**MODULE 4: PROTOCOL DEVELOPMENT AND COMMUNITY REVIEW**

**Proposed Agenda***

- **Opening Activity:** Values Clarification Exercise *(15 minutes)*
- **Slides and Discussion:** *(60 minutes)*
- **Protocol Team Game:** Who’s Who? *(45 minutes)*
- **Small Group Exercise:** Sections of the Protocol *(45 minutes)*
- **Large Group Activity:** CAB Protocol Workbook *(60-75 minutes)*
- **Participant Evaluation** *(15 minutes)*

*Modules may be divided and adapted to fit the available time frame, to meet the specific needs of individual CABs, and to provide adequate break time for participants and trainer(s). Please adapt the participant evaluation forms as needed so that they are appropriate for the training plan.*
OPENING ACTIVITY

Module 4

Values Clarification Exercise

Time frame *(15 minutes)*

**Purpose**
- To stimulate critical thinking about the role of community representatives in protocol development and implementation

**Materials needed**
- Flipchart and marker (or blackboard and chalk) for note taking
- Ball, or balled up sheet of paper to “throw” randomly to participants

**Instructions**
- Write a provocative or challenging statement on the chalkboard or flipchart so that everyone can see it clearly. For this module, we suggest something like: “I don’t think community members have any business working with the researchers planning clinical trials. After all, the community representatives are not scientists. What do they know?”
- Tell participants they have five minutes to think about the statement. They may take notes on their thoughts if they like. They will be asked to share their responses to the statement after they have had time to think about it.
- Start the conversation by tossing the ball to one of the participants. That participant will tell the group what he/she thinks about the statement. List the main themes of the participant’s response on the flipchart or blackboard.
- The participant who spoke first then tosses the ball to another participant, who will add something “new” to the discussion (try not to repeat the same ideas).
- Keep asking for comments until everyone has had at least one chance to speak. Do not stop the game until the participants seem satisfied that they have given an adequate response to your statement.
- Summarize the discussion by reviewing the list of main themes, and talk about how these themes will be part of the training program today.
Module 4

Slides – Insert Here
This teaching tool was developed by the François-Xavier Bagnoud Center at the University of Medicine and Dentistry of New Jersey, with the support of the International Maternal Pediatric and Adolescent Clinical Trials (IMPAACT) network.

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Claire Schuster, BS, MPH
Network Community Coordinator
Social & Scientific Systems, Inc.
Email: cschuster@s-3.com
Phone: (301) 628-3319

Mary Jo Hoyt, RN, MSN
IMPAACT Global Training Director
François-Xavier Bagnoud Center
Email: info@fxbcenter.org
Phone: (973) 972-9230

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Objectives

After completing this training, participants will be able to
- Outline the process of protocol development and areas for community input.
- Explain the roles of protocol team members.
- Describe sections of the protocol important for community review.
- Complete the “Protocol Workbook” as a way of reviewing a protocol from the community perspective.

In the second objective, the term “protocol team” is the same as saying “study team.” Sometimes we will be using one term and sometimes the other term.
This a picture of how the IMPAACT network is organized. Understanding how the IMPAACT network is organized will help you understand how protocols are developed and approved. But also notice that there are opportunities for ICAB representatives to participate in many of the steps involved in developing a protocol. (Trainer: Please note these areas in slide). An ICAB representative is a voting member of the Network Executive Committee (NEC), the Scientific Oversight Committee, and all of the Scientific Committees. ICAB members may also be members of the Resource committees, though they may not deem it necessary to participate in some of them (like the Data Management or Quality Assurance Resource committees).

The scientific committees are shown on the lower left portion of the slide. These committees are where protocols are “born.” Ideas for a study start here, and are first called “capsules.” A capsule is simply a one page description of the idea for a protocol.

Scientific Oversight Committee (SOC): The members of this committee review and approve the capsule before it can be developed further. After approval, a capsule is further developed into a concept sheet. A concept sheet is a longer description (5 pages) of the proposed protocol, including an estimated budget.

Network Executive Committee (NEC): is responsible for must reviewing and approving the concept sheet before a protocol team can be formed.
This is another way of looking at how protocols are developed. As we said in the previous slide, a capsule is usually written by a member of a scientific committee, and then reviewed by the SOC. Once approved, the capsule is written in greater detail, which is called the concept sheet. If the concept sheet is approved, only then may a protocol team be formed, and a protocol written.

These early reviews by the SOC help ensure that the idea for the clinical trial is important enough to spend the resources of the group, that it is within the mission of IMPAACT, and that a similar protocol isn’t already being developed or implemented by another scientific committee or even another network.

Later, while the protocol is being developed, the NEC’s review and approvals process will make sure the clinical trial is as safe as possible, as scientifically accurate as possible, and as sensitive to and respectful as possible of the needs of the community and the participants.

This slide shows again that there are many opportunities for community representatives to take part in the discussion and to influence how the protocol is developed. This is why we want to help you learn about protocols. CAB members are not expected to be scientists, but members can share important ideas and insights into whether the community feels the protocol is important and fair, and whether the way the study is designed is reasonable for the participants and the community.
Once a concept sheet is approved, a team of people, who are experts in different areas related to the study, are asked to become part of the study team. A community representative is also asked to be part of the team and the expertise that person brings to the group is knowledge of his or her community. A community representative on a protocol team is a member of the ICAB or an RCAB.

To review: A protocol begins as a capsule, usually written by members of one of the scientific committees. If the capsule is approved, the scientific committee develops the idea in more detail, and this is called writing a concept sheet. If the concept sheet is approved, then a protocol team will be formed, and a protocol written.

When the protocol is written, it too must be reviewed on many levels to make sure
- it is safe
- the potential benefits of implementing the protocol are greater than the potential risks
- it is fair
- it is scientifically accurate
- it is important enough to spend the resources to implement it

Sometimes this process takes a bit longer than we would like!
Slide 7

This is what the front page of a protocol looks like. Here are some things to note about this page:

- Once a concept sheet is approved and a protocol is going to be developed, it is assigned a number by the IMPAACT Operations Center. In this case, the protocol is called P1032.

