**MODULE 6: RESEARCH ETHICS**

**Proposed Agenda***

- Opening Activity: What Do You Think? *(30 minutes)*
- Part I Slides and Discussion of Case Studies *(75 minutes)*
- Part II Slides and Discussion of Case Studies *(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 6**

What Do You Think?

**Time frame** *(30 minutes)*

**Purpose**
- To give participants a chance to discuss their opinions about research and the principles of ethical research

**Materials needed**
- Flipchart and marker (or blackboard and chalk)

**Instructions**
- To prepare for this activity, write the statement "Participation in a clinical trial of a new, experimental antiretroviral medicine should only be offered to volunteers who have no other antiretroviral options" on the flipchart.

- Explain to participants that you are going to assign each person to a group. Group 1 will think of reasons why they agree with the statement. Group 2 will think of reasons why they disagree. Then the groups will come back together to hear each other's reasons. **NOTE:** Tell participants they do not have to agree with the position they are taking.

- Ask the groups to sit together to discuss their answers for about 15 minutes, and to select a spokesperson to report back to the large group.

- When 15 minutes have almost passed, give the 1-minute warning so the groups can finish their discussions.

- Ask the spokesperson from each group to report the group's conclusions. Help by offering comments, writing important points on the flipchart, and asking what others think about the important points.

- At the end of the activity, summarize the points made. Note that participants' comments included ethical elements, such as respect for persons, fairness, or offering a potential benefit.

- Tell the group ethical principles will be addressed in more detail during the training. Thank everyone for participating.
Module 6

Part I Slides – Insert Here
Module 6
Research Ethics
Part I
Trainer Manual
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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This slide lists the objectives for today’s program.

We will:

- Discuss the basic ethical principles that govern research in humans
- Explain the historical context for some of the protections now in place for research participants
- Discuss special ethical concerns about vulnerable populations. By vulnerable populations we mean people who may be unfairly influenced about participation in research.
- Discuss ethical concerns about informed consent (adults) and assent (children) for participation in research

Some of these objectives are covered in Part II of this module. The slides we will look at now are Part I, which covers the first two of the objectives.
**Vocabulary**

- **Ethics**: a system of moral values; correct behavior
- **Vulnerable populations**: people who are at risk of being unfairly influenced or of feeling unfair pressure to join a study
- **Beneficence**: doing good
- **Justice**: fairness
**Vocabulary**

- **Informed consent**: the process of communicating the information a volunteer needs to have before deciding about participating in a clinical trial
- **Voluntary**: done willingly, without pressure or reward
- **Risk-benefit ratio**: the risks of participating in a study compared with the benefits
- **Recruitment**: inviting people to join a study
Human research ethics rest on 3 basic principles that are considered the foundation of all rules or laws governing research. These 3 basic principles are:

- **Respect for persons**
- **Beneficence** (which means to do good)
- **Justice** (fairness)

These principles apply to everyone. They are universal and are to be followed whenever research on humans is conducted. There are many different ways in which research is reviewed and monitored to make sure these principles are followed. We’ll explain these principles in the next few slides, and later discuss the historical context for the development of the current governance of research ethics and protection of human participants in clinical trials or research.
Respect for Persons

- The role of the health care professional is to present all the facts about the research.

Let’s explain the principles a little further:

- Respect for persons means that all people have a right to make their own choices. It is the job of the research team members to present all the facts about the research to volunteers invited to join the study and to ensure that the volunteers understand the information, understand what choices they have (other than study participation) and understand that participation is entirely voluntary. Although the clinician caring for a volunteer may give advice about what he/she considers the best option for treatment, it is not the job of the research team to pressure volunteers to choose research over other options for care.

- It is also the job of the research team to give information about the research to the members of community. Respect for persons extends to respect for the community where research is being conducted, and giving the community a voice in what is done. CABs help the research team to do this.
Respect for persons means that before a person decides whether to join a clinical trial, the person needs to have the necessary information to make a decision. The process of communicating this information is called informed consent. Respect for persons and the informed consent process are meant to make it possible for a person to make a voluntary decision about participating in the research.

During the informed consent process, all of the questions on this slide and the next slide should be discussed.
- Why is the study being done?
- What are the medicines involved?
- Who will be in charge of my care during the trial?
- Will my regular doctor or nurse also take care of me?
- What will be expected of me?
- What are the risks?

**Trainer:** Please note the participants should have “Informed Consent Pocket Card” that is included with this curriculum from Module 3.
Informed Consent

- How might I benefit from this study?
- If I don’t join the study, what other choices do I have for receiving my treatment?
- Who will know about my participation?
- Who will see my research records?
- When the study ends, will I still get the medicine if it’s helping me?
- What will happen if I change my mind after joining the study?
Discussion: What steps should be taken to make sure that informed consent is freely given by participants and that participants are fully informed about their choices?

It may help to ask:

Who is the person who explains the study to the people who are invited to join the study? What methods does the person use to explain complicated concepts?

Examples:
- Simple language and explanations
- Taking several visits to review the study
- Asking the person questions to check whether they have understood the information
- Using peer-educators to explain some concepts
- Utilizing lists of questions to organize the information (such as the information on the Informed Consent Pocket Card)
Respect for Persons

- **Vulnerable populations:** People who need special protection

- **For example:** Women, children, minorities, the mentally ill, people who don’t have easy access to healthcare, people who may need extra help understanding the study, and people who are overwhelmed with other problems or are very sick

Respect for persons also includes the idea that some types of people are more **vulnerable** than others and need special protection. By vulnerable, we mean a person who may be unfairly influenced or feel unfair pressure to join a study. We’ll give some examples of what we mean by vulnerable persons in the next slide.

**Trainer:**

- Ask participants if they can tell you why any of the groups mentioned in the example need special protection. These groups may be especially at risk for being unfairly influenced or easily pressured into joining a study.
- Who would you identify as the vulnerable populations here (at your site)?

**Examples:**

- In many cultures, women are not decision makers. If a male researcher invites a woman to participate in a research study, is the woman able to make an independent choice? Will she feel comfortable saying no if she really doesn’t want to join the study?

- Some minority populations are routinely discriminated against in society. This can create populations who do not feel empowered to make their own choices when confronted with a recommendation from a health care professional, especially a health care professional who is not from a minority population. In the U.S., examples of such populations might be drug users, African-Americans, and illegal immigrants or anyone who has not had a good education.
Trainer: Case Study 1 would work well here (Or use or create any case study that describes a potential research participant from a vulnerable population).
The next basic principle of ethical research is called beneficence.

**Beneficence** means “doing good”. This means that the researcher is responsible to do everything possible to make sure that the research is not harming the participant in any physical, mental, or social way.

Beneficence also means that the risks associated with the study must be kept as low as possible. The benefit to the participant of joining the research study should be greater than the risk to the participant.

Protecting the participant from harm is more important than any benefit the research may bring to the world. Even if the research study is very important to science or if the study may help many people, it is more important to protect participants than to achieve these benefits.
Another word for “justice” is “fairness.” The principle of justice in research can be put into action in several ways. One way is that the researchers try to make sure there are more benefits for the participant than risks. Comparing the risks to the benefits is called the “risk-benefit ratio.”

A second way to put the principle of justice into action is for recruitment of research participants to be done fairly. (Recruitment means inviting people to join the study). The principle of justice does not allow researchers to place one group of people at risk so another group can benefit. As an example, imagine if we had a research study where all of the participants were very poor people (vulnerable people). Yet after the study is finished, the only people who can have the treatment are wealthy people who can afford to buy the treatment. Such a situation would not be fair, and so would not meet the principle of justice.
Principles of Research Ethics

- How do we know that the principles of respect for persons, beneficence, and justice are followed?
- Do all researchers automatically behave ethically?

How do we make sure that all clinical research follows these principles?

