduce duplication of effort and therefore avoid delay in development of new drugs while maintaining international high standards and safeguards.
**Good Clinical Practice (GCP)**

Official guidelines for good clinical practice (GCP) were established by the United States Food and Drug Administration, in agreement with the ICH. The purpose of the guidelines is to establish standards for designing, conducting, recording and reporting clinical trials. These guidelines establish the requirements needed for effective review and approval of proposed clinical studies.

**Good Participatory Practice (GPP)**

In 2007, UNAIDS and the AIDS Vaccine Advocacy Coalition (AVAC) issued a document titled *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. The document aims to provide internationally recognized standards for community engagement in HIV prevention trials, and is applicable to clinical trials generally. While not an official part of any regulatory approval process, the guidelines provide a universal reference for researchers, funders, trial communities, civil society, etc. in striving for relevant community involvement. They are meant to be put into practice similarly to GCP standards.

The guidelines were drafted and updated with input from a wide variety of stakeholder groups from all over the world, including research staff, community advocates and civil society groups. They are considered a living document to be updated as perspectives on community engagement evolve.

**Role of the Community Advisory Board (CAB)**

Many clinical research centers have active community advisory boards (CABs), which are an important form of outreach to the broader community. These groups act as liaisons between the trial researchers and the community, and they help to tailor and deliver proper information to potential participants and other stakeholders. Over time, CABs, because of their role as a ‘watchdog’ for both the community and the research team, have come to be seen as a key component of ensuring trials is conducted ethically.

**REFERENCES FOR FURTHER INFORMATION**

*VaxLit Core Content*, Chs 2, 9 and 10  
*Research Fundamentals for Activists*, TAG  
*Family Health International Research Ethics Training Curriculum*  
*Nuremburg Code*  
*Belmont Report*  
*International Conference on Harmonisation Guidelines*  
*Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*
SESSION 8  
Research Ethics Fundamentals

[Chapter III]

OBJECTIVES: By the end of the session, participants will be able to:
- Explain how researchers ensure trials are conducted ethically.
- Practice critical thinking about the ethical factors of clinical trials.

METHOD: Group discussion and exercise. Participants will discuss the principles of research ethics and whether certain hypothetical research scenarios are ethical.

PREPARATION: *Facilitator should perform the following steps BEFORE conducting this session. Note that these steps are not part of the exercise session.*
- Read through the CORE INFORMATION section in Chapter III (pp. 71-76) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.
- Make copies of the WORKSHEET (p. 79) for all participants.

EXERCISE DELIVERY: Estimated session time: **60 minutes**

STEP ONE: Briefly explain the purpose of the session and how it will be conducted.

STEP TWO: For a beginner level audience – participants who have had little to no exposure to the information in this session – start with a brief overview of the concepts to be covered. Use relevant information from the CORE INFORMATION section as a guide.

Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member. For an intermediate/advanced audience, the overview can be skipped. Rather facilitate a more in-depth, interactive discussion about concepts during STEP THREE.

STEP THREE: In plenary, discuss the primary principles of research listed below. Use the CORE INFORMATION section of Chapter III as a guide for your discussion. Engage the participants as much as possible in the discussion.
- Beneficence – the act of goodness of kindness
- Respect for persons
- Justice
- Trial review – IRB, other regulatory bodies, DSMB
• Informed consent
• Research imperialism

**TRAINING TIP**

It may be helpful to invite a local research ethicist, or member of your clinical trial team who may have specific expertise in research ethics to lead this discussion. Ensure that you have adequately coordinated with this individual ahead of time.

**STEP FOUR:** Distribute the WORKSHEET and divide participants into small groups to complete the assignment described. Give them about **20-30 minutes**.

**STEP SIX:** Call groups back together and review their answers for each question.

**CLOSING:**

Close the session by making the point that standard ethical principles and guidelines have now governed clinical research for many years. Additionally, trials go through a lengthy review process to ensure ethical conduct. This is true of clinical trials conducted everywhere in the world.

**TEST QUESTIONS:**

Use or adapt the following question in training pre- and post-test.

1. Which of the following practices is not part of ensuring ethical conduct of clinical trials?
   a. Benefits for trial volunteers greatly outweigh any risk from participating in the trial.
   b. The trial protocol is reviewed and approved by external bodies before starting the trial.
   c. The drug being tested, once developed and licensed for use should be relevant and accessible to the trial population and surrounding community.
   d. A Community Advisory Board is in place to serve as a liaison between the research center and the surrounding community.

**TEST ANSWERS**

1. A

**Trainer’s Notes:**
WORKSHEET
Research Ethics Fundamentals

Your session facilitator has just reviewed the primary principles of ethics in research. Now, in your small group, consider the research scenarios described below. For each, answer the following questions:

- What is the risk/benefit balance of participating in the study?
- What ethical principles are being violated and/or followed?
- If necessary, how could the scenario be changed to better follow the primary ethical principles?

