MODULE 5: UNDERSTANDING CLINICAL TRIAL RESULTS

Proposed Agenda*

Opening Activity: Quiz! (15 minutes)
Part I Slides and Discussion (45 minutes)
Activity: Designing a Clinical Trial (45-60 minutes)
Part II Slides and Discussion (45 minutes)
Expert Panel: Abstract/Study Results Review (45-60 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 5

Quiz!

Time frame *(15 minutes)*

Purpose
This exercise can help participants have fun while teaching or reviewing some common information about HIV and HIV research.

Materials needed
- Quiz slides
- Answer sheet (trainer only)
- Small signs so that each participant is able to indicate a response of “1” “2” or “3” (indicating a choice of response to the multiple-choice quiz question). Participants can make their own sign, or simply use their fingers if you prefer.
- Bell or whistle or other noise maker (optional)
- Sweets for prizes (optional)

Instructions
- Review the slides in advance to ensure the quiz questions seem appropriate for your group. Change any question if it seems too easy or too hard or irrelevant for the expected participants.
- Explain to participants that they will see a slide that asks a question and offers 3 possible answers. Only one of the answers is correct. You will read the questions and responses. Participants will be given 15 seconds to select an answer. You will make a noise to indicate time is up (such as ringing the bell, whistling, or clapping hands). They will indicate a chosen response by raising their “sign” indicating a choice of option 1, 2, or 3.
- Use the slides provided so that all participants can read the questions/answers along with you as you read them. If the equipment isn’t available, give participants a copy of the slides (but not the answer sheet!)
- Read each question and the three responses, clearly stating “Answer One: …..”; “Answer 2………..” and “Answer #3……….”
- Give feedback to the group, including the correct answer. Toss a sweet to those who answered correctly (if desired), or give them to all participants or the participant with the largest number of correct responses at the end of the game (optional).
Module 5

Slides – Opening Activity: Quiz!
Insert Here
Module 5
Opening Activity
Quiz!
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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What is a research CAB?

1. A car or taxi service used to support clinical trial participants in meeting their scheduled appointments
2. A support group for HIV-infected or affected people participating in research
3. People from the HIV-infected and affected community who work with researchers as liaisons from the community
What does HAART mean?

1. HIV+ Adolescents on Anti Retroviral Therapy
2. Highly Active Anti-Retroviral Therapy
3. Human Anti-AIDS Retroviral Treatment
Why do we measure CD4 cells in a person with HIV?

1. To monitor the state of the immune system
2. To know the level of virus in the blood
3. To monitor whether medications are causing side effects
What does PMTCT mean?

1. Prediction of Mother to Child Transmission
2. Prevention of Mother to Child Transmission
3. Prognostic Markers in Targeted Clinical Trials
What is a protocol?

1. A procedure for setting up a research network
2. The rules for running a meeting
3. A written plan for a clinical trial
What is IMPAACT?

1. International Methodology for Prescribing Anti-AIDS Continuous Treatment
2. International Maternal, Pediatric, and Adolescent Clinical Trials
3. International Maternal Prevention of AIDS Access to Clinical Trials
What is meant by “Eligibility Criteria”?

1. Rules developed by DAIDS to judge sites applying to participate in an HIV research network
2. Experience needed to serve on an IMPAACT committee
3. Specific conditions or characteristics needed in order to participate in a clinical trial.
Which medicine is most commonly used globally to prevent mother-to-child transmission of HIV?

1. Nevirapine
2. Delavirdine
3. Tenofovir
If an HIV+ person has a CD4 count of 200 or less, what does this mean?

1. They no longer have HIV
2. Their immune system is very healthy
3. They should start antiretroviral treatment
What does the term “double blind” mean?

- Neither the researcher nor the research participant knows to which treatment group the participant has been assigned.
- The participant is unaware of the treatment he/she is receiving.
- The research participant does not know he/she is participating in a clinical trial.
The purpose of randomization is to:

- Ensure that research participants are given the treatment that best suits their needs
- Ensure that health characteristics between groups are equally distributed, and that bias is reduced
- To be fair to research sites by making sure participants from different sites have equal access to different treatment groups
A controlled clinical trial is:

- A trial that is being monitored by an external committee
- A trial where the principal investigator is able to determine (or control) the treatment assignments for participants
- A trial that includes a control group that receives standard (non-experimental) treatment
Module 5
Part I Slides – Insert Here
Module 5
Understanding Clinical Trial Results
Part I
Trainer Manual
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Version 1.0 – May 2007
Objectives

Upon completion of this training module, participants will be able to:

- Define basic terms related to study design.
- Give examples of how study design affects the accuracy of study results.
- Discuss the results of a clinical trial with members of the community.
- Understand the importance of peer review and the format used when publishing study results.
Clinical trials offer healthcare professionals the opportunity to base medical decisions on scientific evidence. The results of a well-designed clinical trial can show us the best ways to treat or prevent a disease or illness.