Most of us know that there have been ethical abuses in research. Although we may be tempted to dismiss these instances as something belonging to the past, the reality is that research abuse of ethics has occurred fairly recently, and it is therefore something that we must always guard against. Unfortunately, there are always outside pressures that can make small or large violations of research ethics tempting.

Fortunately, many rules and laws have been put into place internationally, and many layers of oversight have been developed, so that there are many opportunities to monitor the development of research studies and to watch how that research is done. Often, the rules that have been developed have come about specifically in response to a lapse in ethics………Abuse of research ethics is discovered, and new laws and new ways of making sure similar cases don’t occur in the future are made. This is an ongoing process that must be updated all of the time in order to keep up with new technologies and developments that change the nature of research.
The Nuremberg Code

- During WW II, Nazi doctors performed experiments on concentration camp prisoners.

- One classic example of abuse of clinical research that resulted in new rules and laws happened during World War II. Nazi doctors performed unethical and abusive experiments on concentration camp prisoners during the war.

- For example, there was research in which prisoners had to stay in ice water for very long periods to observe the effects of low body temperature on the functions of the body. The doctors did other experiments with prisoners who were mentally retarded. The doctors also performed unnecessary experimental surgery on prisoners.

- The prisoners did not volunteer for these studies; they were forced to participate. All of the research was done without giving the prisoners any information or obtaining their consent.

- Most of the prisoners died or were permanently crippled because of these cruel experiments.
Nuremberg Code (1947)

- "All of the experiments were conducted with unnecessary suffering and injury and very little, if any, precautions…to protect or safeguard the human subjects from… injury, disability, or death. In every one of the experiments the subjects experienced extreme pain or torture, and in most of them they suffered permanent injury, mutilation, or death..."

- As a result, an American military court began criminal trials on December 9, 1946, in Nuremberg, Germany, for 23 leading German physicians and administrators for participating in “crimes against humanity.”

- Several German doctors argued that their experiments differed little from previous American or German experiments.

- At the time, that was some truth to this argument because no ethical guidelines for research existed and little attention to participant rights was given. No international law addressed the difference between legal and illegal experiments with human beings.

- This worried Drs. Andrew Ivy and Leo Alexander, American doctors who had worked with the prosecution during the Nuremberg trials. So on April 17, 1947, Dr. Alexander submitted a document to the United States Counsel for War Crimes. The document outlined the principles of ethical research.
On August 19, when the verdict in the trials was read, almost all of Dr. Alexander’s points were listed in a section called "Permissible Medical Experiments."

Later, the points were written into a document describing the types of research allowed with human participants. This document is called the Nuremberg code, and researchers continue to follow these rules today.

The Nuremberg code makes clear many of the basic principles of ethical research, especially informed consent. Some of the rules from the code include:

- Participants must have the mental ability to give informed consent.
- Consent to join the study must be voluntary and fully informed.
- Participants may not be pressured to join the study.
- Participants must be free to leave the study at any time.
The Declaration of Helsinki 1964

- This declaration added some new rules to the Nuremberg Code.
- States that researchers cannot use placebos if effective methods exist for treatment or prevention.

At a meeting about 15 years after the Nuremberg Code was written, the World Medical Association established additional rules about research with human participants. These new recommendations were called the Declaration of Helsinki, because the meeting took place in Helsinki, Finland. The Declaration of Helsinki included some of the topics the Nuremberg Code did not. One of the main outcomes of the Declaration was drawing a distinction between therapeutic and non-therapeutic research (research where there is a potential benefit to participants, and research where there is no benefit, such as simple observational research).

A few years ago, The Declaration of Helsinki was changed to address an ethical issue in a HIV clinical trial that was going to be conducted in Africa. For many reasons a large number of people felt that the trial design did not reflect the ethical principle of justice. We will be discussing this case later. Based on the discussion of this proposed study, new rules were developed regarding the use of placebos, and these became part of the Declaration of Helsinki.
In 1974, ten years after the Helsinki Report, the US government established the “National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.” After 4 years of work, the commission issued the Belmont Report.

This report included rules about research involving human participants in the US that were very different from earlier rules. Before this report, researchers could decide what to study, who would participate, and how studies would be conducted. There was no system for a critical review of the research protocol by a group of experts who were not involved in the research.

The Belmont Report changed that by providing protection for human subjects, including a required review of the protocol by a committee of experts not involved in the research.

The Belmont Report identifies three fundamental ethical principles of research that we spoke of earlier -- respect for persons, beneficence and justice. The report said that all research involving human participants had to be based on those principles, which continue to be the basis for the rules researchers follow today.
Despite the guidance provided by these reports and declarations, problems still occurred. One of the most infamous research studies which violated ethical principles was the Tuskegee study of AA men with syphilis. The men were a vulnerable population: Not only were they minorities, but they were poor sharecroppers and laborers with little education. This study was conducted by the U.S. Public Health Service from 1932-1972.

- The goal of the study was to observe the long-term effects of syphilis. When the study was first devised, treatment for syphilis had not yet been discovered, but penicillin (antibiotic) treatment became widely available in the 1940s and later became the standard treatment for syphilis.
- The participants were never made aware of, and were never given treatment. Over three-fourths of the subjects eventually died from complications of syphilis.
- No participant in this study gave informed consent. In exchange for their participation in the study, the men received free physical examinations, free rides to and from the clinic, free hot lunches, and free medicine for any disease other than syphilis.
- The study was finally stopped, but only after a former Public Health Service employee took the information about the study to a newspaper journalist, who exposed the study in 1972. By this time, only 74 of 399 participants were still alive.
From 1963 to 1966, studies were carried out at the Willowbrook State School, a New York State institution for "mentally defective persons" (mentally retarded or mentally ill). These studies were designed to gain and understanding of the natural history of infectious hepatitis, and later to test the effects of a medicine called gamma globulin.

The subjects in the study, all children, were deliberately infected with the hepatitis virus… Investigators defended the deliberate infection by pointing out that the vast majority of them acquired the infection anyway while at Willowbrook, and so perhaps it would be better for them to be infected under carefully controlled research conditions.

During the course of these hepatitis studies, Willowbrook essentially closed admission to the facility to all but those who agreed to participate in the study. Finally, this case became public and caused an outcry, largely because of the perception that parents and their children were given little choice about whether or not to participate in research.
The National Research Act of 1974

- The National Research Act of 1974
  - Establish Institutional Review Boards (IRBs) or Ethics Committees
  - Created the National Commission for the Protection of Human Subjects
- The Belmont Report (1979)
  - Respect for persons
  - Beneficence (maximize benefit and minimize harm)
  - Justice (fair selection of participants)

The National Research Act of 1974 was a very important step forward for research ethics because it required that all institutions conducting U.S. government supported research to establish Institutional Review Boards (IRBs). (IRBs are also called Ethics Committees in some areas). IRBs are committees of scientists, researchers, and community representatives who must review every research protocol to be conducted at their institution to ensure it meets ethical guidelines and the law. To avoid a conflict of interest, the members of the committee do not review any research in which they are personally involved. No protocol can be conducted at the site until approval is granted from the IRB.

A few years later, another report identified the principles of ethical conduct of research that we discussed at the beginning of this training: Respect for persons, beneficence, and justice.
And finally, another group was established to oversee the way research is conducted with U.S. government funds is the National Bioethics Advisory Committee (NBAC). This is important for the IMPAACT research network, because IMPAACT is funded by the U.S. government, and therefore is governed by NBAC.