Scenario #1

A study is being conducted in rural Kenya to determine the safety and efficacy of a new drug to treat TB infection. Adult volunteers with pulmonary TB are divided into two groups: one group receives the standard TB treatment, and the other group receives the experimental treatment. Volunteers who receive the standard TB treatment are followed for 6 months, with sputum testing every week during the first two months, and every month thereafter. Volunteers who receive the experimental treatment are followed for 18 months, with sputum testing every week during the first two months, and every month thereafter. At the end of the study, all participants are evaluated for relapse of infection. Those who received the standard treatment who are still TB sputum positive will be offered the experimental treatment if it has been proven more effective than the standard treatment. Researchers compare the rates of relapse of infection in the two groups.

Scenario #2

A multi-site trial is being conducted in three countries in Africa on Early Bactericidal Activity (EBA) of a novel combination TB regimen for drug sensitive and drug-resistant TB. Previous animal studies showed efficacy of this novel combination against both drug sensitive and drug-resistant TB in mouse models. Trial participants in this EBA study will be receiving this novel combination for the very first time in humans. The length of the trial is 14 days, and after trial participants complete their treatment they will be referred to a local TB clinic for follow up examination. If the EBA study proves effective, this novel combination will move to Phase III clinical studies.
The Wrong Foot: Why Community is Important  [Chapter III]

Session 9

OBJECTIVES: By the end of the session, participants will be able to:
- Explain why it is important to lay foundations in the community for a clinical trial.

METHOD: Modified role play and group discussion. Participants will play the role of a community member responding to news of a TB drug trial in their area.

PREPARATION: Facilitator should perform the following steps BEFORE conducting this session. Note that these steps are not part of the exercise session.
- Read through the CORE INFORMATION section in Chapter III (pp. 71-76) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.
- Make copies of the WORKSHEET (pp. 82) for all participants.

EXERCISE DELIVERY: Estimated session time: 30 minutes

STEP ONE: Briefly explain the purpose of the session and how it will be conducted.

STEP TWO: For a beginner level audience – participants who have had little to no exposure to the information in this session – start with a brief overview of the concepts to be covered. Use relevant information from the CORE INFORMATION section as a guide.

Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member. For an intermediate/advanced audience, the overview can be skipped. Rather facilitate a more in-depth, interactive discussion about concepts during STEP FIVE.

STEP THREE: Distribute the WORKSHEET and ask one participant to read the introductory paragraph.

IMPORTANT!
Be sure to explain that the example used here is not typical. In most cases, clinical trial teams and trial sponsors will do some kind of community preparation before a trial begins.
Divide participants into six groups, and assign one role from the list on the worksheet to each group. Ask group members to role-play the answers to the questions on the handout, according to their assigned role. Circulate among the groups, answering any questions. Allow **10 minutes** for group work.

**TRAINING TIP**

If there are not enough participants for six groups, you can make three groups and assign each group two roles from the worksheet.

STEP FOUR: Bring the groups together in plenary. Ask for several volunteers to demonstrate their role play. Allow **about 10 minutes** for this step.

STEP FIVE: Lead a brief discussion using the following question:

What might happen if a clinical trial is started without informing and educating people in the community ahead of time?

**DISCUSSION PROMPTS**

Some of the possible answers here could include:

- Rumors (positive or negative) may start about the trial, the researchers, and the reason for the research.
- You may raise expectations about new TB drugs.
- People may think they are being used as “guinea pigs”.

Ask the following question:

In this exercise, how many people said they would volunteer or encourage others to volunteer for participation in a clinical trial?

**CLOSING:**

Close the session by making the point that community engagement is critical to clinical trials for many reasons. This exercise has shown that it would be very difficult to conduct a trial without the understanding and support of various community stakeholders.

**TEST QUESTIONS:**

Use or adapt the following question in training pre- and post-test.

1. TRUE/FALSE: While community stakeholders (e.g. community based organizations, media, community leaders) do not generally have a defined or official role in clinical trials, their support, partnership, and advocacy can be critical to successful research.

**TEST ANSWERS**

1. TRUE

**Trainer’s Notes:**
WORKSHEET: The Wrong Foot

_Imagine the following incident:_

Early one morning, a van marked “TB Drug Trial” pulls up to your community center. Three people in white jackets get out of the van, set up a table, and begin distributing brochures explaining that they have come on behalf of an international group to recruit volunteers to test a new experimental drug to treat TB. The brochure explains that this “team” will be available at this location for the next two days to sign volunteers up to participate in the study. Before this there had been no publicity about this TB drug trial, and this is the first time most people in the community have ever heard about the possibility of new TB drugs.

