Understanding the Clinical Research Process and Principles of Clinical Research

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Introduction

This workshop will help those who work to find new AIDS:

- Prevention technologies
- Improved treatment regimens
- A vaccine
- A cure

In this workshop, you will:

- Apply the information you learn in activities and discussions
- Ask questions about information you do not understand
- Practice what you learn

Agenda

- Morning:
  - Introduction
  - Clinical Research
  - Break
  - Clinical Research Process
- Lunch
- Afternoon:
  - Elements and Principles of Clinical Research
  - Break
  - Community Advisory Boards and the Research Process
  - Key Partnerships
  - Conclusion

Housekeeping

Instructions for:

- Fire drills
- Rest rooms/comfort rooms
- Messages
- Breaks and lunch
- Smoking

Remember to:

- Ask questions
- Share what you know
- Participate in all activities
- Have fun!

What Is AIDS?

- AIDS stands for “acquired immune deficiency syndrome”
- It is caused by a virus called HIV (Human Immunodeficiency Virus)
- A person who is infected with the HIV virus develops antibodies to fight the infection—someone with the antibodies in their blood is called “HIV” positive
- HIV disease becomes AIDS when a person’s immune system is highly compromised by the effects of the virus

What Is the History of AIDS?

The history of AIDS is quite short:

- There were cases of AIDS in the 1950s
- AIDS cases grew during the late 1970s and 1980s
- AIDS is now a global epidemic
- AIDS has become one of the greatest threats to human health and development

What Are the Division of AIDS' (DAIDS) Top Scientific Priorities for HIV/AIDS Research Worldwide?

DAIDS has identified six important areas of research to:

- Foster research that unravels the fundamental processes governing host/virus interactions
- Identify and test ways to:
  - Prevent HIV infection
  - Treat HIV disease
  - Cure HIV infection

How Serious Is AIDS?

- At the end of 2007, approximately 33 million people were living with HIV
- Approximately 2.7 million more people become infected with HIV every year
- Approximately 2 million people die of AIDS every year
- HIV is spreading most rapidly in Eastern Europe and Central Asia
- Approximately 400,000 children under age 13 become newly infected with HIV each year
- Without treatment, half of HIV infected infants will die before the age of two

Why is Worldwide HIV Research Important?

HIV is transmitted by different routes…in different people….at different time intervals…with different treatment options…that lead to different outcomes.

No single organization has the resources to complete needed HIV/AIDS research.

What Are the Millennium Development Goals (MDGs)?

The United Nations identified an action agenda for this millennium: eight millennium development goals.

One of the eight MDGs focuses on HIV/AIDS.

The HIV/AIDS millennium development goal calls on the world community to halt and begin to reverse the spread of HIV by 2015.

What Will We Do in This Workshop?

We will look at many important areas about AIDS research. We will learn important information and ask questions. We will also do activities to help you remember what you learn. The objectives of this workshop are to:

- Describe clinical research
- Describe the clinical research process
- Describe the principles of clinical research
- Define ethics
- Describe the role of the Community Advisory Board (CAB) in the research process
- List key partnerships
- Discuss issues affecting AIDS research for various stakeholders

What Do You Know?

Answer 10 questions about clinical research.

CLINICAL RESEARCH

In this section, we will describe and discuss:

- Clinical trials
- The importance of research
- Where clinical trials take place
- The benefits of taking part in a clinical trial
- Possible risks when taking part in a clinical trial

What Is Clinical Research?

Clinical research includes:

- Medical and behavioral research involving volunteer participants
- Investigations that are carefully developed and conducted with clinical outcomes recorded
- Identification of better ways to prevent, diagnose, treat, and understand human disease
- Trials that test new treatments, clinical management and clinical outcomes, and long–term studies
- Strict scientific guidelines
- Ethical principles to protect participants

Research is a systematic investigation to establish fact. Treatment is the care provided to improve a situation.

What Is a Clinical Trial?

Following testing in laboratories and animal studies, the most promising treatments are moved into clinical trials. A clinical trial is sometimes called a clinical study. A clinical trial:

- Is a research study that tests how well an intervention works in a group of people
- Tests for new methods of screening, prevention, diagnosis, or therapy
- Is conducted in phases

During a trial, additional information is learned about an intervention, its risks, and its effectiveness and/or efficacy.

Trials can only be conducted if there is an uncertainty about the outcome—trials cannot be conducted if the outcome is already known from a previous study.