The NBAC added several new ethical rules in 2001, and many relate closely to the work of our network:

- First, NBAC requires that all research in developing (poor) countries address a local health need. There must be a benefit to the community. For example, you cannot research a new vaccine in a poor country if, when the vaccine proves to be effective, the country will not be able to afford it.
- Researchers and sponsors must involve representatives of the community, including potential participants, throughout the research process — CAB!
- Researchers must give good reasons for wanting to use a placebo. If an effective treatment exists, they must give that to the control group instead of a placebo, even if the treatment would not normally be available in their country because of the cost.
- We’re going to discuss ethical issues related to the use of placebos in a case study.
The 3 basic principles of ethical research -- respect for persons, beneficence, and justice – form the basis for all of the regulations and laws that govern research. There are guidelines and laws at every level: internationally, nationally, and locally. At every research site, international, national, and local guidelines have been adapted so that these 3 principles are followed. Laws and regulations may change from place to place because of local culture, and economic conditions, but the principles must still be followed.

U.S. government funded-researchers (including those in the IMPAACT group) must follow U.S. government regulations about clinical trials. But all sites must also follow the national and local laws. Generally, there is not a conflict between these different levels of law.

At each site, the Ethics Committee or the Institutional Review Board reviews and monitors research at the site to make sure all laws and regulations are followed. There is also a significant amount of monitoring done at the national level, and the international level. All researchers must take a course in Good Clinical Practice and Human Subject Protection to understand the ethical principles and the laws and guidelines that exist.

Ethical considerations always outweigh scientific the benefits to science or society. Human subjects must be protected.
Case Study
Module 6

Part II 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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Objectives

After completing this training, participants will be able to:

- Discuss informed consent and assent.
- List the responsibilities of investigators, sponsors, and supervisory committees or agencies.

This slide lists the objectives (or goals) for today’s program. The slides we will show and the activities planned for this training all relate to these objectives.
In all research involving human beings, it is necessary for each participant to go through the process of informed consent before joining the study.

During this process, the participant will learn, and have the chance to ask questions about, important information that all research participants must know and understand before making a decision about joining the study.
Informed consent is basic to a well-designed, ethical research study. “Ethical” means that moral values were considered in the planning of the study, and that the study is fair to participants.

To ensure the research participant receives the information necessary for making an informed decision, it is important to provide each participant with the following information:

- The research and what the participant will have to do
- Known risks
- Expected benefits
- Alternatives to participation
- Explanation of the privacy of participant information
- Safety procedures
- Whom to ask about the research or the rights of the participant
- The information that participation is voluntary

Getting informed consent from a participant demands time, creativity, and an understanding of the participant population. Understanding the population is an important role for the CAB when members review the informed consent process and the informed consent document.
After going through the process of informed consent, the participant will decide whether to perform the action of giving informed consent.

The action of informed consent is defined as: the agreement to participate in the study, given by a competent individual, who has received the necessary information about the research, understood the information and, after considering the information, arrived at a decision about participating without any pressure to do so.

Being competent means able to understand the role of a participant and what is expected of a participant

**Trainer:** Ask the participants to give examples of people who may not be competent to give informed consent. (Some examples: young children, people with severe mental disorders, people who cannot understand the information for other reasons)
It’s important for the research team to always be aware that the informed consent process starts before the participant joins the study, and continues during the study.

After a participant has joined a study, the researcher talks with the participant about any new information about the study and discusses procedures for the study visit.

Ethics boards (or IRBs) normally ask that “significant” new information be given to participants and that the researcher obtains a new informed consent. “Significant” new information is information that changes the risks or benefits of the study. A new informed consent is also required if there are changes to the study procedures (such as new tests or study visits).

Participants should also be informed of the results of the study when it is completed. IMPAACT investigators must provide a summary of study results that the participants and the community can understand.
The challenge of informed consent is to provide enough information to help the person make a decision, while at the same time presenting this information in a manner that can be understood. Support materials, such as brochures or fact sheets may be helpful. CAB members may review informed consent forms to make sure that members of the community will be able to understand them.

In studies where risks can be high, field-testing the informed consent may be considered. A research team member can “role play” informed consent with community members and then test to see if they understood the information. Areas of confusion can be corrected.

Informed consent must be obtained without pressure. The researchers status should not play a role in inducing the participant’s decision. Sometimes it may be better to have informed consent obtained by a neutral party rather than by a researcher. Vulnerable participants may require special attention and protection from pressure to participate in a study.

**Discussion:** What role can the CAB play?
At one time, it was assumed that all children and adolescents lacked the ability to participate in the decision about joining a clinical study.

There were several ethical concerns. Depending on his or her age, a child might not be able to understand the risks and benefits of a study. Also, children could be manipulated by parents and other authority figures, so they did not have the ability to decide freely whether or not to participate.

Therefore, they could not volunteer to participate in research and give informed consent the same way an adult could. So parents or guardians went through the informed consent process and gave what was known as “proxy consent.”

In 1964, The Helsinki Declaration (discussed in the first part of this training) changed all that. It permitted children to participate in research this way: by allowing a parent or legal guardian to give informed consent, while obtaining the agreement of the child, whenever possible.
In 1978, the Belmont Report introduced the concept of getting *assent* from a child and consent from the parents.

Thinking changed and people began to see that children of a certain age could be informed about a research study and could be asked to participate. Getting a child or adolescent’s assent is included in the guidelines ethics committees use when reviewing pediatric research protocols.

It is the opinion of The American Academy of Pediatrics that children ages 7 years and older can be involved in some kind of assent process.
Slide 11

Assent Case Study
All international regulations require that before any study with human participants can be “opened” (enroll patients), an independent committee must review the protocol and the investigators plans on how the study will be conducted at the site. In the U.S., these committees are called Institutional Review Boards (IRBs); elsewhere they are often called Ethics Committees (ECs).

This committee supervises the study from beginning to end, through the data analysis stage and the reporting of the study results. The role of the committee is to protect the rights of participants in clinical trials. Protecting the interests of participants is always more important than the interests of the researcher.

The people on this committee should come from different backgrounds and not be directly involved in the research (and have no conflict of interest). Members should be selected carefully, and must include community representatives.
The EC/IRB must address at least 6 issues:

- Are enough measures in place to make sure the well-being of participants is protected? How will the study be monitored to keep participants safe?
- Is the study design safe and appropriate? Do the data that will be collected support the design?
- Will the community benefit from the research?
- Are there plans to protect vulnerable populations and to recruit fairly?
- Does the informed consent process address all of the issues? Can this informed consent form be understood by members of our community?
- Will privacy of participants be protected?
World Health Organization guidelines require that some members should have a background in science or research. Other members should not have that kind of background. That way, the review can be balanced.

An ethics committee may also include religious or other community leaders or community members who have been participants in earlier studies. They will help the committee consider how the research might affect the community. The opinions of these members must be considered with the same level of respect as the opinions of members with scientific backgrounds.

The genders, ages, ethnic, and cultural backgrounds of the committee members should vary.

An ethics committee should be able to call on outside consultants with special expertise.
Researchers have a number of responsibilities. These are not only legal requirements, but are also the ethical norms that healthcare professionals must follow. It is important to keep in mind that researchers may ask other staff members to do some of the research work. But asking others to do the work does not relieve the researchers of responsibility. One major responsibility is protection of human participants (or subjects).

Protection of human participants includes

1. Developing scientifically and technically correct research protocols
2. Placing the well-being of participants above the interests of society
3. Communicating all the information necessary to the person thinking about participating for informed consent.
4. Protecting the privacy of the participants.
The researcher must conduct the study according to the protocol, and may only make changes with the approval of the Ethics Committee (EC) or Institutional Review Board (IRB). The researcher is also responsible for making sure all staff are well-trained, that the data are genuine, and that all medical records are private. (“Data” refers to the information collected from or about the participants during the study.)

The researcher must report to the EC or IRB and to the study sponsor any serious adverse events that occur during the study. (“Funder” refers to the group giving the money for the study to be done.) Any instances where the protocol was not followed correctly must also be reported.