- The official title of the protocol is often very long, because it very completely describes the focus of the study. Usually, a “short title” is provided for the informed consent form, but people often refer to the study by its number rather than its name.

- As you can see by the bold lettering in the middle of the slide, the scientific committee that developed and “sponsored” the protocol is always listed, along with the chairs of that committee. This protocol originated with the Perinatal Scientific Committee.

- In addition, the Chairs, the DAIDS representative and the Clinical Trials Specialist are listed on the title page. We’ll talk about some of the roles of people on the study team as we go on.
These are the major parts of every protocol. Every protocol Table of Contents lists these major sections, in this order. There may be sub-sections added, depending on the characteristics of the protocol, but every IMPAACT clinical trial protocol is structured like this.

The sections that have the red asterisk after the name are sections that are especially necessary for the community representative to pay attention to, and we'll work on how to do that later. The other sections of the protocol are not as important from the community perspective, although the Introduction may give some useful background information.

The appendices always include the Informed Consent Form and the Schedule of Evaluations. The schedule of evaluations tells you when participants will have research visits, and what tests and evaluations will be done at each of these visits.

The appendices also have other items that may not be important for the community to review.
The first pages of the protocol include the Protocol Team Roster—a listing of every member of the protocol team along with all of their contact information. We'll talk about the roles of these team members in the upcoming slides. But please note that the roster always includes, at the top of the page, the “team log-on”. This is the e-mail address that is used for any communications to the team. When this address is used, the e-mail reaches all members of the protocol team, and the question or comment in the e-mail will be responded to by whomever is the most appropriate member of the team to respond.

The Clinical Trials Specialist (CTS) organizes this information, ensures that e-mails are addressed by one of the team members, and is generally in charge of team communications. The CTS also schedules conference calls, sends out the agenda for calls based on information from the protocol chair, and keeps a record of the conference call discussions. The CTS is the center of communications, and the keeper of all of the protocol-related documents.
Protocol Team Members

- **Chair**: Overall management of the scientific development of the protocol. Assigns tasks to other members of the team. May have a Co-chair and/or a Vice-Chair to share these responsibilities. Work from their local sites.

- **Investigators**: Often have specialized knowledge related to the protocol. Assist the Chair in the scientific development of the study. Work from their local sites.

- **-Ologists**: (Virologist, Immunologist, Neurologist): A protocol team may require specialized expertise to advise the team and to write sections of the protocol.

- **Chairs, co-chairs**: Have overall responsibility for the development, implementation, conduct, and reporting of the study. Lead protocol meetings and calls, assigns team tasks.

- **Investigators**: Assist in the development and implementation of the study. Assist with aspects of the study related to clinical science and patient care. Investigators and chairs normally activate and support the protocol at their own clinical research sites (CRS).

- **-Ologist**: By this we mean special or investigators who specialize in a certain field, such as psychology, neurology, virology, etc. Virologists study viruses, immunologists specialize in the immune system. Often, protocols need some advice and support one or more specialists, depending on the characteristics of the study.
**Protocol Team Members**

- **Clinical trials specialist (CTS):** Protocol administrative manager. Manages all communications to and from the team and its members, schedules conferences, and writes many sections of the protocol based on information from the team members. Works from the IMPAACT Operations Center in Silver Springs, MD.

- **Field representative:** Often an experienced research nurse at a local site who advises the team on the practical issues related to implementing the protocol “in the field”. Answers the questions related to “Can this be done at the sites?” or “How can we get this done at the sites?”

**Clinical Trials Specialist (CTS):** The CTS is the project manager and the lead writer for the team. Information is “fed” to the CTS, who manages all the information and communications and turns it into a comprehensive protocol that follows the standard sections we looked at on the earlier slide. The CTS is the focal point for information and problem solving, and works from the IMPAACT Operations Center.

**The Field Representative** is the person on the team most experienced in actually working with participants and implementing the protocol at a local site. This person is often a research nurse or study coordinator, who really understands what problems arise when local research teams try to implement the protocol “in real life”. As always, it is easier to ask for certain tests or exams to be done by writing them in the protocol than it is to actually get the tests and exams done in the clinic. The Field Representative has a good sense of what is realistic and possible to do at local research sites.
### Protocol Team Members

- **Data manager**: Creates case report forms and receives and organizes data collected by sites. Located at Frontier Science and Technology Research Foundation (FSTRF) in Buffalo, New York. Also called the DMC, or Data Management Center.

- **Statistician**: Advise the team on issues related to study design so that the results will be as accurate and unbiased as possible. Analyzes the data and advises the team on interpretation and reporting of results. Located at the Statistical and Data Management Center (SDAC), Harvard University in Boston, MA.

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- The **Data Manager (DM)** is located at the **Data Management Center** in Buffalo, New York. The full name of their company is on the slide. This person’s title tells you what the job entails—keeping track of how to gather the data, and then organizing the data electronically in a way that makes it possible for the statisticians to analyze it. The DM creates Case Report Forms (CRFs) for the study. The research team at the site, when seeing a study participant, completes the CRFs with all of the patient information, and then that information is sent back to the DM, who keeps electronic records of all of the information from all of the participants at all of the sites. The DM also keeps track of what CRFs or information is missing or late, and queries sites about missing or confusing data.

- The Data Manager passes all of the data sent to the DMC and organized at the DMC to the **Statistician**. The statistician helps the protocol team to design the study so that it is scientifically accurate and designed in the way best suited to answering the research question and minimizing the risk of bias. The statistician also analyzes the data so that the results of the study can be known. This is done during the study as well as at the end of the study.
The **laboratory representative** advises the team on all laboratory testing and writes the instructions for collection and shipping of specimens. IMPAACT has identified and funded a few “Core Laboratories” where specialized testing for the research studies is done. These are located at local research sites, and the laboratory representative is usually someone who works at one of the core laboratories.