Why Is Research Important?

Research is important because:

- Clinical trials test how well new approaches and interventions work in people
- These approaches can be medical, behavioral, or management
- Each study answers scientific questions
- Each study helps scientists prevent, screen for, diagnose, manage, and treat a disease

People who take part in clinical trials contribute to the knowledge of how a disease progresses.

Group Discussion

Clinical research approaches can be medical, behavioral, or management.

1. Can you give an example of a medical approach?
2. Can you give me an example of a behavioral approach?
3. Can you give me an example of a management approach?

Where Do Clinical Trials Take Place?

Clinical trials take place all over the world:

- Health care providers' offices
- Medical centers
- Community and university hospitals and clinics
- Veterans' and military hospitals

Clinical trials may include participants at one or two highly specialized centers. Or they may involve hundreds of locations at the same time.

What Are Some Benefits of Taking Part in a Clinical Trial?

- Participants have access to promising new approaches often not available outside the clinical trial setting
- The drug, vaccine or other intervention being studied may be more effective and/or efficacious than the standard approach (although there is no guarantee that participants will receive the experimental drug, vaccine, or other intervention)
- Participants receive careful medical attention from a research team of doctors and other health professionals
- Participants may be the first to benefit from the study
- Results from the study may help others in the future

What Are Some of the Possible Risks Associated with Taking Part in a Clinical Trial?

- New vaccines, microbicides, and other strategies under study are not always better than the standard care to which they are being compared
- New treatments may have unexpected side effects or risks that are worse than those resulting from standard care
- Health insurance and managed care providers may or may not cover all participant care costs in a study
- Participants may be required to make more visits to the doctor than they would if not in the clinical trial
- Participants in randomized trials are not able to choose the kind of intervention they will receive

Group Discussion

1. What are some benefits of taking part in a clinical trial in your country?
2. What are some possible risks associated with taking part in a clinical trial in your country?

Clinical Research Activity

With your group:

- Review the case study you are given
- Read the two questions
- Review the benefits and risks of taking part in a clinical trial page in your Participant Guide
- Brainstorm some possible benefits for the person in the case study
- Brainstorm some possible risks for the person in the case study
- Share your group's ideas with the class (be sure to describe the person in your case study)

CLINICAL RESEARCH PROCESS

In this section, we will describe and discuss the elements of the clinical research process.

What Is the Clinical Research Process?

- Pre-clinical testing
- Investigational New Drug Application (IND)
- Phase I (assess safety)
- Phase II (test for effectiveness)
- Phase III (large-scale testing)
- Licensing (approval to use)
- Approval (available for prescription)
- Post-marketing studies (special studies and long-term effectiveness/use)

What Is Pre-Clinical Testing?

Pre-clinical testing is required before testing humans. Pre-clinical testing is often conducted on animals. Many pre-clinical studies use a review committee to determine if the use of animals is warranted. The review committee also checks to see if the research can be improved by reducing or replacing animals. Laboratory and animal studies are conducted to:

- Find out if there is a potential benefit of the drug, vaccine, or other product
- Explore general safety concerns

If a vaccine, microbicide, or other strategy has a potential benefit, it is prepared for human testing. Pre-clinical testing takes approximately three to four years.

What Is an Investigational New Drug Application (IND)?

For studies that involve a new vaccine, microbicide, or other strategy, after completing pre-clinical testing, an investigational new drug application (IND) must be filed:

- Describing the results of pre-clinical testing
- Clearly defining how future studies will be conducted

The U.S. Food and Drug Administration (FDA) has 30 days to review the IND. If the FDA approves the IND within 30 days, the vaccine, microbicide, or other strategy can proceed to a phase I trial.

What Is Phase I (Assess Drug Safety)?

The goals of phase I clinical trials are:

- Assess safety for humans
- Select the dose to be used in future studies

During phase I, the study is designed to determine:

- How the human body reacts
- What side effects occur as dosage levels are increased

For the first time, the vaccine, microbicide, or other strategy is introduced to humans. Testing occurs in a small number of HIV negative volunteers (20 to 100).

This initial phase of testing usually lasts several months to 1 year. About 70% of experimental drugs pass this initial phase.

What Is Phase II (Test for Safety and Effectiveness)?