The researcher and the study sponsor must do all that is possible to make sure that the local community has access to the benefits of treatments after the study is finished.
Research may be monitored by several different groups. These groups usually include the sponsor of the research, government agencies, or community groups. We'll talk briefly about each of these.
As the sponsor, DAIDS must monitor the research conducted by IMPAACT. DAIDS must:

- Provide a research setting that promotes honesty, objectivity, and the highest ethical standards of research.
- Select only well-trained researchers and provide them with all the tools they need to conduct ethical research.
- Provide all researchers with written policies, methods, and guidelines before they begin the research.
- Internationally, DAIDS must discuss with local partners the importance of the research for meeting local needs, and the potential benefits of the research for the participating communities. Once the research ends, DAIDS must also make reasonable efforts to make the results of the research available to the participants and their communities.
As the sponsor of IMPAACT research, DAIDS must send *independent* monitors to all IMPAACT research sites at least 4 times per year. In this case, independent means that the monitors are not part of the research group in any way.

The monitors

- Check that an EC or IRB is reviewing, approving, and supervising the research;
- Make sure the study is being conducted exactly as the protocol says it must be done;
- Verify all of the data;
- Look for adverse events (side effects or other problems that occur with the experimental treatment) and the response of the researcher to the adverse events that occur.
Government agencies have oversight responsibilities. The Food and Drug Administration (FDA) is one U.S. government agency that monitors clinical trials.

National governments usually have more than one agency that monitors research or specific parts of a study. For example, there are pharmacy monitors that make sure record keeping is accurate and study medicines are handled safely, and there are laboratory monitors that check the safety and accuracy of the research laboratories.

The FDA is a government agency, with power over all clinical trials that involve medications. Although the FDA does not routinely monitor specific research sites and check specific data, they will do this on occasion.
The Data Safety and Monitoring Board (DSMB) is a group of people assigned to look at research results while the study is ongoing. While an Ethics Committee looks at the study data only from one institution or country, the DSMB looks at data collected for the study from all hospitals, institutions, and countries where the study is being conducted. The DSMB checks all available study data at specific times during the clinical trial—for example, at one month, 3 months, and 6 months.

The DSMB monitors safety. For example: Are there more side effects or problems than expected in any of the study groups? Have there been any unexpected serious side effects? If so, as mentioned earlier, the study may be stopped or changed to protect participants.

The DSMB also monitors effectiveness (how well the medicine is working). For example: If a study is comparing two medicines, and it becomes clear from the data collected that one medicine is not working at all, and the other medicine is working well, the DSMB would stop the study and offer all participants the more effective medicine.

The DSMB will stop a study if they discover any safety issues or effectiveness issues that they feel compromise the well-being of participants.
A conflict of interest can affect the ethical conduct of research. A conflict of interest means that the researcher has an interest in the outcome of the study that may cause him/her to be biased (want the outcome of the study to be one way or another). For example, a researcher who works for a pharmaceutical company may want the study to prove that the medicine invented by that company is effective and safe.

When very strong conflicts of interest are present, they may contribute to a situation that can lead to scientific wrongdoing on the part of the researcher or the institution –behavior that is not ethical, such as falsifying data, exerting pressure on subjects to join the study, etc.

Conflicts of interest are present in most research studies, and that is part of the reason that there are many safeguards, such as monitoring groups, to make sure research is done ethically and honestly.
Scientific Misconduct

- Includes:
  - Making up data or results
  - Changing or leaving out data or results
  - Stealing from another person’s work

- Sites are monitored to confirm EC or IRB review, data accuracy, and safety

Scientific misconduct includes lying, making up data, stealing the work of others, and other practices that differ from those that are commonly accepted in the scientific community. Misconduct does not mean honest error or honest differences in interpretations or judgments of data. Scientific misconduct is purposely making up, changing, or leaving out data, or stealing from another person’s work.
Summary

- Informed consent and assent are ongoing processes—not one-time events.

- Researchers, institutions, sponsors, and oversight agencies have a responsibility to monitor research to protect human participants.

- Conflicts of interest can cause behavior that is not ethical in the conduct of research, including scientific misconduct.
**Trainer:** Case Study 6 will illustrate the concept of Conflict of Interest
Module 6
Ethics Case Studies
CASE STUDIES
Module 6
Notes to Trainer

In the following pages, several case studies are outlined that show situations where ethical problems occur during clinical trials. The participants have these cases, along with the discussion questions that follow each case, in the participant manual. Trainer notes are provided (only in the trainer manual) as a guide to identifying all of the issues relevant to each case.

The case studies can be used in different ways. The slide sets for this module include several slides that say “Case Study,” so you can stop the slide presentation to discuss a case. By doing this, you help participants to deepen their understanding of the ethical principles you are trying to teach them. But as the trainer, you may decide when and how to present the case studies and you are encouraged to change the cases or create new ones for your participants and unique clinical trial site. You can have the participants discuss the cases in the large group, with you as facilitator, or they can discuss the same case in small groups, with each group later reporting their discussion and conclusions to all of the participants and to you.

The trainer manual also includes recommends to discuss certain cases at specific times during the slide presentations (e.g. Case Study 5 is recommended for discussion immediately following the information on the ethics of placebo use).

How to analyze a case study
The case-study method may be new to some participants. Explain that a case study is a useful way of beginning to apply the principles they are learning during this training. Emphasize that when discussing a case study, there will be people who have different points of view. And that most of what they will learn during this exercise will come from listening to the different opinions and experiences of their fellow participants. Suggest that as they work through the case and answer the questions with their group, they respect these differences of opinion, with the goal of agreeing on an approach to the case. Let the participants know that there is no one right answer to a case analysis. Yet there are answers or solutions that are reasonable based on the information they will have.
CASE STUDIES

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Tips for Participants: Analyzing a Case Study

1. Read the case once and then read it again.
2. Review the case questions. They may contain clues about the problems the case presents.
3. Then decide what is the main problem, issue, challenge, or opportunity the case presents?
   (There may be more than one.)
4. What is its (or their) importance?
5. What are the actions the people in the case could take?
6. Which is the best alternative and why?
CASE STUDY 1:
INFORMED CONSENT FOR PMTCT
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Dana is a 21-year-old woman who is 30 weeks pregnant. She was diagnosed with HIV infection at her second antenatal visit, which was 2 weeks ago. She delayed her first visit to monitor her pregnancy because she is not a legal resident, and was therefore a little fearful about whether the clinic would report her to government authorities (which they have not done). Dana is a high school graduate, unemployed since she lost her last job when the store where she was working closed. Though she has not been ill, Dana’s CD4 count is very low, so she needs ARV therapy.

She is receiving counselling and support from the clinic social worker, but Dana has not disclosed her status to anyone. She and her partner of 3 years have never discussed HIV. Her partner has a job, though not highly paid, and money is tight.

At this 30-week visit, the clinician tells her there is a clinical trial going on that she should consider joining. It is an antiretroviral (ARV) therapy trial for HIV-infected pregnant women. The trial will test one regimen against another for PMTCT and for postpartum treatment of women who qualify for antiretroviral therapy. The doctor explains the study, including the risks and benefits associated with the study. Before her next visit in 2 weeks, Dana must decide if she wants to join the trial.

Dana doesn’t yet know much about HIV or treatment or clinical trials, but she likes the idea that the medicines would be free, that she and the baby will be carefully monitored, and that the clinic will arrange free transportation for the study visits.

- What are the issues in this case concerning Dana’s ability to gain enough understanding of the trial?

- What are the other issues in this case that may affect her decision?

- What steps would you suggest to improve the informed consent process in this case?

Trainer Notes:

- Dana may have too much on her mind to be able to understand the complexities of the decision she is going to make. If so, this would violate the basic ethical principle of respect for persons.

- From the description above, it does not appear that the clinician discussed other options for treatment with Dana. It only indicates that the clinician discussed the clinical trial. Does Dana know what her choices are in this case?