These review words are important because they help us determine if study results are really valid.

**Trainer:** Review vocabulary on the slide.
In other words, was this study designed and conducted in a scientific way, so the results are not biased? Can we use the information this study provides to make decisions about treatment and prevention?

Put even more simply, we want to know a “good” study from a “bad” study.

**Trainer:** Review vocabulary on the slide.
Evidence-based health care

- Healthcare decision making based on information from scientifically accurate and reliable research
- A study should be designed so the results may be used for evidence-based healthcare decisions

Evidence-based health care means that treatment decisions are based on data from scientifically valid clinical trials. This is usually the most desirable way to make decisions about treatment. Healthcare professionals get the most recent information from clinical trials by reading scientific journals and attending conferences.

CAB members can also find the most recent information available by following the results of clinical trials. [MJ: WHAT ARE THEIR SOURCES OF INFORMATION?] Once CAB members master a good understanding of clinical trials, CAB members can explain research results to help others in the community understand treatment options and best practices.

But how do CAB members learn how to read study results and decide what the results mean for treating individuals in the community? How will CAB members know if a study is scientifically valid? How do we know that a study was designed in a way that doesn’t bias the results?

CAB members are not scientists or statisticians (people who analyze the data). However, there are certain principles of research that can help you understand clinical trial results, and can help you have a sense of whether the information from the clinical trial is really valid and useful. This is important, because people can make many claims about curing or treating or preventing HIV or AIDS that are questionable. How do you know whom to trust? What can you tell people in your community about claims that are not valid?
Study design

- Understanding some of the issues related to study design will help you
  - understand study results
  - explain results to others

- The goal is to design the most reliable study possible under the circumstances.

- Understanding some of the issues related to study design will help you to understand study results, and to explain results to people in the community.

- The goal is to design the most reliable study possible under the circumstances. It is not always possible or ethical to study every health question through a blinded, controlled, randomized clinical trial, even though this type of study is the best type for reducing the risk of bias.
In a clinical trial, the word **population** means *all* of the people who can benefit from the results of the study. For instance, this slide represents a study about prevention of mother-to-child transmission of HIV. The population for this study is HIV-infected mothers (and their infants).

But, the population of HIV-infected women is very large, and the entire population cannot possibly be enrolled in the trial. Instead, the study team must select a **sample** of pregnant women with HIV. The characteristics of the women who are part of the study sample are defined by the inclusion and exclusion criteria. For example, in this study the inclusion criteria state that participants must be HIV-infected, pregnant, and have a CD4 count higher than 200/mm³. The results, therefore, cannot be applied to women with a CD4 count lower than 200/mm³.

In the “real” world we may not always have choice of not applying the results of a study to a population that wasn’t represented in the study. But it is still important to remember that this is not the best use of study results. So when reading study results, be sure to pay attention to the **population studied**, and do not assume the results can safely be applied to someone who does not fit the same criteria as the study sample.
Think of other inclusion-exclusion criteria that could be part of this study.

**Trainer example:**
- Imagine that all women in this study must have a very low viral load in order to enroll—so low that it cannot be measured. If the results of this study showed that the treatment was very, very effective in PMTCT, would you expect the same result if a woman had a *high* viral load?

- The answer is no, we would not expect the same result. A high viral load increases the risk of MTCT, and therefore the results may be different.
The science of **statistics** is used to design clinical trials and to analyze the data collected in clinical trials. Reports of clinical trial results always tell us if the difference between treatment groups is **statistically significant**. Statistically significant means that the difference between a control group’s results and an experimental group’s results is too large to be the result of chance alone. It means that the difference is the result of the treatment (and not of chance). A statistician knows how to determine if a result is statistically significant.

Here is an example (refer to slide): Imagine a study where infants of breastfeeding HIV-infected mothers are randomized to receive a vaccine to prevent HIV transmission due to breast feeding (the experimental group) vs. receiving the standard of care (ARV treatment without a vaccine) (the control group). The results show that 15% of the infants in the control group become infected with HIV, and 4% of the experimental group becomes infected with HIV. A statistician determines if this result is statistically significant. In this study, it may be that the results are due to the differences in treatment received rather than to chance alone. But we need more information to be sure (such as how many infants were enrolled in the study).