The **Medical Officer** is either a doctor who works for the IMPAACT sponsor, the Division of AIDS (DAIDS) within the National Institute of Allergy and Infectious Disease (NIAID). Some protocols are sponsored by the National Institute of Child Health and Development (NICHD), and in this case a Medical Officer from NICHD would be part of the protocol team. As the sponsor of IMPAACT and IMPAACT research, the Institutes have final responsibility for the research, and they must approve a protocol before it can be implemented.
Community Representative on the Protocol Team

- Community responses, questions
- Eligibility criteria, barriers to enrollment
- Flexibility of study design (are the requirements more strict than is really needed?)
- Advice on recruitment and retention
- Liaison to CABs and community
- Informed Consent review
- Participant rights, support, expectations

The CAB representative reviews the protocol with these thoughts in mind:

- Do people understand why the study is being done? Is this study important to people? Is there a strong interest in participating?
- Do people perceive this study as “high risk”?
- Do any of the inclusion/exclusion criteria create a barrier to participation that seems unnecessary or unfair?
- Is the design of the study as flexible as it can be? For example, if a study visit is scheduled for “Day 14”, does the schedule permit a day or two leeway in scheduling the visit?
- Is there any information that may help the team recruit and retain participants?
- What information might be important for me to share with CAB members and the community?
- Is the informed consent written so that I can understand it? Will others understand it?
- Are the requirements for the study visits reasonable?
- Are the rights of participants respected?
- Is there any information and other support available to help participants continue to meet the requirements of the study?
**Protocol Team Game: Who’s Who?**

**Trainer:** Please see the separate Trainer Instructions for this game.
Slide 16

**Group Exercise:**

**Sections of the Protocol**
Protocol Workbook Activity
PROTOCOL TEAM GAME: WHO’S WHO?

Module 4

Trainer Instructions

Time frame *(45 minutes)*

Purpose
This exercise is intended to help participants understand the roles of some of the protocol team members. It will also help participants gain a deeper understanding of the role of the community representative on a protocol team.

Materials needed
- Flipchart and marker (or blackboard and chalk) for note taking
- Protocol schema (provided)
- List of “job descriptions” for select protocol team members (provided)
- Prepared list of statements attributed to specific protocol team members. The participant manual will include all of the statements, but will not include which type of protocol team member made the statement. (provided)
- Sweets or other small rewards for prizes (optional)

Instructions
- Review the protocol schema with the group, explaining terms and ensuring that the participants have a basic understanding of the study design and the primary objective.
- Divide participants into groups of 2-8, depending on the size of the group. Pair experienced CAB members or research team members with inexperienced participants if needed.
- Each group or pair must review the statement list, and make a decision as to which protocol team member is the most likely person to have made the statement. Encourage groups to spend only a couple of minutes per statement, and to move on if they get “stuck” on any one statement. Tell the groups to write down their decision for future discussion.
- Give the groups 15 minutes for this review. Warn them after 5 minutes that they have 10 minutes left and after 10 minutes that time is coming to an end. Move among the participants during the discussion to answer questions or clarify concepts.
- Explain that the groups will take turns selecting one of the statements and describing why they chose their answer. (For example: “We decided that this statement was made by the Principal Investigator because…….”).
**Trainer:** It would help make this exercise more fun and less stressful for participants if groups were rewarded with a sweet or other simple treat for each attempt at an answer and explanation.

- Tell the next group to select a question that has not been discussed. Cross out each statement after the question is answered correctly.
- Do this until the groups identify all of the speakers.
- Give each group equal opportunity to provide an answer. Ideally, the number of statements answered by each group should be equal, but do not force a group to answer if they seem uncomfortable or overwhelmed by the task.
- Congratulate all participants for their effort.
PROTOCOL TEAM MEMBERS’ STATEMENTS: WHO’S WHO?

Module 4

Trainer Answer Sheet

1. I’ve scheduled our next two calls, and will send an e-mail notice to the team later today. Clinical Trials Specialist

2. The agenda for the next call will be to come to a final decision about the length of time women will breast feed. Protocol Chair

3. The dosing of this medicine needs to be increased every month, depending on how much weight the infant gains. Pharmacist

4. The people I have spoken with in my neighborhood are really concerned about stopping breastfeeding earlier than is normal in our culture. Community Representative

5. I’m concerned that staff members are not all qualified to teach mothers about exclusive breastfeeding earlier than is normal in our culture. Field Representative

6. Do the babies really need to have these blood tests every month? Mothers in my community will be worried about taking so much blood from an infant. Community Representative

7. I’d like the Pharmacist and the Laboratory representative to prepare their sections of the protocol prior to our next call. Protocol Chair

8. I will send an e-mail to all of the research sites this week to inform them the protocol has been completed and approved. Clinical Trials Specialist

9. My staff is concerned that the amount of data you want us to collect is going to make it a very difficult study to manage. Field Representative

10. Women in my community are worried that if they join the study, everyone will know about their HIV status because they will have to come to the clinic so often. Community Representative

11. The viral culture requires at least 3 mL of blood in a red top tube. Laboratory

12. Nevirapine is active in the blood for a much longer period than the other drug. Pharmacist

13. I wrote the second section of the protocol and will send it to the team by e-mail tomorrow. Clinical Trials Specialist

14. Before the next call, the laboratory representatives must work with the pharmacist to review the laboratory requirements and schedule for consistency. Protocol Chair

15. I will send the protocol to the Scientific Oversight Committee for review once everyone has signed off on this final version. Clinical Trial Specialist
PARTICIPANT HANDOUT
Module 4
Schema for Protocol Team Game

A Phase II Comparison Study of Drug X + ZDV + 3TC vs. Drug X + NVP for the Prevention of Mother to Child Transmission of HIV Infection during the Breastfeeding Period*

*Please note that this schema was developed for training purposes only.