- Do the ethics of this situation change if Dana will have no way of receiving any treatment for her own health if she does not join the study
- Does the offer of free treatment and free transportation amount to unfair encouragement to participate in this clinical trial? Generally, Ethics Committees would say treatment at no charge and reimbursement of costs to participants while on the trial are reasonable and expected.

- The case says that “the decision must be made before the next visit in 2 weeks.” Does this give Dana enough time to understand the study and to address the disclosure issues? Is the time pressure to decide fair to Dana?

Would it be ethical to require that Dana disclose her HIV status and her trial participation to her partner? In general, Ethics Committees would not allow forced disclosure. In addition, there is no requirement that consent for participation must be sought from the father of the fetus.
CASE STUDY 2:
INFORMED CONSENT FOR A CHILD

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Anne is a 34-year old HIV-infected woman, married for 7 years to a man who is also HIV-infected. Unfortunately, they were unaware of their HIV status until their daughter Sarah was diagnosed with HIV-related growth failure at the age of 4 years. Anne and her partner James have been adjusting to the news, and their main concern has been for the health of their daughter, whose infection is more advanced than that of her parents.

Sarah started ARV therapy almost immediately after her diagnosis, but she experienced a serious side effect from the nevirapine. Now the nevirapine has been stopped, replaced with a protease inhibitor to take along with the other 2 ARVs. Unfortunately, the PI is extremely bitter and Sarah’s parents are having an increasingly difficult time giving her the necessary medications. The twice-a-day dosing has become a twice-a-day battle, which has been going on for a year. Thankfully, Sarah, now 5 years old, has been doing well on the medicines. Her viral load is very low, and the CD4% is rising well above her original low level of 6%. But her parents are frustrated that no easier option is available. They plan to give Sarah a “vacation” from ARVs for at least a few weeks when she starts school next month. They discuss this with Sarah’s doctor.

Sarah’s doctor tells the parents that Sarah may be eligible for a clinical trial of a new ARV combination treatment. The other choice, she says, is to teach Sarah how to swallow tablets so she can stop taking the liquid medication that tastes so bad. If she can learn to swallow the tablets, she can stay on the same very effective combination. Anne and James have some doubts about whether Sarah can learn to swallow tablets. After the doctor explains these choices, she tells Anne and James that they should read the consent form for the study and let her know if they have any questions.

- How do you feel about having Sarah join the clinical trial, thereby stopping treatment that has proven successful?
- What are the issues in this case that may affect her parents’ decision?
- What about the consent process? Have Sarah's parents been completely informed? Has the doctor fully discussed the option of teaching Sarah to swallow tablets? (With training, swallowing tablets is possible for a 5-year old child.)
- What steps would you suggest taking to improve the informed consent process in this case?

Trainer Notes:

- The treatment that Sarah is receiving has been successful in terms of Sarah’s health, but has it been successful in terms of the well-being of Sarah and her parents?
- It’s very likely that Sarah’s current treatment will eventually fail because the parents are very likely to begin to miss doses….or Sarah will learn to spit out the medicine. Therefore, some change is not only ethical but is necessary. But, if we know that Sarah can learn to swallow pills and therefore continue an ARV regimen that is successful, is it ethical to offer an unproven, experimental treatment?

- If Sarah joins the clinical trial and the treatment fails, what is the likelihood that she will have developed resistance to her current ARV therapy?

- In sum, the three most important things for Sarah’s parents to understand are 1) Sarah can learn to swallow pills; and 2) The experimental treatment cannot be guaranteed successful and cannot be guaranteed to be safe. Sarah already had a serious reaction to another ARV; 3) Is there a risk of ARV resistance with the study treatment?
CASE STUDY 3: ADOLESCENT ASSENT

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Mary is a 15 year old girl who acquired HIV through mother-to-child transmission. She had done well and was stable on ART until she was about 13 years old. At that time, she became very rebellious and began to skip doses of her medicines. Not only that, but there were times when her mother believed she had taken the medicines, but in fact Mary had hidden them, and later threw them in the garbage. Mary became very angry about her HIV status and furious at her mother for “infecting her.” Her father left the family just after Mary’s HIV infection was diagnosed, and she never sees him.

Now the ARV therapy is beginning to fail because of Mary’s non-adherence to the regimen. Mary insists she does not care. She stops going to school, and is spending time with a much older boy who has quit school. Her mother cannot control the situation, and is seeking help from the staff at the clinic where Mary is treated for HIV. The nurse at the clinic has started a support group for adolescents with HIV, and she invites Mary to join. So far, Mary has attended two meetings, but has not spoken at the meetings yet.

Meanwhile, because Mary’s viral load is now very high, and her CD4 count has fallen so low that she is at risk of AIDS-related illness. Her clinician proposes that Mary enter a clinical trial for adolescents who have failed at least one ARV regimen. The clinical trial offers a chance to be treated with a simple regimen that requires many fewer tablets than Mary was taking with the old regimen.

Mary’s mother spends a lot of time with the researcher, with the research nurse, and with a CAB member who counsels patients about clinical trials. She decides that the trial is right for Mary. In fact, she is really excited that Mary may finally have treatment that is successful but less of a burden than Mary has lived with for the last several years.

The researcher and the research nurse speak with Mary about the trial. Mary is not at all interested. She says she is tired of people examining her and asking her questions all the time, and that she hates taking tablets and being different from all of her friends. She does not want treatment, she does not want to come to the clinic if they insist on giving her treatment, and says she would rather die.

- How do you feel about giving Mary control over her treatment by requiring her assent to participate in the trial?
- What steps would you take at this point, since Mary has refused treatment and seems very near to refusing to come to the clinic at all?
- What could the clinic and/or research staff have done to improve the process of assent for Mary?
- Do you believe Mary understands the issues involved in refusing treatment?
Trainer Notes:

- Ethically, Mary does have the right to refuse further treatment. There is a great deal of experience in medicine with adolescents refusing possibly life-saving treatment, especially in cancer care and HIV, where quality-of-life may be (or may seem to be) affected negatively.

- In addition to giving Mary support for her right to refuse and her decision, ethically the health care team must have a clinician assess Mary for depression or other psychiatric illness, and work with Mary to improve her view of her life and to see options other than stopping treatment. The team has moved in the right direction by including Mary in the adolescent support group. Addressing these issues in the group may help Mary move in a more positive direction and accept treatment.

- Participating in a research study will only increase the number of people and amount of attention given to Mary as a patient with a disease—exactly what she is fighting against. If Mary did NOT have the right of refusal, would enrolling her in the trial be ethical?
CASE STUDY 4:  
INFORMED CONSENT, PRIVACY, AND CONFLICT OF INTEREST

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A new ARV medicine has been discovered. Scientists believe it may be able to prevent HIV infection in persons at very high risk of becoming HIV-infected. In addition to testing this medicine for preventing mother-to-child transmission of HIV, the researchers would like to study the medicine as an HIV prevention method for women who are sex workers in a country with a very high incidence of HIV. These women are often exposed to HIV, even though there has been a strong educational program about the use of condoms. Because condoms are not 100% effective and are not used 100% of the time, sex workers continue to be exposed to and at risk for HIV.

All of the women who enroll in the study will receive intensive counselling about ways to reduce their risk of HIV infection, and all women will receive free condoms. The women will be randomly assigned to receive the experimental medicine or to receive placebo. They will be followed closely, asked to give details of possible sexual exposure to HIV, and tested for HIV and all other sexually transmitted infections at no cost. Treatment for other STIs will also be provided by the study.

The research team will discuss the study with brothel owners, who have control of the sex workers and pay them. For the brothel owners, the study is a good thing because it saves them money. They will not have to pay for condoms or medical examinations or treatment for STIs. Illness and disability among their employees costs the owners money, and having the sex workers enroll in the study will reduce the expense of keeping the women healthy.

Although the support of the brothel owners is necessary for the study to be successful, the consent of the women who enroll is required.