When you read study results, you will want to find out if there is a statistically significant difference between the effectiveness of the treatments. You will also want to find out if there is a statistically significant difference between other results, such as the number of reported side effects with one treatment vs. the number of side effects with the other.
**Discuss:** Why would it matter if there were just a few babies enrolled in this study? Would having a small study sample affect whether the results of the study are **valid**?

- Here’s an example: only 20 infants were enrolled in the study (10 per group); 2 infants in the control group were infected, and 1 infant in the vaccine group was infected. *Would you be confident that this difference could not be related to chance alone, rather than the treatment?*

- If 500 infants were enrolled in the study, 50 infants from the control group, and 25 infants from the experimental group would be infected. *Would you be more, or less confident that the difference between these results was the result of treatment, and not the result of chance?*

**Trainer:** Larger sample sizes—that is, more participants—are considered more reliable than small sample sizes. A larger number of participants produces more data, making it less likely that the observed results are simply due to chance.
Discuss: Why would it matter if in this same study of a vaccine to prevent breastfeeding transmission of HIV the babies were not randomly assigned to a treatment group vs. a control group? Instead, participants would be allowed to choose which group they would be in.

Trainer: Another important aspect of designing a study is to make sure that the two groups being studied have the same characteristics. Results of the study can be trusted ONLY if the two groups we are comparing are about the same. If participants are NOT randomly assigned to a treatment group, the results may be different in one group than in the other, but the researchers will not know if the difference is a result of the treatment. The difference could be due to another characteristic. What are some characteristics of the infants that could make the groups different? (Viral load of the mother, prematurity of the infant, caesarean delivery vs. vaginal delivery—all of these are characteristics that can affect the risk of MTCT).

Example 1: What if the women in this vaccine study who chose to have their infants receive the vaccine were women who knew the risk of HIV transmission for them was high because they had high viral loads and were not receiving ARV treatment? A high viral load increases the risk of MTCT, so if one group has an average higher viral load than the other group, the results of the study might not be valid.

Example 2: What if the women who asked to receive the vaccine did so because they had delivered their babies prematurely? (Prematurity increases the risk of MTCT.)
Discuss: Would it make a difference in the validity of the study results if the infants were enrolled in the study for 8 weeks vs. 52 weeks? Why would the study be more valid if data were collected over a longer period of time?

Trainer:

- In general, larger amounts of data are considered more reliable than smaller amounts of data. In this study, it is especially true because it is very likely that women are continuing to breastfeed for much longer than 8 weeks. HIV-infected women who breastfeed their infants generally do so because, despite the risks, it is their best option.

- The difference between the two groups may be very large at 52 weeks vs. 8 weeks because the infants have had considerably more exposure to HIV. Eight weeks would also not be long enough to determine if there were other risks related to the vaccine not evident in only a few short weeks.
Studies that look back in time at events that happened in the past are called **retrospective studies**.

**Prospective studies** enroll participants and follow them forward in time to observe if and how they change.
In this example of a retrospective study, children known to be taking ARV treatment are enrolled. The researcher then reviews the medical record of each participant, checking the type of treatment received and recording information such as growth, infections, viral load, CD4 count from the point of enrollment and looking backward at the 5 years before enrollment.
In contrast, if this were a prospective study, the children would be enrolled in the study, then started on ARV treatment, and from the baseline visit, data such as growth, infections, viral load and CD4 count are collected for 5 years going forward.

Discuss: Which type of study (retrospective vs. prospective) is likely to give the most accurate and valid information? Why?

- Generally, prospective studies are considered more valid. Retrospective studies are considered less valid because it is not possible to know about other participant characteristics that might have affected the study results. These characteristics are called confounding factors. Can you think of any examples of confounding factors? (previous ARV treatment, viral load with previous treatment, etc).
Discuss: This is an example of a study where no control group is used. All of the infants are going to receive a vaccine to prevent MTCT during breastfeeding. What do you think about the accuracy and reliability of the study results if all of the infants (no control group) were given vaccine to see if it would prevent mother to child transmission of HIV through breastfeeding?