Design:  Phase II, two arm, randomized, open label

Sample Size:  150 women and their infants

Population:

Women who are pregnant who:
- are 28-39 weeks gestation (pregnant)
- are HIV-infected
- are not eligible for (in need of) ARV treatment for their own health and do not plan to start ARV therapy for their own health within 12 weeks following delivery
- have a CD4+ count of at least 250 cells/mm³
- live in resource-limited settings where breastfeeding is the norm
- are committed to exclusive breastfeeding for at least 3 months

Women in labor who:
- are HIV-infected
- are not eligible for (in need of) ARV treatment for their own health and do not plan to start ARV therapy for their own health within 12 weeks following delivery
- have a CD4+ count of at least 250 cells/mm³
- have no indication of a fetal abnormality
- live in resource-limited settings where breastfeeding is the norm
- are committed to exclusive breastfeeding for at least 3 months

Regimen:

Arm A:  Drug X + ZDV + 3TC for 3 months
Arm B:  Drug X + NVP for 3 months
Women will be randomized to Arm A or Arm B upon protocol entry.

Primary Objective:

- To evaluate the effectiveness of Drug X + ZDV + 3TC versus the effectiveness of Drug X + NVP for reducing the risk of mother-to-child transmission of HIV during the breastfeeding
PARTICIPANT HANDOUT

Module 4

Job Descriptions for Select Protocol Team Members

**Protocol Chair:** Approves the agenda for and leads protocol meetings and conference calls. Assigns work to other members of the protocol team. Has overall responsibility for the development and the conduct of the study.

**Clinical Trials Specialist:** Project manager. Manages all e-mail communications to and from the team. Schedules and records calls and meetings. Has overall responsibility for writing most of the protocol document and making corrections as directed by the team.

**Field Representative:** Provides information to the team about patient care and other issues related to how easy or difficult it will be for nurses and others to actually enroll and manage the demands of the study with patients at the sites.

**Pharmacist:** Works with data manager to develop a prescription file for the study treatments. Approves final prescription prior to activation. Writes some or all of the Study Treatment section of the protocol.

**Laboratory:** Advises about and monitors laboratory quality control and safety. Works with investigators to plan for complete and accurate lab specimens, and processing and storage of samples.

**Community Representative:** Advises the study team about issues specific to the community as they relate to the protocol. Communicates protocol issues to the community as needed. Reviews the Informed Consent Form to make sure it will be easily understood by community members. May discuss the study and the consent form with potential participants.
PARTICIPANT Handout

Module 4

Protocol Team Members’ Statements: Who’s Who?

1. I’ve scheduled our next two calls, and will send an e-mail notice to the team later today.

2. The agenda for the next call will be to come to a final decision about the length of time women will breast feed.

3. The dosing of this medicine needs to be increased every month, depending on how much weight the infant gains.

4. The people I have spoken with in my neighborhood are really concerned about stopping breastfeeding earlier than is normal in our culture.

5. I’m concerned that staff members are not all qualified to teach mothers about exclusive breast feeding. We may need to provide training on breastfeeding counselling.

6. Do the babies really need to have these blood tests every month? Mothers in my community will be worried about taking so much blood from an infant.

7. I’d like the Pharmacist and the Laboratory representative to prepare their sections of the protocol prior to our next call.

8. I will send an e-mail to all of the research sites this week to inform them the protocol has been completed and approved.

9. My staff is concerned that the amount of data you want us to collect is going to make it a very difficult study to manage.

10. Women in my community are worried that if they join the study, everyone will know about their HIV status because they will have to come to the clinic so often.

11. The viral culture requires at least 3 mL of blood in a red top tube.

12. Nevirapine is active in the blood for a much longer period than the other drug.

13. I wrote the second section of the protocol and will send it to the team by e-mail tomorrow.

14. Before the next call, the laboratory representatives must work with the pharmacist to review the laboratory requirements and schedule for consistency.

15. I will send the protocol to the Scientific Oversight Committee for review once everyone has signed off on this final version.
Module 4

Group Exercises
GROUP EXERCISE

Module 4
Sections of the Protocol

Time frame (45 minutes)

Purpose
This exercise will help participants become more familiar with the parts of a clinical trial protocol of greatest importance to community representatives when evaluating a protocol from their perspective as community advocates.

Materials needed
- Flipchart and marker (or blackboard and chalk) for note taking visible to the group
- Please provide copies of the following items to participants. These items can be found in this manual after the “Protocol Workbook Exercise” trainer instructions.)
  - Protocol Summary (For training purposes only! Not an official document)
  - Schema and Objectives
  - Study Design
  - Selection and Enrollment of Subjects
  - Schedule of Evaluations
  - Sample Informed Consent and/or Sample Assent for Children (Because the IC documents are very long, we have included only a partial IC for this exercise)
  - Protocol Worksheet

Instructions
- Direct participants to the items you have provided (from the list above).
- Read the protocol summary aloud for the group. Answer any questions they may have about the summary. However, for the purposes of this exercise, it is not necessary to provide more detailed information about the protocol.
- Divide participants into groups of about five people. If possible, pair experienced CAB members or research team members with inexperienced participants.
- Assign each group one or two sections of the protocol documents provided (depending on the number of groups).
- Ask each participant to take 15 minutes to read their group’s assigned protocol section.
- Ask participants to consider the questions on the protocol worksheet and discuss the questions as a group for 15 minutes. Tell them they will be reporting their responses to all participants at the end of the exercise, so they may wish to make notes about their discussion. Reassure the participants that you (and an assistant if available) will rotate among the groups to offer assistance.
- In the order of the protocol sections as listed above, ask the groups to report on their discussion. Some suggested discussion points are provided on the Trainer Manual Worksheet.

- Although it is important to correct any misinformation, in many instances, there are no “right” or “wrong” answers. So encourage the groups frequently!