- What are the ethical issues that you can identify in this case?
- While preparing for the study, the researchers will discuss the study with the brothel owners. Do you feel that the researchers will spend enough time consulting the community while preparing for the study?
- What do you suggest the researchers change in their approach to preparing to start the study?
- How do you feel about the use of a placebo in this study?

Trainer Notes:

- It seems likely that the brothel owners will pressure the women to participate in the study, since there is an economic benefit for the owners. This violates the principle of “Respect for
Persons’ because the women cannot make a free choice. The brothel owners have a conflict of interest. In addition, the privacy of the participants is at risk.

- What do you think of the researchers’ approach to community participation? In this case, the researchers discussed the study with the brothel owners. But they did not speak with any of the sex workers while planning this study. This is not ethical, because the women in the population to be studied have never had a chance to ask questions of the researchers or state their concerns. This problem, along with the bias introduced by having the brothel owners pressure the women to participate, are serious ethical problems.

- According to the principles of research ethics, and all current laws and rules, the use of placebo in this instance is correct. The researchers must, as stated in the protocol, provide all of the proven methods available to protect the women from HIV infection (condoms, education, and STI treatment). As described in the case, they will be doing this. There is no other known method available to prevent HIV infection except avoiding sex altogether, or limiting sex to one uninfected partner. These options are not available under these circumstances. The researchers may ethically be allowed to use a placebo if no other treatment is available. The placebo group will receive the same proven methods of prevention as the experimental group. This is an example of an ethical use of a placebo group in a clinical trial.
Case Study 5: Strategies for Management of Antiretroviral Therapy (SMART) Study

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- This study was designed to determine if simplifying the ARV regimen would provide the same benefit as taking the standard regimen.

- Participants in the control group received the standard, continuous ARV therapy for viral suppression. Those in the experimental group received ARV therapy less frequently, based on their CD4 count. The goal of this strategy was to reduce exposure to ARVs (also called the drug conservation strategy).

- The trial was not blinded, so investigators and participants were aware of treatment they were receiving. Researchers enrolled 5,472 patients from 318 sites in 33 countries.

- The control group’s regimen was consistent with the 2003 guidelines for the use of ARVs in adults and adolescents. According to these guidelines, available ARV regimens were to be used in an uninterrupted manner, with the goal of maximal and continuous suppression of HIV replication (in other words, to maintain an undetectable viral load).

- The experimental group’s regimen was irregular because the use of ARV therapy was based on each participant’s CD4 count: antiretroviral therapy was withheld until the participant’s CD4 count decreased to fewer than 250 cells/mm³ (per cubic millimeter). At that time, the researcher started ARV therapy (or restarted, depending on how long the participant had been enrolled) and continued until the CD4 count increased to more than 350 cells/mm³.

- The protocol also permitted researchers to begin (or re-start) ARV therapy if symptoms of HIV infection developed or the CD4 percentage was less than 15%. Once the CD4 count was higher than 350 cells/mm³, the researchers stopped ARV therapy and restarted it only when the CD4 count was lower than 250 cells/mm³.

- The CD4 count levels for stopping and starting ARV therapy were chosen based on information from previous studies. These studies determined at what level a CD4 count creates an increased risk of disease progression, opportunistic infections, or death.

- There were two scenarios (also called primary and secondary endpoints) when researchers were supposed to stop ARV therapy:
  - Primary endpoint if the participant developed a new or recurrent opportunistic disease
  - Secondary endpoint: if the participant developed major cardiovascular, kidney, or liver disease.
A Data Safety Monitoring Board reviewed the results of the SMART study regularly to decide if the study needed to be changed or stopped. These were the conditions under which they would stop the study: (1) results showing participants in one group were doing better than those in the other group, (2) substantial evidence of benefit or harm, or (3) evidence that continuing the study would not answer the study questions about the differences between the treatments.

After its sixth meeting, the DSMB recommended stopping enrollment because the results showed that the SMART study was unlikely to show that the experimental treatment was better than taking ARVs continuously (the standard regimen). At this time the participants had been enrolled for an average of 16 months. Participants in the experimental group then went back to receiving standard ARV therapy.

The SMART study was terminated early because the experimental group experienced statistically significantly more adverse events than the control group — new or recurrent opportunistic infections and major cardiovascular, kidney, or liver disease.

Why would the researchers have wanted to reduce a patient’s exposure to ARV medicines?
- Decrease side effects or negative effects of drugs
- Give patients a break from daily demands of taking ARVs.

This was not a blinded study. What effect could that have had on how the researchers assigned participants to the control or experimental group? Was it ethical to design this as an unblinded study?

**Trainer Notes:**

- Usually, earlier studies have been done that show that it may be beneficial to take ARVs less frequently. If the researchers in this study did not have any proof from earlier studies that the conservation strategy might be as effective as the standard regimen, was it ethical to take a group of participants off ARV medicines completely and wait for their CD4 count to drop to 250 cells/mm³?

- If the study results had shown that the experimental treatment was as effective as the standard regimen, should those results have been used to recommend a change to stopping ARV therapy when a patient’s CD4 count increases to 350 cells/mm³?
CASE STUDY 6:
USE OF PLACEBO AND HIVNET 012

The history of the successful use of ARVs to reduce the risk of mother-to-child transmission of HIV began when data from the clinical trial ACTG 076 was analyzed mid-way through the study. The results showed that the risk of transmission was greatly reduced with the use of zidovudine (ZDV, AZT) as compared to placebo. (As a reminder, no ARV therapy was the standard of care at the time the study was conducted. It was not known 1) if ZDV would lower the risk of transmission, or 2) if ZDV might have harmful side effects. No ARV was used during pregnancy as the standard of care at the time. Therefore, it was considered ethical to compare ZDV with a placebo.) This study was stopped as soon as the results were reported to the protocol team because ZDV was found to prevent PMTCT, and all women in the study who had not yet delivered were offered ZDV for PMTCT. This is a classic example of how putting ethical principles into action can protect study participants.

However, this study also created an ethical problem. The 076 regimen was expensive and complex. Resource-limited settings were not able to implement the ZDV regimen as used in the study. Not only was the medicine too expensive, but the health care infrastructure to support the complex and intensive regimen was not in place. Therefore, even though the results of ACTG 076 showed that the ZDV regimen was effective, the regimen could not be offered publicly in settings without the rich resources required for implementation.

Unfortunately, no one knew if the 076-ZDV regimen would be effective if it were simplified. In the 076 study, women received ZDV orally starting at 28 weeks of pregnancy, then received ZDV by intravenous infusion during labor and delivery, and then the infants received ZDV orally for 6 weeks after birth. No one could know if the treatment would still be effective if the time period was shortened, or if the regimen was made simpler to make it easier and less expensive for countries unable to manage the original protocol regimen.

So a new protocol was developed for resource-limited settings, where they could test the effectiveness of a very simple and inexpensive regimen for PMTCT. HIVNet 012 would test nevirapine (NVP)—as a single dose to the mother and a single dose to the infant—in countries where the current standard of care was that no ARVs were given for PMTCT.

In the original study design, researchers planned to test the NVP against a placebo control group. But there was much disagreement about whether the researchers should be allowed to test NVP against a placebo. Some people felt it was unethical to use a placebo, because the effectiveness of ZDV for PMTCT had been proven. Others felt that it was ethical to test nevirapine against placebo in settings where the ZDV-076 regimen could never be offered publicly because the resources were not available.