A phase II study provides comparative information about relative safety and effectiveness and/or efficacy. Most phase II studies are randomized trials. This means:

- One group receives the experimental vaccine, microbicide, or other strategy
- A second "control" group receives the standard of care or placebo

Some phase II studies are “blinded.” This means participants and researchers do not know who receives the experimental vaccine, microbicide, or other strategy. This testing may last from several months to 2 years. It may involve from 100-300 participants/volunteers. Only about 30% of experimental vaccines, microbicides, and other strategies successfully complete both phase I and phase II studies.

What Is Phase III (Large-Scale Testing)?

This large-scale testing (1,000-3,000 participants/volunteers) provides a better understanding of:

- Effectiveness and/or efficacy
- Benefits
- Range of possible adverse reactions
- The comparison to standard of care treatment

Most phase III studies are randomized and blinded trials with specific entry criteria. Phase III studies typically last several years. 70-90% of vaccines, microbicides, and other strategies that enter phase III studies successfully complete testing. After a phase III study is successfully completed, a company can request marketing approval from the FDA.

Group Discussion

1. During Phase I of a clinical trials, why do you think only HIV-negative volunteers can participate in the trial?
2. What are the potential risks of taking part in a Phase I clinical trial?
3. What are the potential risks of taking part in a Phase II trial?

What Is Licensing (Approval to Use)?

After all three clinical trial phases are complete and, if the research demonstrates that the vaccine, microbicide, or other strategy is safe and effective, a New Drug Application (NDA)/ Biologics License Application (BLA) is filed with the FDA. This NDA/BLA must contain all scientific information compiled over the course of the trials.

The FDA is allowed at least 6 months to review the NDA/BLA. However, this review process can sometimes take up to 2 years, depending on specific country requirements.

What Is Approval (Available for Prescription)?

Health care providers are able to prescribe. Even after approval, reviews continue to ensure safety over time. For example, all cases of adverse events must be reported, and quality control standards must be met (sometimes studies to evaluate long-term effects are also required).

The accelerated approval process for serious diseases is designed to:

- Help development of treatments
- Speed review for serious diseases (like AIDS)
- Fill an unmet medical need to get important new treatments to patients faster

Accelerated approval can occur if a treatment will have an impact on survival, day-to-day functioning, and likelihood that a disease, if left untreated, will progress from a less severe condition to a more serious one.

Accelerated approval does not compromise the standards for the safety and effectiveness of the treatments that become available through this process.

What Are Post-Marketing Studies?

Post-marketing studies (special studies and long-term effectiveness/use) are also called phase IV studies. These studies are often performed in special populations not previously studied (for example, children or the elderly). The studies are designed to monitor:

- Long-term effectiveness and/or efficacy
- The impact on a person's quality of life

Some studies help determine the cost-effectiveness of a therapy compared to other traditional and new therapies.

Group Discussion

1. A New Drug Applications/Biologics License Application is filed with the Food and Drug Administration (FDA). The FDA is an organization in the United States. Why do you think FDA approval is important for licensing in other countries?
2. Kaletra was reviewed and approved in 3.5 months (a very quick approval) in September 2000. How much do you know about the impact of early approval of Kaletra?

Clinical Research Process Activity

With your group:

- Review the additional information about your case study
- Review your Participant Guide and the Glossary in your Participant Guide to find definitions to the words assigned to you
- Select one of the assigned words
- Practice explaining the word to the person in your case study
- Demonstrate to the class how you would explain the word (be sure any new information about the person in your case study)

ELEMENTS AND PRINCIPLES OF CLINICAL RESEARCH

In this section, we will describe and discuss important elements and principles of clinical research, including:

- Protocols and protocol reviews
- Sponsors
- Eligibility criteria
- Informed consent
- Types of clinical trials
- What happens during clinical trials
- Who can participate in clinical trials, including inclusion and exclusion criteria
- The importance of ethics in clinical research

What Are the Elements and Principles of Clinical Research?

- Protocol
- Protocol review
- Sponsor
- Eligibility criteria
- Informed consent
- Types of clinical trials
- Phases of clinical trials
- Activities during clinical trials
- Clinical trial participants

What Is a Protocol?

Clinical research is conducted according to a plan (a protocol) or action plan. The protocol acts like a "recipe" for conducting the trial. The plan describes what will be done in the study, how it will be conducted, and why each part of the study is necessary. The protocol or plan is carefully designed to safeguard the participants' health and answer specific research questions. The same protocol is used by every doctor or research center taking part in the trial. A protocol describes:

- Who is eligible to participate in the trial
- Details about tests, procedures, medications, and dosages
- The length of the study and what information will be gathered

A protocol is led by a principal investigator. The principal investigator is often a doctor. Members of the research team regularly monitor the participants' health to determine the study's safety and effectiveness and/or efficacy.