Trainer: A controlled trial is one in which the treatment (or vaccine in this case) is compared against either a placebo (inactive treatment) or an existing effective treatment (standard care). In a controlled vaccine trial, the control group would not receive the vaccine. The use of a control group is another way to help minimize bias and confounding factors that may make the study results less accurate. In this example, the information collected would still be valuable, but not as valuable as information from a controlled study, because without the control group there is a greater risk of bias.
There are many other types of research studies in addition to clinical trials. For example, medical journals sometimes publish **case reports**. Case reports are simply the story of what happened to one person. The value of a case report is that it tells about something very unusual or interesting. For example, we first learned of a new infectious disease because the CDC published a summary of a few case reports they had received from doctors caring for very sick young men with some sort of immune deficiency illness causing them to have very rare infections. This disease was later called AIDS and found to be caused by HIV.

Observational studies enroll participants but do not provide any treatment or intervention. These are studies where participants are followed forward in time (prospectively) and health data are collected. IMPAACT/ PACTG has a long-term observational study that monitors children exposed to ARV therapy for side effects or other occurrences that may not be seen in clinical trials of these medicines that only last a year or two.

IMPAACT conducted an observational study of children exposed to anti-retroviral therapy, and continued it over a very long period of time (Much longer than most treatment trials). This has helped researchers to gather a large amount of information about what happens to children over the long-term. This study is continuing in collaboration with some other agencies, such as the CDC.
Slide 19

Summary

- There are many types of trial designs.
- There is no design that is the best design for all circumstances.
- Some study designs are stronger than others. This means they give the strongest evidence to support the conclusions of the study.

- There are many types of trial designs (controlled, non-controlled, randomized, non-randomized, retrospective, prospective, case study, etc.)

- There is no design that is the best design for all circumstances. However, when evaluating a research study, it’s important to know that some study designs are stronger than others. This means they give the strongest evidence to support the conclusions of the study.

- As this training continues, we will continue to discuss some simple hints and definitions that can help you to determine the strength or validity of a study design. But don’t feel it is up to the CAB determine (on your own) the relative value of one study or another. This training is meant to help you understand some of the terms used, and to have a general sense of how study design impacts the importance/strength/value of a study.
DESIGNING A CLINICAL TRIAL

Trainer Instructions

Module 5
(Exercise for Small Groups or Pairs)

Time frame *(45-60 minutes)*

Purpose
- To reinforce information and knowledge from the slide presentation in a fun and non-threatening way

Materials Needed
- Research questions (samples are provided)
- Flip chart and markers (best) or chalkboard/chalk (optional)
- Blank sheets of paper and pencils for participants
- Tape
- Prizes (optional)

Instructions
- Organize participants into small groups or pairs. Try to group less-experienced participants with more-experienced participants (If there are very few participants in the training, this exercise can easily be led by the trainer and done with the whole group).

- Assign a research question to each group or pair. More than one group can work on the same research question if needed.

- Give each group one or two “practice” blank sheets of blank paper.

- Explain that you would like the group to discuss a possible design for a clinical trial to answer the research question. For example, the group will decide if the trial will be retrospective or prospective, controlled vs. not controlled, will involve a placebo or no placebo, will be blinded or not blinded, randomized or not randomized, etc. They may use their notes, glossary, or any other materials on hand to review the terms and design issues.

- Reassure participants that there are no wrong answers in this exercise. The activity itself will simply help learners think about the issues involved, and practice with the terminology and concepts. Your discussion will reinforce the best types of study design.

- Ask them to draw their study design in a similar fashion to the slide graphics used previously (using boxes, arrows, etc.). If applicable, they may also write their suggested eligibility criteria or specific information about the design. They may use the scrap paper to work on it, but at the end of their discussion, they will be asked to draw and/or write the design on a large sheet of paper (from the flip chart) or on the blackboard so that the work can be shared with the whole group.
If the group has some experience and prior knowledge of clinical trials, also ask them to write some suggested eligibility criteria.

Have each group present their work (as time allows). Tape their work to the wall or chalkboard so that all participants can see (Alternatively, the trainer could write the results of the discussion on the board as it is discussed). Spend time on discussion and explanation if any concepts are particularly difficult or seem confusing to participants.

When complete, thank participants for their hard work. Give prizes (optional).
DESIGNING A CLINICAL TRIAL
Suggested Research Questions
Module 5
(Exercise for Small Groups or Pairs)

Trainer Note: Below are some suggested research questions that you may want to use for this exercise. You may make up your own, or describe a study that is being done, or will be done, at your site. Alternatively, ask the training participants to develop their own research questions. These questions are not “real” clinical trials, and can be adjusted or changed as needed for your group.

Below, study designs and suggested discussion points are provided.