**Note:** Depending on the knowledge and experience of the group, you may need to assign a smaller portion of the IC than is provided. Or you may want to suggest that the group read only the “Risks” section.
PROTOCOL WORKBOOK EXERCISE

Module 4

Trainer Instructions

Time frame (60-75 minutes. You may divide this exercise into 2 parts as needed)

Purpose

- This interactive exercise will give participants first-hand experience with reviewing a protocol using the Community Advisory Board Protocol Workbook. Protocols are intimidating because of their size, and because there are many sections that are highly scientific and difficult to understand for non-researchers. Our goal is to help the participants to:
  - Practice reviewing a protocol for the first time with the support and encouragement of their colleagues and the trainer.

The goal for the trainer is to encourage participation and help participants become comfortable asking questions, making comments, and expressing their concerns about a study. Explain that all questions and comments are important and will be addressed.

Materials needed

- Community Advisory Board Protocol Workbook
- P1060 Study Protocol (You may use a different protocol, but you will want to also provide a protocol summary and protocol model. The protocol summary and model for P1060 are provided with this manual, along with the other sections listed below).
- Flipchart and marker (or blackboard and chalk) (optional)
- For participants:
  - Protocol Summary
  - Schema and Objectives
  - Study Design
  - Selection and Enrollment of Subjects
  - Schedule of Evaluations
  - Sample Informed Consent and/or Sample Assent for Children (Because the IC documents are very long, we have included only a partial IC for this exercise)

Instructions

- Participants should work in groups of 2-5, depending on the number of participants. Each group will work with one or two of the sections of the protocol listed above. (If you have a small group of training participants, you can facilitate the same discussions and work as would happen in small groups).
- Complete your own copy of the Protocol Workbook in advance, so you can dedicate your attention to engaging participants in the discussion.
Assign each group a part or parts of the protocol. They will use their section(s) of the protocol and try to complete the corresponding parts of the Protocol Workbook, working together as a group. (For example, if the group is assigned the Informed Consent document, then they will work on the section of the protocol related to Informed Consent). Walk from group to group so you can answer questions, listen to comments, and offer assistance if a group requests it.

When the time is up, have the groups come together to discuss their work and their conclusions for the benefit of all of the participants. Usually, we ask that one person from each group report to the larger group. Make notes of important findings on the flipchart, and correct any misinformation before ending the session.
**PROTOCOL WORKSHEET**

**FOR “SECTIONS OF THE PROTOCOL” GROUP EXERCISE**

**Module 4**

After you read the section of the protocol assigned to your group, discuss these questions. Take notes of your discussion so you can talk about it with the rest of the participants at the end of the small group discussion.

1. Describe (in your own words) the purpose of this section of the protocol:

2. Discuss why this section of the protocol should be reviewed by a community representative. What questions or concerns might be addressed by a community expert?
P1060 PROTOCOL SUMMARY

Module 4

Background: HIV-infected pregnant women can take anti-HIV medicines during pregnancy and/or around the time of delivery to decrease the risk of passing HIV to the baby.

Most HIV-infected pregnant women in resource-poor settings take at least one dose of nevirapine (NVP) right before or during delivery, and the baby is also given one dose of NVP to lower the risk that HIV infection will be passed from the mother to the baby during labor and delivery. Unfortunately, some babies who were given NVP will still be born with HIV infection because NVP does not prevent all cases of mother-to-child transmission of HIV.

In some babies who are infected with HIV, the exposure to NVP may cause a change in the HIV in their body. This change makes the virus appear to be resistant to NVP. If this change in the virus occurs, it means that NVP may not work against HIV if it is taken again in the future (we don’t know). In other words, because these HIV-infected babies were exposed to NVP to try to prevent the HIV infection, NVP may or may not work to treat their HIV infection.

This study is designed to answer the question of whether NVP will be effective for treating HIV-infected infants exposed to NVP for prevention of mother-to-child transmission of HIV. This is a very important question because using NVP as first-line treatment, in combination with other ARVs, is very common. First-line treatment is the recommended combination of ARV medicine to be given when patient begins treatment. Nevirapine is simpler, less expensive, and generally has fewer side effects than ARV regimens that use a protease inhibitor instead of NVP.

To answer this question, the study will:

- See how well children who received NVP at the time of birth respond to a combination of medicines that includes NVP, compared to a combination of medicines that does not include NVP.
- See how well children who did not receive NVP at the time of birth respond to a combination of medicines that includes NVP, compared to a combination of medicines that does not include NVP.
- See how well those children who take a combination of medicines that includes NVP respond, compared to those children who take a combination of medicines that does not include NVP.
Infants *exposed vs. NOT exposed* to NVP will be randomly assigned to Treatment Group 1 (NVP-based regimen of ARVs) or Treatment Group 2 (protease inhibitor-based ARV regimen).

- **Cohort I**: Nevirapine Exposed Infants
  - Group 1: AZT + 3TC + NVP
  - Group 2: AZT + 3TC + LPV/r

- **Cohort II**: Infants not exposed to nevirapine
  - Group 1: AZT + 3TC + NVP
  - Group 2: AZT + 3TC + LPV/r
**P1060 Schema**

**Module 4**

**Phase II, Parallel, Randomized, Clinical Trials Comparing the Responses to Initiation of NNRTI-Based versus PI-Based Antiretroviral Therapy in HIV-Infected Infants Who Have and Have Not Previously Received Single Dose Nevirapine for Prevention of Mother-to-Child HIV Transmission**

**Design:**
Phase II, randomized, controlled trial of two parallel (going on at the same time) study cohorts

**Sample Size:**
576 subjects (participants) (288 per cohort, 144 per group)

**Population:**
HIV-infected infants and children ≥ 6 months and < 36 months of age who are eligible for ART as defined by World Health Organization

**Stratification:**
Equal numbers to be enrolled above and below 12 months of age within each group (also known as a cohort)

**Treatment (ARV combination therapy):**
In Cohort I, there will be two groups: NVP-exposed infants/children will be randomized to receive either
- NVP-based treatment (Group 1)
- LPV/r-based treatment (Group 2)

In Cohort II, there will also be two groups. NVP-unexposed infants/children will be randomized to receive either
- NVP-based treatment (Group 3)
- LPV/r-based treatment (Group 4)

**Note:** In the event of ZDV side effects, d4T may be substituted (d4T 1 mg/kg q12 hours) and will be supplied by the study.