What Is a Protocol Review?

Clinical trials in the United States must be approved and monitored by an Institutional Review Board (IRB). The IRB ensures that risks are minimal and are worth any potential benefits. An IRB is an independent committee. Physicians, statisticians, and members of the community belong to an IRB.

The committee ensures that clinical trials are ethical and that the rights of all participants are protected.

An IRB must initially approve and periodically review the research. Some research institutions have more than one IRB. During protocol reviews, networks review and assess what other networks are doing to see what information applies to what they are doing.

What Is a Sponsor?

Clinical trials are sponsored or funded by various organizations or individuals, including:

- Physicians
- Foundations
- Medical institutions
- Voluntary groups
- Pharmaceutical companies
- Federal agencies such as the National Institutes of Health, the Department of Defense, Centers for Disease Control and Prevention (CDC), and the Department of Veterans Affairs

Trials can occur at hospitals, universities, doctors' offices, or community clinics.

What Are Eligibility Criteria?

Eligibility criteria are guidelines that describe characteristics that must be minimally shared by all participants. The criteria differ from study to study. Criteria include:

- Age
- Gender
- Medical history
- Current health status
- Lab values

Eligibility criteria often require that participants have a particular type and stage of a disease. Some HIV prevention studies may require that participants have certain risk factors for HIV infection.

Enrolling participants with similar characteristics helps to ensure that the results of the trial will be a result of what is under study and not other factors. In this way, eligibility criteria help researchers achieve accurate and meaningful results. These criteria also minimize the risk of a person's condition becoming worse by participating in the study.

Group Discussion

1. How do you think a protocol is able to be used by doctors and research centers taking part in the same trial but in different countries?
2. In your country, where are some places that clinical trials take place?
3. What are some eligibility criteria for some of the clinical trials you are familiar with?

What Is Informed Consent?

Informed consent is the process of providing potential participants with important facts about a clinical trial before they decide to participate. This explanation helps people make a decision that is right for them. Informed consent is not a contract or just a piece of paper—it is a process. Informed consent must be provided:

- In the participants' native language (translation or interpretive assistance can be provided)
- At an appropriate educational level

An informed consent document includes details about the study, including its purpose, duration, required procedures, who to contact for more information, and an explanation of risks and potential benefits. The participant then decides whether to sign the document.

Group Discussion

1. How can you inform potential research participants about informed consent?
2. How can you find out if a person is able to understand the informed consent document?

What Are Some Types of Clinical Trials?

Treatment	Test new treatments, new combinations, new approaches to surgery or radiation therapy, or clinical management strategies.
Prevention	Look for better ways to prevent a disease in people who have never had the disease. In the case of diseases other than HIV/AIDS, to prevent the disease from returning. Better approaches may include medicines, vaccines, and/or lifestyle changes.
Diagnostic	Determine better tests or procedures for diagnosing a particular disease or condition.
Screening	Test the best way to detect certain diseases or health conditions.
Quality of Life (or Supportive Care)	Explore and measure ways to improve the comfort and quality of life of people with a chronic illness.

What Happens in a Clinical Trial?

Usually, clinical trials compare a new product, vaccine, management strategy, or therapy with another that already exists. This comparison helps to determine if the new one is as successful as, or better than, the existing one. Important terms used in clinical trials are:

- Placebo
- Randomization
- Single- and double-blind studies

Who Can Participate in a Clinical Trial?

The main goal for using volunteers in a clinical trial is to prove, by scientific means, the effects and limitations of the experimental treatment on a wide variety of people. Research procedures with volunteers are designed to develop new knowledge, not to provide direct benefit to study participants. Before joining a clinical trial, a person must qualify for the study.

Some research studies seek participants with illnesses or conditions to be studied in the clinical trial. Some research studies need volunteers who do ***not*** have the disease being studied.

What Are Inclusion/Exclusion Criteria?