Question 1: A new vaccine meant to protect HIV-positive children from tuberculosis has been discovered and tested in Phase I and II studies. The vaccine works by stimulating the child’s immune system to create an antibody that will recognize and kill the germ if it is found in the child’s body. This antibody can be measured in the child’s blood a few weeks after receiving the vaccine.

An appropriate response to a vaccine requires that some immune system functioning is available. Therefore, researchers would like to first test whether this vaccine be effective in children with HIV who are stable on HAART.

Trainer:

Design Issues:

- Children within each of the groups (also called cohorts) above will be randomly assigned to receive or not receive the vaccine. Children will also receive the standard of care for prevention of tuberculosis (If a child is known to have been exposed to tuberculosis, the standard of care calls for a preventive medicine to be given for 6-12 months). Children who develop tuberculosis disease will be treated according to the national standards.

- If you want to add complexity to the question, a second question involves whether the response to the vaccine vary based upon the level of CD4 cells? Because response to the vaccine depends heavily on the functioning of the immune system, it will be important to enroll children at different CD4 levels and to group the children according to these levels when the data is studied. This grouping of study participants is called stratification. In this case, the study grouped participants like this:

  Group 1: CD4% prior to HAART below 15%, CD4% at study screening under 15%.
  Group 2: CD4% prior to HAART under 15%, CD4% at study screening over or equal to 15%
  Group 3: CD4% prior to HAART 15%-25%, CD4% at study screening over or equal to 15%
  Group 4: CD4% prior to HAART over 25%, CD4% at study screening over or equal to 25%
**Question 2:** Although most vaccines are used to prevent disease (such as the measles vaccine or the polio vaccine), some vaccines are given to people who already have a disease. This type of vaccine is meant to give the person’s immune system a “boost” so that the immune system is more effective at fighting the disease, or controlling it. This type of vaccine is called a therapeutic vaccine. (Vaccines meant to prevent a disease are called preventative vaccines).

Imagine that the first-ever experimental therapeutic vaccine for HIV has been developed, and is being tested in adults with HIV infection. Researchers would next like to test if the vaccine will be safe and effective in adolescents with HIV infection. The vaccine will first be tested in adolescents who are on stable and effective ARVs (the participants will have an undetectable HIV viral load and CD4 cells above 350). How should this study be designed?

**Trainer:**

**Design Issues:**

- This study could be a placebo controlled study. It is ethical to use a placebo in this study because the vaccine has not been proven effective, and no other therapeutic vaccine is available to compare with the new vaccine.

- Adolescents should be randomly assigned to the control vs. the experimental group.

- The study could be double-blinded (neither the participant nor the researcher know whether the participant is assigned to receive vaccine or placebo). This will eliminate bias.

- These components (control group, randomization, and blinding make this a very reliable and accurate study if enough participants are enrolled and followed for a long enough period of time (scientists and statisticians will make those decisions).
Question 3: A new ARV medication has been developed, and researchers are hopeful that it may prove to be more effective for prevention of mother-to-child transmission of HIV (PMTCT) than nevirapine given as a single dose to the mother and a single dose to the infant. The new medicine is exciting because it could also be given as a single dose, making it possible for use in low-resource settings that aren’t able yet to manage or afford more complex types of PMTCT regimens.

How would you design a study comparing the New Treatment vs. NVP for PMTCT?

Trainer:

Design Issues:

- This is a good study for discussion of research ethics. The first question about this study would be “Is it ethical to have an experimental group randomized to receive TNF when single-dose NVP is already known to be safe and effective? Can you ethically withhold NVP from any participant, even though you believe that TNF will be equally good or better?

- Women who enroll in this study would be randomly assigned to a treatment group vs. a control group. In this case, because of the ethical concerns, women would be randomized to receive NVP alone, or NVP plus TNF.

- It would, of course, be important to collect data related to the delivery, the viral load/CD4 count and health of the mother, and any other issues that can effect mother-to-child transmission of HIV.
Module 5

Part II Slides – Insert Here
Module 5
Understanding Clinical Trial Results
Part II
Trainer Manual
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After a clinical trial is completed and the data have been analyzed, the protocol team usually presents the results to their colleagues via publishing in a scientific journal, and/or by presenting at a professional conference. Publicizing the information learned from the trial allows clinicians to keep up with the most recent knowledge in their area of medicine.

Also very important, publicizing the results provides an opportunity for the public, including CAB members, to critique the study.

The best professional journals do not publish study results without a strict review process. The review process also occurs for information presented at good scientific conferences.
Peer review

- The process of having clinical trial results examined and reviewed by qualified outside experts before the study is accepted for publication in a medical journal or is presented at a major scientific conference.