What are your thoughts about whether using a placebo was ethical in this situation? In the context of a research study, the ZDV-076 regimen could have been used, even though it was not publicly available. What ethical questions would arise if the 076 regimen would have been used and tested against the NVP regimen?
Trainer Notes:

- Placebos cannot be used when effective treatment exists. In this case, effective treatment did exist. The argument for using a placebo in this study was based on the fact that effective treatment existed, and therefore must be offered to participants in the study. But on the other hand, the ZDV-076 regimen was not available as the standard of care in the setting where the clinical trial was to be conducted. The researchers could have provided the 076-ZDV regimen to participants in the study, but it could not be provided to the population in general. There are pros and cons on both sides of this dilemma. Would it be fairer to provide the ZDV-076 regimen to study participants, or would it be fairer not to provide the 076 regimen so that a regimen that was simple and affordable (NVP) could be easily tested?

- If the experimental medicine, nevirapine, was successful in this trial, it would be of tremendous benefit in resource-limited settings where the ZDV-076 regimen could not realistically be used. On the other hand, if the ZDV-076 regimen was tested against the NVP and had proven more effective than the NVP regimen, it would have been meaningless to the communities where the trial was done, because their government would not be able to afford to provide the medicine. Would it have been fair to have proven the success of a ZDV regimen in a setting where it would not be available?

Note: The end result of this dilemma was that the trial was designed without the use of a placebo. However, the control group of women and their infants did not receive the 076 regimen of ZDV. Instead, they received a modified version of the 076 regimen, using ZDV orally (not intravenously) for a short period of time. Fortunately, the NVP group had a significant reduction of HIV transmission to infants compared with the ZDV group, and the NVP regimen was implemented in many resource-limited setting that had previously not been able to offer any ARV for PMTCT....
CASE STUDY 7: RESEARCHER CONFLICT OF INTEREST

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Noah is an 11-year-old boy who was perinatally infected with HIV. His parents have died of AIDS, and he is being cared for by his elderly grandmother. He has responded well to antiretroviral therapy, and has a very low viral load and a high CD4 count. His grandmother has some trouble understanding the complexities of HIV and HIV treatment, but she has been thoroughly trained in giving the medicines, and Noah is cooperative and helpful.

Noah’s doctor is the principal investigator for IMPAACT at his site, and she also participates in the scientific committee for developing protocols to test the effectiveness of using the body’s own immune system to fight HIV. She is the co-chair of a protocol that will test an experimental vaccination, that may boost the immune system enough to allow it to control HIV. Noah will continue his ARV medicines if he joins the study, and his immune responses will be monitored carefully to check his body’s response to the vaccination.

Noah’s doctor is under a lot of pressure from many sources. She feels personal pressure because she believes the protocol is very important, and that the vaccine will possibly save the lives of many children in the world who are infected with HIV.

The doctor also feels outside pressures. First, funding for her site depends upon steady enrollment of participants into clinical trials. If their funding is lowered because of low enrollment, she may have to reduce expenses by firing one member of the research team. Second, as co-chair of the protocol, she is under pressure to enroll participants from her site, and so far, she has not done so. Third, her department at the medical school highly values publications, and she feels pressure to get the study done so she and her team can publish it.

Noah’s doctor tells Noah’s grandmother about the study. Even though the doctor explains the study completely, including the possible risks for Noah, the grandmother states again and again, “Whatever you think is best, Doctor” or “I don’t know about all that, but I know you and I trust you to make the best decision for Noah”.

Next, the doctor speaks to Noah about the study. She explains it using words that he will understand, and he listens carefully. However, this forces her to explain the study in the simplest of words, without a lot of detail, because Noah is only 11 years old and not yet able to understand the complex nature of the study.

- What are the ethical issues related to this case?
- Do you feel it would be ethical to enroll Noah in this study?
- What steps might be taken to make sure the grandmother’s consent is truly “informed”?
The concept of beneficence is important to this case, because it means “to do good.” Part of the principle of beneficence is “to do no harm.” In this case, it would not be ethical to put a child in a research study that will expose him to risk if neither he nor his guardian truly understands the risks of being in the study. This is especially so because Noah is doing so well on ARV therapy and there is no medical reason to change his treatment. He will continue the successful ARV treatment, but cannot know in advance what effect, if any, the vaccine will have on his health.

Before any discussion of the research study, Noah’s grandmother must understand that Noah cannot be enrolled in this study unless the researcher is convinced that the grandmother is fully informed and that she feels free to approve or not approve Noah’s being enrolled in the study. Noah must also understand he is being invited to join a research study and that he has a right to say yes or no to participation.

To enroll Noah in an ethical manner into this protocol, the researchers must be absolutely sure that Noah and his grandmother understand that Noah is doing well, and that while the vaccination may be helpful to him, it also may not be helpful, or may even cause him side effects. Being in the study also will mean he will get shots he would not otherwise get, and he will have more clinic visits and more blood tests. These are facts Noah’s grandmother should be able to understand. If his grandmother cannot understand these basic concepts, then it will not be ethical to allow Noah to participate in the study. If she does understand these concepts, then slowly and carefully the researcher can add more details that explain the risks, benefits, tests and visits, etc. It will not be possible to get informed consent during the course of a single clinic visit. The information will need to be given during several other visits as well.

Sometimes the protocol team, or the research team on site, will write a one-page summary of the protocol to give people interested in participating a “first look” at the study using simple language that can be understood by non-scientists. This can help people avoid the feelings of confusion that may be associated with reading long and complex protocols. (The IRB or Ethics Committee must review and approve this summary before it may be used).

A peer educator, counselor, or CAB member may be more successful in starting the discussions with this family and helping them understand the basic concepts addressed above.
CASE STUDY 8:
LEGAL GUARDIANSHIP AND CONSENT FOR CHILDREN

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Noemi is a 5-year-old girl who has AIDS and lives with her grandmother. Her mother died soon after Noemi was born, and her father died before she was born. Noemi was recently hospitalized with pneumonia and is now at home, but still very weak and thin. She needs treatment for HIV, but the only ARV regimen available at her site is one she cannot take, because she has experienced bad side effects with one of the medicines in the 3-drug regimen.

Recently, the doctors spoke to her grandmother about enrolling Noemi in a clinical trial that would give her access to a new group of ARV medicines. Noemi is eligible for the trial, and her grandmother has spent a lot of time with the research nurse, a CAB member, and the doctor, and she feels she understands the trial quite well. She knows the risks and benefits, and she understands Noemi can leave the trial anytime her grandmother feels it is in Noemi’s best interest.

But before Noemi’s grandmother could sign the informed consent form, the research nurse asked her if she had any documents showing that she was the child’s legal guardian. The grandmother does not. It is an expensive and time-consuming task to become a legal guardian in her country, and she is poor and alone. She sells vegetables and baskets in the market, and just makes enough to keep them fed and housed. She is trying to save money to pay for Noemi’s school fees.

The government in their country has not addressed this guardianship issue, although it is a common problem for families impacted by AIDS. The AIDS epidemic has hit this country very hard, and many children have lost one or both parents. Often, children are cared for by a relative. At other times, a neighbor may take care of the child or children of a parent who has died. But rarely are these arrangements made official or legal, with paperwork to prove the relationship. Orphans are allowed to enroll in school and are given care in local health clinics even without official guardianship papers.

The research team is not sure how to move forward. Noemi needs the treatment that the trial can offer her. The team is concerned about whether it is an ethical problem for them to allow the grandmother to give informed consent for Noemi without proof that she is the legal guardian.

- What principle of research ethics applies to this situation?
- Do you think that the grandmother has the moral/ethical right to make decisions for her granddaughter?

Trainer Notes:

- One of the principles of ethics relevant to this situation might be “justice”. It could be said that it is unfair to exclude children who are orphans and who could benefit from a clinical trial because of this (apparently common) problem with legal guardianship.
- If this trial were a simple observational trial of no real benefit to the child, then the principle of justice would not apply. The child would not need to join the trial.

- Local law and customs vary between different countries. In the U.S., the guardianship issue is likely to be a serious legal issue, and the child would need the supervision of a government agency or the courts to participate in a trial. In other countries, it is less of a problem.