All clinical trials have guidelines about who can participate—these are specified in the inclusion/exclusion criteria:

- Factors that allow someone to participate in a clinical trial are "inclusion criteria"
- Factors that exclude or do not allow participation in a clinical trial are "exclusion criteria"

These factors may include:

- Age
- Gender
- The type and stage of a disease
- Previous treatment history
- Specific lab values
- Other medical conditions

Group Discussion

Earlier in this workshop, you practiced explaining some common research terms. Some other important terms are important for you to understand and explain to others. How would you explain these terms to other less-experienced people?

- Single-blind study
- Double-blind study
- Control
- Patient volunteer
- Inclusion and exclusion criteria

What Is Ethics?

Ethics means:

- Respect for persons
- Beneficence, which means to do good—in clinical research, beneficence means even more—to do no harm, or maximize possible benefits and minimize possible harm
- Justice, or fairness

What Is Respect for Persons, Beneficence, and Justice?

Respect for Persons	Beneficence	Justice
People have a right to make their own choices	Researchers do everything possible to make sure the research does not harm participants in any way	There are more benefits for the participant than risks
All the facts about the research are presented to potential participants	The risks of the study will be kept as low as possible	Participants are fairly recruited as research participants
Volunteers must not be pressured to choose research over other options for care	The benefits of participating in the research study should be greater than the risks	
The community where research is being conducted is respected	It is more important to protect participants than to achieve benefits	
The community has a voice in what is done during the research (Community Advisory Boards help the research team do this)		

Who Is Responsible for Ethics?

Everyone is responsible for ethics. An Ethics Committee (EC) or Institutional Review Board (IRB) must be trained to approve, monitor, and review research involving humans. Its purpose is to protect the rights and welfare of the research subjects to:

- Protect research participants
- Review protocols before trials may be conducted
- Ask researchers to change protocols, when needed
- Supervise a study from beginning to end
- Oversee scientific design
- Review community interests
- Review recruitment plans
- Enforce informed consent
- Enforce confidentiality

Group Discussion

1. What does an Ethics Committee (EC) or Institutional Review Board (IRB) do in your location?
2. Describe the different kinds of people who are members of the EC/IRB in your area?

Elements and Principles of Clinical Research Activity

With your group:

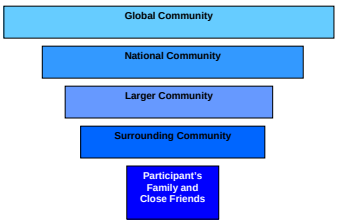
- Review the additional information about your case study
- Discuss possible answers to the questions (keep in mind what you learned about ethics and the role of the research team)
- Present your answers to the rest of the class:
  - Be sure any new information about the person in your case study
  - Provide any opinions or beliefs that helped you answer the questions in your case study

COMMUNITY ADVISORY BOARDS (CABs) AND THE RESEARCH PROCESS

In this section, we will describe and discuss the role of a Community Advisory Board (CAB) in the research process, including:

- A definition of "community"
- The history of CABs
- CAB members
- How CABs are involved in a community
- How researchers and CABs interact

What Is the Role of a Community Advisory Board (CAB) in the Research Process?



What Is a Community?

A community shares common:

- Geography
- Racial or ethnic makeup
- Values, culture, beliefs, and interests

People can belong to many communities at the same time. Communities and the demographics of a target population are always changing.

Group Brainstorm and Discussion

1. Who is in YOUR community?
2. Why is it important to have different kinds of people in a community?

What Is the History of CABs?

In the 1980s, AIDS activists in the U.S. and Europe demanded that researchers and regulatory authorities move more quickly to find medications to fight HIV. With knowledge about scientific research and HIV, a group of activists looked for opportunities to review trial proposals. Through protests, letter-writing and by lobbying the U.S. government, they succeeded in changing the U.S. drug approval process.

This process resulted in creation of Community Advisory Boards (CABs) made up of non-scientists. These non-scientists review protocols, monitor trials, and help educate and inform the rest of the community.

Now most CABs are comprised of individuals representing various parts of the community, such as religious groups, schools or universities, media and non-government organizations/community-based organizations.

Who Participates on a CAB?

CAB participants include volunteers from a broad range of backgrounds representing different groups within a community. Some volunteers are paid, but usually they are not. CABs can set their own guidelines. CAB participants are a group of people from a local community (research site).

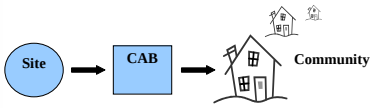
CAB members are diverse in gender, age, race, and risk group.

Ideally, 40% of the CAB's members are from the target population of a site's trials.