**Treatment Duration:**
All subjects will continue on study treatment for 24 weeks from the time the last subject is enrolled.
OBJECTIVES

Primary (Most Important or Largest) Objectives:
1. Among subjects exposed to NVP for MTCT prevention (Cohort I): To compare rates of treatment failure at 24 weeks in subjects receiving a NVP-based treatment (Group 1) versus a LPV/r-based treatment (Group 2).
2. Among subjects not exposed to NVP for MTCT prevention (Cohort II): To compare rates of treatment failure at 24 weeks in subjects receiving a NVP-based treatment (Group 3) versus a LPV/r-based treatment (Group 4).
3. To compare rates of treatment failure at 24 weeks in NVP-exposed versus NVP-unexposed subjects receiving a NVP-based treatment (Group 1 versus Group 3) and NVP-exposed versus NVP-unexposed subjects receiving a LPV/r-based HAART treatment (Group 2 versus Group 4).

Secondary Objectives:
1. Among subjects exposed to NVP for MTCT prophylaxis (Cohort I): To compare long term rates of treatment failure in subjects receiving a NVP-based HAART treatment (Group 1) versus a LPV/r-based HAART treatment (Group 2).
2. Among subjects not exposed to NVP for MTCT prophylaxis (Cohort II): To compare long term rates of treatment failure in subjects receiving a NVP-based HAART treatment (Group 3) versus a LPV/r-based HAART treatment (Group 4).
3. To compare long term rates of treatment failure in NVP-exposed versus NVP-unexposed subjects receiving a NVP-based HAART treatment (Group 1 versus Group 3) and NVP-exposed versus NVP-unexposed subjects receiving a LPV/r-based HAART treatment (Group 2 versus Group 4).
4. To compare the safety profile of NVP and LPV/r in the two treatment treatments (Groups 1 and 3 versus Groups 2 and 4).
5. To compare the rates of resistance and types of resistance mutations in NVP-exposed subjects (Cohort I) and NVP-unexposed subjects (Cohort II) who meet failure criteria.
6. To assess the relationship of pre-existing, baseline resistance mutations (in plasma virus and proviral DNA) to the rate of virologic failure using standard and highly sensitive methodologies.
7. To evaluate the impact of time since NVP exposure on risk of virologic failure and antiretroviral drug resistance.
8. To evaluate the genetic relationship of NVP-resistant variants at baseline and at the time of failure.
9. To evaluate the impact of HIV-1 subtype on risk of virologic failure and ARV drug resistance.
This is a Phase II, randomized, controlled trial of HIV-infected infants and children between 6 months and 36 months of age who are eligible for ART as defined by WHO (CD4% less than 20% if less than 18 months of age, or less than 15% if more than 18 months of age, or AIDS-defining illness). Infants/children will be enrolled in one of two cohorts based on NVP exposure. Within each cohort, they will be randomized to one of two ARV treatments as outlined below. A total of 576 infants/children will be enrolled; 144 per group. An equal number of infants/children above and below 12 months of age will be enrolled in each cohort.

Cohort I: NVP-exposed infants/children
- NVP-based treatment (Group 1)
- LPV/r-based treatment (Group 2)

Cohort II: NVP-unexposed infants/children
- NVP-based treatment (Group 3)
- LPV/r-based treatment (Group 4)

All subjects will complete at least 48 weeks of follow-up, continuing on study treatment until 24 weeks from the time the last subject is enrolled. Specific study requirements are outlined in Appendix I.

Note: Subjects who are diagnosed with active tuberculosis during the study and who require rifamycin-containing treatment will discontinue (stop) study treatment and receive the best available treatment outside of the study.

Study Endpoints
Subjects experiencing any persistent or recurrent treatment-related Grade 3 or non-life-threatening Grade 4 toxicity, treatment-related clinical hepatitis or a single, treatment-related, life-threatening Grade 4 toxicity, will be considered to have met a toxicity endpoint.

Any one of the following constitutes a virologic endpoint.
- Confirmed plasma HIV-1 RNA level <1 log10 copies/mL below study entry value at 12 to 24 weeks
- Confirmed plasma HIV-1 RNA level >400 copies/mL at 24 weeks
- Confirmed viral rebound, defined as 2 consecutive plasma HIV-1 RNA values >4,000 copies/mL after 24 weeks
P1060 SELECTION AND ENROLLMENT OF SUBJECTS

Module 4

Inclusion Criteria: Cohort I and Cohort II

- Age > 6 months to < 36 months (up to but not including the 3rd birthday)
- Confirmed diagnosis of HIV infection, defined as two positive assays from two different samples. The two results may be any combination of the following:
  - At any age: DNA PCR, HIV culture, or RNA PCR if >10,000 copies/mL
    - At >4 weeks of age: p24 antigen detection
    - At >18 months of age: HIV antibody test (rapid HIV test or any licensed ELISA test kit, and confirmation by either ELISA, Western blot, or plasma HIV-1 RNA)
  - HIV-1 RNA >5,000 copies/mL within 30 days prior to screening.
  - ARV naïve except for ARVs used in attempts to prevent intrapartum MTCT. (Infant ARV use for < 1 week postpartum for prevention of MTCT is allowed.)
  - Treatment eligible as defined by the WHO pediatric algorithm (shown below and in Appendix III). This criterion may be modified if WHO releases a new pediatric treatment algorithm, in which case either a Letter of Amendment or protocol amendment would be prepared.
  - CD4% <20% if <18 months of age or <15% if >18 months of age

OR

- History of AIDS-defining conditions or AIDS-defining opportunistic infections

Note: Subjects with active opportunistic infections are not eligible for study participation until they have been treated and are clinically stable.

- Parent or legal guardian able and willing to provide signed informed consent and to have the subject followed at the clinical site.