Now pretend that you are one of the following people from the community, and answer the questions at the bottom of the page, as if you were that person:

- A local religious leader
- A nurse in the provincial hospital
- Someone who is infected with TB
- Someone who is not infected with TB
- A journalist who covers this province for a national daily newspaper
- A provincial-level Ministry of Health official

QUESTIONS:
1. Do you think somebody in your position would understand what a “TB drug trial” is?
2. Do you think someone in your position would understand the need for new TB drugs?
3. Would you volunteer for this trial? Would you advise others to volunteer? Why or why not?
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<tr>
<th>Session 10</th>
<th>The Role of CABs in TB Drug Research</th>
<th>[Chapter III]</th>
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<tr>
<td><strong>OBJECTIVES:</strong></td>
<td>By the end of this session participants will be able to:</td>
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<td></td>
<td>• Describe why CABs are essential to clinical trials.</td>
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<td></td>
<td>• Discuss the roles CABs play as the link between researchers and community.</td>
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<td><strong>METHOD:</strong></td>
<td>Group discussion and case studies.</td>
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<td><strong>PREPARATION:</strong></td>
<td><em>Facilitator should perform the following steps BEFORE conducting this session. Note that these steps are not part of the exercise delivery.</em></td>
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<td>• Read through the CORE INFORMATION section in Chapter III (pp. 71-76) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.</td>
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<td>• Make copies of the WORKSHEET (pp. 85-86) for all participants.</td>
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<td>• Gather a flip chart and markers.</td>
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<td><strong>EXERCISE DELIVERY:</strong></td>
<td>Estimated session time: <strong>45 minutes</strong></td>
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<td><strong>STEP ONE:</strong> Briefly explain the purpose of the session and how it will be conducted.</td>
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<td><strong>STEP TWO:</strong> Lead a group discussion about CABs. First, ask if anyone can explain the definition of a CAB. If there are any CAB members in the trainee group, ask them to give their own definition and to give some examples of CAB activities.</td>
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<td>Discussion prompt: Ask if anyone can explain what it means by saying the CAB is the bridge between researchers and the community.</td>
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<td><strong>STEP THREE:</strong> Distribute the WORKSHEET to all participants. You may either lead a full group discussion, as described in the worksheet, or if you have a large group, divide participants into groups of 3-4 and ask them to complete the worksheet. Bring the groups back together and have several volunteer their answers.</td>
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<td><strong>CLOSING:</strong></td>
<td>Close by emphasizing that CABs have an active role to play, both as advocates for the trial site, but also to bring community concerns to researchers and other decision-makers.</td>
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<td><strong>TEST QUESTIONS:</strong></td>
<td>Use or adapt the following question for training pre- and post-test.</td>
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1) TRUE/FALSE: While community stakeholders (e.g. community based organizations, media, community leaders) do not generally have a defined or official role in clinical trials, their support, partnership, and advocacy can be critical to successful research.

TEST ANSWERS: 1. TRUE

Trainer’s Notes:
**WORKSHEET: The Role of CABs in TB Drug Trials**

*Instructions: Your facilitator has just reviewed to role of CABs in TB clinical drug trials. Now, either in a full group, or in small groups of 3-4 participants, you will review the following case studies and discuss how a CAB or CAB member would respond and take action.*

*Have one person read each case study, and then answer the questions as a group.*

**CASE STUDY #1**
A TB drug trial is being conducted in a rural area of Malawi. The CAB has been involved in community outreach and is receiving repeated reports that community members are unhappy with certain aspects of the trial. They say that many people are screened out (excluded from participation) without an explanation from the trial staff; further, when people are screened out, they are not referred anywhere else for treatment. CAB members find it difficult to answer questions because they are not familiar with specific inclusion and exclusion criteria, or why trials involve such criteria. They have taken this feedback to the site staff, but the Principal Investigator has not met with them about their concerns.

- What potential ethical violations are occurring in this scenario?
- Why is it important for CAB members to have a solid understanding of given trials as well as basic trial concepts?
- What action should CAB members take in this case?

**CASE STUDY #2**
A Phase III TB drug trial is taking place in Nairobi, Kenya. The community has been informed of the trial, and the CAB has been involved in outreach. News that the trial has been concluded reaches the community and soon after, an inflammatory article appears in the major Kenyan daily newspaper. The article reports that researchers are keeping results from the community; further, that patients who received the experimental drug are not going to receive standard treatment now that the study is over. CAB members know that this information is false and for some reason the reporter wishes to spread misconceptions about the trial.

- Why is it important for the CAB to take action in this case?
- What information would CAB members need when trying to clear up these misconceptions?
- Describe the specific actions a CAB might take to resolve this situation.
CASE STUDY #3

A Phase III TB drug trial has just been completed throughout Africa. CABs have been very active at all trial sites, and have been a key element in ensuring partnership with civil society groups, policymakers, the media and other stakeholders.

The trial results show that the experimental regimen is just as effective – if not more – as the standard treatment, in a much shorter time period. Word is spreading in the community, however, that the new regimen is not going to be licensed and distributed to people who need it. Many of the civil society groups and policymakers the CAB has been working with are very upset about this news and want to take action.

- As a CAB, how would you take action? How could you mobilize the partners to potentially make the new regimen available?
- What information would the CAB need from the research team in order to move forward?