- In this case, the team decided to meet with Ethics Committee to discuss how to handle this and other similar cases. This is a good solution. Ethics Committee approval for the child to participate in the trial would resolve the ethical issues.
CASE STUDY 9:
QUESTIONABLE CAPACITY FOR TRULY INFORMED CONSENT

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Tego is an 18-month-old baby boy who is very ill and in desperate need of HIV treatment. He has been in the hospital for 2 months, and has only recently been stable enough to consider ARV treatment. The only treatment available for Tego is through a clinical trial of antiretroviral therapy for infants less than 2 years of age. No other treatment is available where he lives.

The research team is concerned that Tego's mother is not really able to give informed consent for the study. She seems to be overwhelmed with the many problems in the family, including her own illness. Members of the team have had several meetings with her to discuss the study, but none of the team members has felt they are able to help her understand the issues involved in the study. They have tried to explain them, and have read parts of the consent to her, but she is unable to answer basic questions when they try to test her understanding. Tego's father works several hours north of their home and he returns every few months. He is not expected to be available for several weeks.

The research team does not know what to do. Tego is a sweet baby, and his mother is kind and caring. The team really would like to help the family, but they are not sure what the most ethical course of action would be. Tego’s mother is anxious to get help for her son, but she admits she is a bit confused about what to do.

What is the principle of research ethics that applies to this situation?
Do you think it is ethical for the research team to enroll Tego in the study?
What would you do to address the ethical challenges in this case?

Trainer Notes:

The principle that applies to this situation is “Respect for Persons.” Tego’s mother is in charge of his care, and has a right to make informed decisions about his care. But the situation is complex: Tego also has a right to the best care available to him in his situation.. But the research team has a conflict of interest—the team cannot ethically make a decision about what is best for Tego. His mother (or father) has to do that.

What can be done?
First, think about whether there are other family members to help discuss Tego’s needs and the available choices for treatment. It may be that another family member will be able to help Tego’s mother understand the issues and feel comfortable with making a decision.

Find out if the hospital or clinic has a medical ethics committee, or if there is someone else who can provide guidance in this situation. The decision about Tegos mother can consent for his participation in the clinical trial with her full understanding must be made by someone who understands the choices completely and is a neutral party to the situation.. This means someone who has nothing to gain from Tego participating, someone who is not a part of the research team, and can think about the potential risks and benefits for Tego and judge his mothers feelings about the study without bias.
**PARTICIPANT EVALUATION FORM**

**Module 6 Part I**

Research Ethics

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

<table>
<thead>
<tr>
<th>Question</th>
<th>0= No effect</th>
<th>1= Some effect</th>
<th>2= Much effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The basic principles of research ethics</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Special ethical concerns about vulnerable populations</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Ethical issues related to informed consent</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. The effect of discussing case studies on my ability to understand ethical analysis of research</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. Understanding the role of monitoring groups, such as the Ethics Committee or IRB.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Question</th>
<th>0= Not useful</th>
<th>1= Useful</th>
<th>2= Very useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. The materials in the training manual were…</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. This training as a whole was…</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
PARTICIPANT EVALUATION FORM

Module 6 Part II
Research Ethics

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 - 2, 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. Informed consent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Responsibilities of the following for the ethical conduct of research: investigators, sponsors, and supervisory committees or agencies.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</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>3. The materials in the training manual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. This training as a whole</td>
<td></td>
<td></td>
<td></td>
</tr>
</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 this information?

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

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 6
Research Ethics

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

<table>
<thead>
<tr>
<th></th>
<th>NO IMPROVEMENT</th>
<th>SOME IMPROVEMENT</th>
<th>BIG IMPROVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Understanding of the basic ethical principles for clinical research</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Ethical issues related to the informed consent process and the process of assent for children</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Understanding of the need for protection of vulnerable populations in clinical research</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. Understanding the role of monitoring groups (e.g. IRB or ethics committee)</td>
<td>0</td>
<td>1</td>
<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?
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

Is there any part of this training that needs to be followed up?
____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

Trainer Name:                                           Signature:                                           Date:

Please use the back of this form for additional comments and suggestion
Module 6

Appendix
APPENDIX

SAMPLE ASSENT FORM

CHILDREN 7-12 YEARS OF AGE

Module 6

Title: Longitudinal Epidemiologic Study to Gain Insight into HIV and AIDS in Children and Youth (LEGACY)

INTRODUCTION

This is an assent form. It gives you information about the study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to be in this study, you will be asked to sign this assent. Your parent or legal guardian must allow you to be in the study. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

We are asking you to be in a research study about kids, teens and young adults who have HIV infection. We want to learn more about how HIV is different in kids, teens and young adults. We want to learn more about how to prevent problems from HIV drugs. We want to learn more about the medicine they take and how it affects them. We also want to learn more about how to stop teens and young adults from getting HIV. This study will last at least 3 years. At the end of the first study cycle, we will ask you if you would like to stay in the study.

WHAT DO I HAVE TO DO TO BE IN THIS STUDY?

Your parent (or the person taking care of you) has given permission for you to be in this study. If both you and your parent (or the person taking care of you) agree for you to be in this study, we will copy facts from your chart each time you come to the clinic. The LEGACY abstractor will collect facts from the clinic. The facts will be about your hospital visits, other doctor visits, or telephone calls about your health. We will copy facts about:

- Your birthday, your race, and your sex.
- What your doctor or nurse wrote about your visit to the clinic or hospital.
- Your blood tests.
- Your urine tests.
- Any other tests your doctor asked for.
- Patient care notes in other parts of the hospital or clinic like hospitalization records, social work notes, etc.
- If you agree to be in this study, you don't have to do anything else after you sign. You do not have to come for extra clinic visits. We will also ask you to let us draw some extra blood during a regular blood draw. The blood would be drawn up to one time
every twelve months. Later in the study, we might ask you to be in a sub-study about HIV. Special tests or visits might be done in the new study to look at the medicines’ side effects. We will ask you again if you want to be in that study. Nothing will be done unless you and your parent (or the person who takes care of you) agrees.

CAN YOU SAY “NO”?
You and your parent (or the person taking care of you) do not have to be in this study if you do not want to be. Your doctor will still take care of you in the same way whether you are in the study or not, or if you decide to quit later.

WILL THIS STUDY HURT?
It will not hurt to be in this study.

HOW MAY THIS STUDY HELP YOU?
You may not be helped directly by this study, but you may be able to help us find out ways to help keep other children or young adults with HIV infection healthy.

WILL MY FACTS BE KEPT PRIVATE?
Your records in this study are strictly private. No one other than study staff can ever look at them unless you agree to it. This is so because this study has been given a Certificate of Confidentiality. This means anything you tell us will not have to be given out to anyone, even if a court orders us to do so, unless you say it’s okay. Your name will not be in the LEGACY database with the facts from your medical chart. Only a code number will be attached to the facts."

If you have any questions about your rights as a human subject, you may contact:

- Director, Institutional Review Board
  (973) 972-3608
- Or
- Chair, Institutional Review Board
  (973) 972-3608

If at any time you feel that you have been harmed by being in the LEGACY study:

- Arry Dieudonne, MD
  Department of Pediatrics
  (973) 972-5066
**Signature Page:**

I have been told about the study. I agree to be in this study.

<table>
<thead>
<tr>
<th>Child’s Name</th>
<th>Child’s Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Type or print)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Staff Conducting</th>
<th>Study Staff Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Discussion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(print)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Witness Name</th>
<th>Witnesses Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Type or print)</td>
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</tbody>
</table>

**Investigator’s Affidavit:**

I have explained the purpose of this study to the volunteer. To the best of my knowledge, s/he is aware of the purpose, procedures, risks and benefits of this study.

<table>
<thead>
<tr>
<th>Investigator’s Name</th>
<th>Investigator’s Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Type or print)</td>
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</table>