Inclusion Criteria: Cohort I ONLY

- Clinic/hospital documentation of maternal and/or infant NVP exposure is highly preferable. If not available, a verbal report that is considered ‘highly reliable’ by the site investigator is acceptable.

- Maternal use of ARVs during pregnancy and/or during labor is permitted (including maternal NVP use).

- One or more of the following three criteria:
  - Strict formula feeding
  - Infant HIV diagnosis <60 days of age
  - AIDS-defining event by WHO criteria <60 days of age
Inclusion Criteria: Cohort II ONLY
- Maternal use of ARVs during pregnancy and/or during labor is permitted with the exception of NNRTIs (refer to Section 4.6).

Exclusion Criteria: Cohort I and Cohort II
- Grade >2 AST or ALT at screening.
- Any Grade >3 laboratory toxicity at screening.
- Receipt of ARVs other than for prevention of intrapartum MTCT.
- Infants who received ARVs past the first week of life (e.g. for prevention of breast milk transmission) are excluded from study entry.
- Acute, serious infections requiring active treatment (prophylaxis allowed [e.g. PCP, cryptococcal meningitis]). Subjects can be receiving treatment for active TB if this does not include rifamycin drugs.
- Chemotherapy for active malignancy.
- History of cardiac conduction abnormality.

Exclusion Criteria: Cohort I ONLY
- Breastfeeding, unless the breastfed infant has a positive HIV diagnostic assay at <60 days of age, or the infant has experienced an AIDS-defining condition by WHO criteria at <60 days of age.

Exclusion Criteria: Cohort II ONLY
- Report of any maternal NVP or other NNRTI exposure prior to or during the pregnancy with this child, including single-dose NVP, documented by either verbal report or through the clinic or hospital record (use of ARVs from the NRTI or PI classes is allowed).
- Report of infant NVP exposure at any time, including during the first week of life, documented by either verbal report or through the clinic or hospital
## P1060 Schedule of Evaluations

### Module 4

<table>
<thead>
<tr>
<th></th>
<th>Screen(^1)</th>
<th>Entry</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 48</th>
<th>q12 weeks(^2)</th>
<th>Off Drug/ On Study(^0)</th>
<th>Early Disc./ End of Study</th>
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<tr>
<td><strong>Clinical Evaluations</strong></td>
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<td>Informed Consent</td>
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<td>History(^2)</td>
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<td>Physical exam(^3)</td>
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<td>Assessment of HIV-related symptoms</td>
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<td>Pediatric Adherence Questionnaire</td>
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<td><strong>Laboratory Evaluations</strong></td>
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<td>Hematology(^4)</td>
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<td>Chemistries(^5)</td>
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<td>Triglycerides/cholesterol</td>
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<td>Plasma HIV-1 RNA PCR(^6)</td>
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<td>Lymphocyte subsets(^6)</td>
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<td>Stored specimens(^7)</td>
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</table>
| **Total Blood Volume** | 5-7 ml       |       | 7 ml   | 2-4 ml | 3-5 ml | 2-4 ml  | 6-8 ml  | 3 ml    | 7-9 ml  | 3 ml    | 7-9 ml         | 6-8 ml                   | 6-8 ml                   | 7-9 ml
P1060 SCHEDULE OF EVALUATIONS, CONTINUED

1. Screening evaluations must be completed within 30 days prior to Entry (exclusive of HIV diagnostic assays).
2. A complete history is required at Screening and Entry. A targeted history is sufficient at subsequent visits.
3. Include height, weight, head circumference, and vital signs in the physical exam.
4. Include a complete blood count with differential and platelet count ...
5. Include AST, ALT, BUN, and creatinine at screening, and AST/ALT at subsequent visits. [MJ: WILL ALL HAVE AST AND ALT, REBECCA ASKS? SHE SUGGESTS SAYING “LIVER FUNCTION TESTS.”] Draw the minimum amount of blood required by the local lab.
6. HIV-1 RNA PCR and lymphocyte subsets must be performed at DAIDS VQA-certified and IQA-certified laboratories, respectively.
7. Stored plasma (and PBMC, where feasible) will be used for resistance testing and minority variant assays. Refer to Appendix IV.
8. Prepare PBMC aliquots at baseline visit only (where feasible). Refer to Appendix IV.
9. After Week 48, a visit should continue to occur every 12 weeks for the duration of the study (24 weeks from the date the last subject is enrolled).
10. For subjects who prematurely discontinue study treatment but continue to be followed (“off drug/on study“): Follow-up study visits will proceed according to the same schedule, but only those evaluations listed in this column are required at each visit after discontinuation of study treatment.
WHY IS THIS STUDY BEING DONE?
HIV-infected pregnant women can take anti-HIV medicines during pregnancy and/or around the time of delivery to decrease the risk of passing HIV to the baby. Most HIV-infected pregnant women take at least one dose of nevirapine (NVP) right before or during delivery, and the baby also takes one dose of NVP. But in some babies who take NVP or whose mothers take NVP, HIV changes – or becomes resistant to – NVP. This means that NVP may not work against HIV if it is taken again in the future.

Children who are infected with HIV at the time of birth may need to take a combination of anti-HIV medicines in the future to stay healthy. This study will

- see how well children who received NVP at the time of birth respond to a combination of medicines that includes NVP compared to a combination of medicines that does not include NVP,
- see how well children who did not receive NVP at the time of birth respond to a combination of medicines that includes NVP compared to a combination of medicines that does not include NVP, and
- see how well those children who take a combination of medicines that includes NVP respond compared to those children who take a combination of medicines that does not include NVP.

You should know that some very small studies have been done that suggest children may not respond as well to NVP treatment if they have also received NVP at the time of birth. But this is still not known for sure. We will closely monitor the safety of the children in this study and response to study medicines.