This process is called “peer review.”

- A “peer” is a research scientist who is an expert in the same area of research as the study’s investigators. This process ensures that the study has been thoroughly reviewed by peers NOT involved with the study. Peer reviewers decide if the study is appropriately designed and the results are valid.

- All IMPAACT study results are published in journals or presented at conferences that require peer reviewed.

- The results of studies that have not been peer-reviewed are less trustworthy. Knowing if a study has been peer reviewed is first step in determining the worthiness of a study.

- It is important for CAB members and the community to know about the peer review process because when a study has been published in a peer review journal, it is much more likely that the study results are valid. The same is true for studies that are presented at high level scientific meetings; they have also gone through the peer review process.

- Peer review happens after a study has been conducted, but before it is accepted for publication or accepted for presentation at a scientific meeting.

- CAB members may be asked by members of the community about other, non-IMPAACT study results. One simple way for CAB members to evaluate such study results is whether the results have been accepted for publication in a peer-reviewed journal or presented at a scientific meeting. If not, then the study results require more scrutiny.
There are different types of professional journals and scientific conferences. Some are general and broad (such as the journal *Science*, which publishes non-medical research as well as medical research). Some medical journals may include articles on many different health-related issues (such as *The Lancet* or the *New England Journal of Medicine*). The third type of medical journal is a specialized journal, devoted to one type of medical problem such as infectious diseases (*Clinical Infectious Diseases* and the *Journal of Virology*) or to a specific infectious disease like HIV (the journal *AIDS*).

Scientific conferences are organized in a similar fashion, although they are more often devoted to a single area of study.

All journals and presentations at professional conferences report clinical trial results in the format similar to the one shown on this slide (review). We’ll briefly tell you what each of these sections includes in the next slides.
The abstract is a short summary of a research article, which describes the goal of the study and the study design and methods, as well as the results, their statistical significance, and a very brief conclusion. The conclusion is a one or two-sentence “take home” message, summarizing how the study team believes the results will affect clinical care and future research.

The abstract is a good starting place to help community members begin to understand the results of a study and what importance it might have in the clinical treatment or prevention of HIV.

The abstract is useful because it is briefer and less complex than a detailed description of a study. While the abstract gives a summary, it doesn’t give you the opportunity to critique the study or understand it in-depth.

It is also useful for CAB members to know that there are a number of non-profit organizations that review the medical literature and summarize it in language the community can easily understand. We will list a few of these organizations in the last slide of this training.
The introduction (or background) section of a study publication will include a summary of the problem or issue to be investigated, a brief review of what is already known about the problem, the reason for the study, and what the authors believe the study will show (the **hypothesis** for the study).

The hypothesis is the theory on which the researchers based the clinical trial.
For example, in the study shown on this slide, the experimental group will receive an experimental vaccine to boost immunity to HIV as well as the standard ARV treatment given for PMTCT. In the introduction or background section of the published results of the study, the researchers would describe standard ARV treatment for PMTCT and describe whatever evidence is currently available to support the testing of the experimental vaccine in HIV-exposed infants.

The researchers will hypothesize that giving HIV exposed infants this vaccine to boost their immunity to HIV infection will reduce their risk of acquiring HIV during the breast feeding period as compared to giving ARV treatment alone. **Trainer:** you may want to give other examples of a hypothesis relevant to research at your site.
Design and methods

- Design and implementation

**Design example:** “This was a Phase II, parallel, randomized, controlled study. Perinatally HIV-infected infants were assigned to treatment with NVP-based HAART vs. HAART with a protease inhibitor. Two groups of infants were enrolled: those who had been exposed to NVP perinatally, or those who had not been exposed to NVP.”

- This section of the publication will give detailed information about how the study was designed and carried out. It will describe the population that was studied, what type of tests and evaluations were performed, what data were collected, and how the data were analyzed.

- The example on the slide gives this type of information, although there would be much greater detail given in the publication than we can show on this slide. We discussed study design in Part I of this training. This is the section of the publication where you will need to rely on that knowledge to understand the words used to describe the design.
The publication of clinical trial results will include:
- an in-depth description of data collected
- results of the statistical analysis

The results section of the publication gives a very detailed and in-depth description of the information collected by the researchers and the statistical analysis of the data. In addition to being described in the text of the article, results of the data analysis are often displayed in graphs and charts. The graphic displays of data often give an “understanding at a glance” of the impact of the treatment that was studied.