How Are CABs Involved in the Community?

CABs are now a significant piece of prevention and therapeutic trials in both developed and developing countries. They serve as primary liaisons between the community and the trial researchers.

CAB members take on active roles in planning for and implementing AIDS prevention and therapeutic trials.



How Do Researchers and CABs Interact?

Researchers and CAB members cooperate to ensure ethical research, share scientific and community information during a trial, and manage their activities collaboratively. Researchers know it is important to have general support from the communities that will be involved in the research for a trial to be successful.

How Researchers and CABs Interact

RESEARCHERS		COMMUNITY ADVISORY BOARD
• Protocol development • Protocol implementation • Site preparedness • Community preparedness • Trial operations • Site monitoring/data analysis • Human subject safety/liability	→ Ethical Research Information during Trial Issues Management ←	• Participatory communications • Community education • Advice on recruitment and retention • Representative voice for participants

Community Advisory Boards (CABs) and the Research Process Activity

With your group:

- Review the additional information about your case study
- Brainstorm possible answers to the questions
- Present your answers to the rest of the class: be sure any new information about the person in your case study

KEY PARTNERSHIPS

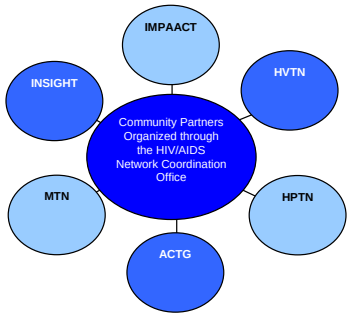
In this section, we will describe and discuss:

- The clinical trials network
- The Community Partners organization

What Is a Clinical Trials Network?

A clinical trials network is made up of researchers from hospitals and clinics in different areas of a country or parts of the world that cooperate to answer the same research questions. Each clinic in the network is a clinical research site (CRS). Representatives from different networks and institutes work together to keep each other informed of the work of their networks.

What is Community Partners?



What Are Some Cross-Network Activities?

- Cross-network activities include:
- Community involvement
- Data management
- Evaluation metrics
- Training development and distribution
- Scientific leadership
- Laboratory processing
- Research site management and clinical trials logistics and issues identification and resolution
- Behavioral science integration

Which Organizations Support the Six Clinical Trials Networks?

- The National Institute of Allergy and Infectious Diseases (NIAID) created the Division of Acquired Immunodeficiency Syndrome (DAIDS) in 1986 to develop and implement the national research agenda to address the HIV/AIDS epidemic
- The HIV/AIDS Network Coordination (HANC) project works with the six HIV/AIDS clinical trials networks funded by DAIDS of the U.S. National Institutes of Health (NIH) with the intent of creating a more integrated, collaborative and flexible research structure
- Statistical and operations centers
- Central laboratories
- Contract Research Organizations (CROs)

Who Are the Primary Partners with the NIH?

The National Institute of Health is made up of 27 institutes and centers. Each focuses on specific research areas. More than 80% of NIH research activities are conducted by scientists around the world. Important NIH organizations that focus on AIDS-related research are:

- National Institute of Allergy and Infections Diseases (NIAID)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Mental Health (NIMH)
- National Cancer Institute (NCI)
- National Institute on Drug Abuse (NIDA)
- National Institute of Dental and Craniofacial Research (NIDCR)
- Office of AIDS Research (OAR)

Who Are Other Network and NIAID Partners?

NIAID alone cannot manage all of the complex issues associated with HIV/AIDS treatment and prevention research. NIAID also partners with the Centers for Disease Control and Prevention (CDC) and other organizations to address the complex global research needs, including:

- The Bill & Melinda Gates Foundation
- The International AIDS Vaccine Initiative (IAVI)
- The Center for HIV-AIDS Vaccine Immunology (CHAVI)
- William J. Clinton Foundation
- The Global Fund to Fight AIDS, Tuberculosis and Malaria
- UNAIDS, the Joint United Nations Programme on HIV/AIDS

CONCLUSION

In this workshop, we:

- Described clinical research
- Described the clinical research process
- Described the principles of clinical research
- Defined ethics
- Described the role of a Community Advisory Board (CAB) in the research process
- Listed key partnerships
- Discussed issues affecting AIDS research for various stakeholders
- Applied the information you learn in activities and discussions
- Asked questions about information you do not understand
- Practiced what you learn

What Do You Know?

Answer 10 questions about clinical research.