If you agree to let your child be in this study, your child will be randomly assigned (like flipping a coin) to receive one of two combinations of anti-HIV medicines. The combinations are:

- NVP plus zidovudine (ZDV) and lamivudine (3TC), or
- Lopinavir/ritonavir (LPV/r) plus ZDV and 3TC

If your child has side effects related to the ZDV, your child may take a different anti-HIV medicine called stavudine (d4T) in place of ZDV. The branch of the U.S. government that approves new drugs, called the Food and Drug Administration (FDA), has approved the use of these medicines in HIV-infected children.
WHAT ARE THE RISKS OF THE STUDY?

Medication Side Effects
The medicines used in this study may have side effects; some of them are listed below. These lists include the more serious side effects and the more common side effects, but they do not include all the side effects. If you have questions concerning side effects, please ask the clinical or research staff at your site.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:
- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Non-Nucleoside Reverse Transcriptase Inhibitor
Nevirapine (NVP, Viramune®)
Rash is the most common side effect with nevirapine. Rash occurs more often in females and usually occurs early during treatment. Most of the time, the rash is not severe. Rarely, the rash may be severe and cause death. Most rashes occur early during treatment. One of the risk factors for developing serious skin reactions includes failure to take nevirapine properly during the first 14 days of treatment.

Liver damage is the most serious side effect with nevirapine. Severe liver damage that can result in death may occur and is often associated with a rash. Being female or having a higher CD4 cell count, regardless of gender, increase the risk of developing liver damage. Women with CD4 cell counts greater than 250, including pregnant women receiving chronic nevirapine therapy, are at greatest risk for developing liver damage. Men with CD4 cell counts greater than 400 are also at increased risk. However, these reactions can happen at any CD4 count in both men and women. Children who have abnormal liver function before starting nevirapine and children with active hepatitis B or C are also at higher risk for liver damage.

If your child has one or more of the following, he or she may be developing liver damage:
- Tiredness
- Flu-like symptoms
- Loss of appetite
- Nausea
- Pale stools
- Dark urine
- Yellowing of the skin or whites of the eyes
- Liver tenderness or abnormal liver function tests

Hypersensitivity reactions (Allergic reactions) also may occur. They rarely are fatal. If your child is having an allergic reaction, you may notice rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, and/or red, itchy eyes, and a general feeling of discomfort.

The risk of people developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your child develops any of the side effects listed above, no matter how long your child has been receiving nevirapine, you must contact your child’s health care provider right away and before
your child’s next dose. Your child’s health care provider will instruct you on what to do next.

**Nucleoside Analogues**

**Zidovudine (ZDV, Retrovir®)**

Lactic acidosis (Elevated lactic acid levels in the blood and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure in children receiving nucleoside analogues and other complications and death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate elevated lactic acid levels include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, weakness, dizziness, and shortness of breath.

**Zidovudine (AZT, ZDV)**

The following side effects have been associated with use of zidovudine:
- Decrease in the number of white blood cells that help fight infection
- Decrease in the number of red blood cells that may cause weakness, dizziness, and fatigue
- Muscle aches, weakness, and wasting
- Headache
- Upset stomach
- Vomiting
- Decrease in appetite
- Vague overall feeling of discomfort
- Lack of energy
- Feeling tired
- Sleeplessness
- Heartburn

**Risk of Resistance**

This study will see how well children who received NVP at the time of birth respond to a combination of medicines that includes NVP compared to a combination of medicines that does not include NVP. If your child received NVP at the time of birth, or if you received NVP during labor, it is possible that your child’s HIV has changed – or become resistant to – NVP. If this has happened, it is possible that NVP may not work as well against HIV when your child takes NVP again as part of this study. Because of this, we will closely watch your child’s HIV blood levels during this study. If the levels get too high, your child will be taken off the study medicines and you can talk to your doctor about other available HIV medicines for your child.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

There may be a direct benefit to your child from being in this study, but no guarantee can be made. It is possible that the study medicines will slow your child’s HIV infection. It is also possible that your child may receive no benefit from being in this study. Information learned from this study may help other children with HIV.
**PARTICIPANT EVALUATION FORM**

**Module 4**

*Protocol Development and Community Review*

**INSTRUCTIONS:**
- Your opinion is important to us.
- There are no RIGHT or WRONG answers.
- Your answers are private. You do not need to put your name on this form.
- Please answer ALL the questions to help us improve this training.
- For questions 1 - 7, please rate the effect the training has had on your understanding of the following:

<table>
<thead>
<tr>
<th>No effect, 1= Some effect, 2= Much effect</th>
<th>No Effect</th>
<th>Some Effect</th>
<th>Much Effect</th>
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</thead>
<tbody>
<tr>
<td>1. How protocols are structured/Content of protocols</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td>2. How community representatives can effectively contribute to protocol development and/or review</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td>3. The protocol development process</td>
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<td>4. How to review an informed consent form</td>
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<td>5. How to review the Schedule of Evaluations</td>
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<tr>
<td>6. How to identify and describe protocol design…</td>
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<tr>
<td>7. How to locate sections of the protocol</td>
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*Please continue on the next page.*
Please answer the following questions to the best of your ability:

After this training, what help might you need to apply what you have learned?
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What changes would you suggest to make the training more useful?
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What part of this training did you find the most useful?
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What other training programs do you feel are important for CAB members?
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Other comments:
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Thank you for your comments!
TRAINERS’ ASSESSMENT: POST-TRAINING

Module 4
Protocol Development and Community Review

Please help us evaluate the training for this module by telling us about the level of improvement you observed in the participants’ knowledge of Protocol Review.

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<th>SOME IMPROVEMENT</th>
<th>MAJOR IMPROVEMENT</th>
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<tr>
<td>2. Role of CAB representatives in protocol development and implementation</td>
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<td>3. Sections of the protocol that are especially important for the community to review</td>
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<td>4. How to review sections of the protocol</td>
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What changes would you suggest to make the training more useful?
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What part of this training did you find the most useful?
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Trainer Name:  
Signature:  
Date:  

Please use the back of this form for additional comments and suggestions.