The chart on this slide shows the viral load of two groups of study participants at different points of time during the study. (This is NOT real data.) The green columns display the average viral load results of the participants receiving NVP, and the dark blue columns represent the average viral load of the group receiving a protease inhibitor. The labels under the columns indicate the week of the study when the data were collected, with Week 0 being the baseline values. (Trainer: help participants understand the graph and point to the areas as you describe them). Overall, this graph shows that the group receiving NVP had a higher viral load at weeks 4, 12, and 24 than the group receiving a PI.
In this section, the researchers explain the results of the study, drawing conclusions and discussing what their findings mean. Usually, they will describe how the results might affect clinical practice. In the example on this slide, which does not reflect real study results, the authors are saying that their original hypothesis was supported by the study results, and that clinical care for HIV-infected infants exposed to NVP perinatally is as effective with a NVP-based regimen as with a PI-based regimen of HAART. (In reality, this has not been proven. Rather, this is the subject of an ongoing IMPAACT clinical trial.)

This is the area of the publication where the researchers will also acknowledge any problems with the study that weaken the impact of the results. For example, if a large number of participants did not complete the study, the data are not as trustworthy as if all participants were followed until the end of the study as planned.
Lay Summary

- Good news! IMPAACT protocol teams must write a “lay summary” of the study results. The lay summary describes the study and results but is written in language a non-scientist can understand.
Peer review is a process that helps to ensure publications are of high quality and meet rigorous scientific standards.

Not all publications are peer-reviewed.

Clinical trial publications are nearly always written in the same basic format.

IMPAACT provides the community with a lay summary of trial results. There are some websites that also provide this service (see next slide).
Websites that summarize HIV clinical research findings

- http://www.WomenChildrenHIV.org
- http://sfaf.org/beta
- http://hivinsite.ucsf.edu
- http://www.who.int/reproductive-health/stis/mtct/monthly_publications/listing_mtct_reports.htm
RESEARCH PANEL PRESENTATION: REVIEWING CLINICAL TRIAL RESULTS

Module 5

Trainer Instructions

Time Frame (45-60 minutes)

Purpose
To give participants the opportunity to review and discuss results of a completed and published clinical trial with an investigator and the study team

Materials needed
- Copies of a published report of a clinical trial for participants. If possible, select a research study done at your site (or at least relevant to people in your area).
- Some PACTG/IMPAACT studies that have been published have provided a “lay summary” on the IMPAACT website. A lay summary would be useful for this exercise. If a lay summary is not available for the study you would like to select for this panel, it’s possible that a member of the research team would be willing to provide an unofficial lay summary for the purpose of this exercise. (A sample lay summary is provided following these instructions)
- Flipchart and markers, or chalkboard and chalk to note important comments (optional)
- Prepare a list of questions about the study in advance to help facilitate the discussion as needed. Questions should relate to the issues discussed in this training module, for example:
  - In what type of publication was the study published?
  - What type of study design did the researchers use?
  - What were the characteristics of the study population?
  - How do you think the study results might affect the clinical care of patients with HIV?
  - How might the study results influence future research?

Instructions
- Ask an investigator and one or two members of the research team to participate in a panel discussion to review the publication you have chosen. You may want to help participants to think of questions for the panel before the members of the panel arrive.
- Review the study abstract in advance with the training participants.
- Facilitate the discussion of the study results. Begin by asking the investigator (or designate) to give an overall picture of the study design and the results.
- Utilize the pre—prepared question list (see 3rd bullet under “Materials needed”) to help the discussion as needed.
If time allows, ask the panel to review the “Tips for Researching Medical Information” included in this manual in the following pages.

End the panel by asking participants to suggest how they could draw the study design, in the same manner as done in the training exercise utilized earlier in this module. Alternatively, you may ask the panel to draw the design (show them sample of a graphic representation of a study design as used in the power point slides for this module.

Wrap up the discussion by summarizing the major points discussed with the panel, and thank all participants for their time.
SAMPLE LAY SUMMARY OF CLINICAL TRIAL RESULTS

PACTG P1026s, Pharmacokinetic Properties of Antiretroviral Drugs During Pregnancy: Reduced Lopinavir Exposure During Pregnancy

The PACTG 1026s study team has studied the levels of lopinavir/ritonavir (Kaletra) in the blood during late pregnancy and approximately 6 weeks after delivery in women receiving the standard lopinavir/ritonavir dose of 3 capsules twice a day. Information was collected on 17 pregnant women, and 13 postpartum women.

The results of this study may lead to a change in the dosing of lopinavir/ritonavir for pregnant women. Many HIV-positive pregnant women use lopinavir/ritonavir, although until this study was done, no one knew if the dose was appropriate for pregnant women.

When the P1026s team looked at all 17 pregnant women on the study, the lopinavir blood levels were found to be below the target level in approximately 80% of the women. The levels at the 6 week postpartum visit were much closer to the average levels found in previous studies of lopinavir.

These findings are interesting and important for 2 reasons:

- If the drug levels of lopinavir are too low, the virus may not be completely suppressed, and pregnant women may develop higher viral loads. Higher viral loads could lead to a resistant virus or increase the risk of HIV transmission to the baby. We learned that we need to study higher doses of lopinavir during late pregnancy.
- Pregnancy changes the way a woman’s body handles lopinavir, and it will be important to do further studies to understand these changes better.

The P1026s study was revised to evaluate a higher dose of lopinavir/ritonavir during the last 3 months of pregnancy, and those results will be available soon. The new Kaletra tablets will be studied in the next version of P1026s.
TIPS FOR RESEARCHING MEDICAL INFORMATION*

- Check that the information comes from a credible source (e.g., federal government, universities, medical societies, highly regarded nonprofit organizations or patient advocacy groups).
- Check if the information is attributed to an author or an organization; check for medical affiliations or evidence that the information has undergone scientific peer review.
- Check whether the information includes references, which suggest that the information is credible and provide leads for further research.
- Make sure the information is recent. HIV/AIDS treatment information more than a year or two old may not reflect the current state of the art.
- Be wary of information provided by commercial entities (such as pharmaceutical companies or other businesses promoting a product) which may be slanted to present data in a positive or negative light for the sake of profit.
- Be wary of advice offered in chat rooms or e-mail, which is often anecdotal.
- Ask a physician or other healthcare professional to confirm the information; do not attempt self-diagnosis or treatment based solely on online material.
- Use common sense: If a claim sounds too good to be true, it probably is not true.

## PARTICIPANT EVALUATION FORM

**Module 5 Part I**

**Understanding Clinical Trial Results**

**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 - 4, please rate the effect the training has had on your understanding of the following:

<table>
<thead>
<tr>
<th></th>
<th>No Effect</th>
<th>Some Effect</th>
<th>Much Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The OPENING ACTIVITY –“Quiz!” had ____________ for encouraging me to participate in the training and to think about the role of the community in HIV Clinical Trials.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Defining basic terms related to study design</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Ability to understand how study design affects the accuracy of study results</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. Ability to better explain study results to members of the community</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
PARTICIPANT EVALUATION FORM
Module 5  Part II
Understanding Clinical Trial Results

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 - 3, please rate the effect the training has had on your understanding of the following:

<table>
<thead>
<tr>
<th>0= No effect, 1= Some effect, 2= Much effect</th>
<th>No Effect</th>
<th>Some Effect</th>
<th>Much Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The importance of peer review</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. The format used in scientific journals and at conferences for reporting study results</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. My ability to evaluate the quality of a published research study</td>
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</table>

For the last 2 questions, 0= not useful, 1= useful, 2= very useful

<table>
<thead>
<tr>
<th>0= No effect, 1= Some effect, 2= Much effect</th>
<th>No Effect</th>
<th>Some Effect</th>
<th>Much Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. The materials in the training manual were…</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td>5. This training as a whole was…</td>
<td>0</td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

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?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

What changes would you suggest to make the training more useful?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

What part of this training did you find the most useful?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

What other training programs do you feel are important for CAB members?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

Other comments:

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

Thank you for your comments!
### TRAINERS’ ASSESSMENT: POST-TRAINING

#### Module 5
Understanding Clinical Trial Results

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

<table>
<thead>
<tr>
<th>NO IMPROVEMENT</th>
<th>SOME IMPROVEMENT</th>
<th>MAJOR IMPROVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Definitions for the following terms that are important to understand when evaluating a study design:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Randomized</td>
<td></td>
<td></td>
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<tr>
<td>• Controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Retrospective, prospective</td>
<td></td>
<td></td>
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<tr>
<td>• Statistically significant</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. How study design can affect the accuracy of study results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. The importance of peer review</td>
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<td></td>
</tr>
<tr>
<td>0</td>
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<td>2</td>
</tr>
</tbody>
</table>

What changes would you suggest to make the training more useful?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

What part of this training did you find the most useful?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

Trainer Name:  
Signature:  
Date:

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