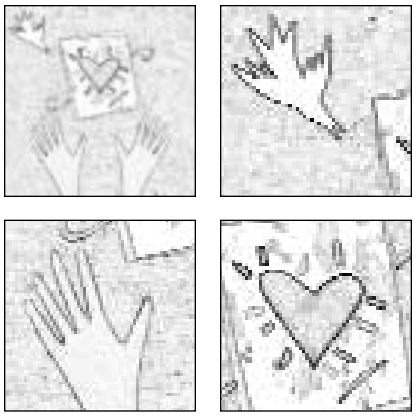
Canadian HIV
Trials Network

A Primer

for Members of Community Advisory Boards in HIV/AIDS Clinical Trials



Dedication

This publication would not have been possible without the knowledge and experience of the people sitting on the Canadian HIV Trials Network's Community Advisory Committee (CAC) between 1995 and 1997.

In particular, the leadership and commitment of Maggie Atkinson, Committee Chair from 1993 – 1997, provided the life blood of the project from beginning to end. While Maggie has since left the committee to pursue other avenues of HIV treatment advocacy, she remains committed to enlarging the number of HIV positive people who can meaningfully participate in planning and improving HIV/AIDS research.

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Introduction & History

Who is this manual for?

This manual is for anyone who wants to serve on an HIV/AIDS clinical trials community advisory board and who needs to know more about the clinical trials process and the ethical considerations involved in clinical trials. This manual may also be of benefit to community-based treatment information providers who wish to help clients understand specific informed consent forms.

What will I learn?

This manual concentrates on the core information about clinical trials you need to be a productive and valued member of an advisory board. However, effectively reviewing a clinical trial requires more knowledge than we can summarize in this manual. In addition to understanding ethical issues, basic terminology, and the informed consent process, committee members must eventually understand a scientific protocol (plan for the research study) and learn to evaluate the results of previous trials upon which the research plan is based.

This manual will walk you through the first of these parts: ethics, clinical trial terminology, and the informed consent process. A future project of the Canadian HIV Trials Network is to develop more advanced materials to walk a new committee member through a full trial protocol and to help him or her critically evaluate the conclusions reached by the trial's results.

The manual is divided into four chapters, followed by appendices:

Chapter 1 briefly describes the concept of ethics, the history of research involving human participants, and some basic ethical principles to consider when reviewing informed consent forms. It also provides information regarding the history and role of community advisory boards in the clinical trials process.

Chapter 2 provides an overview of HIV clinical trials. This chapter describes: a protocol, the four phases of a trial, different trial types, potential benefits and risks for trial participants, participant rights, and other information specific to HIV clinical trials.

Chapter 3 focuses on the informed consent process. This chapter defines informed consent, and includes a comprehensive list of the elements of an informed consent form, as well as questions you should ask when reviewing such a form.

Chapter 4 is a hands-on practice section where you can practice what you have learned in this manual.

Appendices include: a resource list of HIV/AIDS organizations; a list of literature relating to clinical trials and ethics; and a glossary of terms used in this manual.

Context of HIV/AIDS Community Advisory Boards

Before the community of people affected by HIV/AIDS organized themselves, there was very little active participation of study volunteers in the review of clinical trials either in Canada or the US.

Beginning in the late 1980's, people living with AIDS demanded more access to the decision making process regarding AIDS research. The scientific community responded to these demands by adding people living with AIDS to existing committees, and, in the case of the Canadian HIV Trials Network (CTN), adding another level of review by community-based reviewers. The CTN's Community Advisory Committee (CAC) was formed in 1993 to provide support and input for the community members sitting on the other CTN committees. By offering a broader, national perspective from an eight member committee, the community felt their input was more representative of the community at large.

Researchers and community activists now realize a study can benefit from community input...

Now, the HIV/AIDS scientific community has come to rely on this input to determine if trials may or may not be of interest to participants and if specific changes can be made to make the study more attractive to these participants. Researchers and community activists now realize a study can benefit from this input without risking our ability to determine the effectiveness of a new drug or drug regimen.

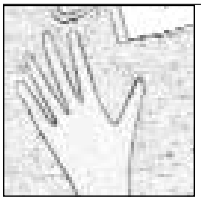
Now, many years after the CTN's Community Advisory Committee was formed, pharmaceutical companies regularly ask the community for their input into HIV clinical trials, as do other research bodies.

In general, community advisory boards exist to:

- ensure the proposed research is of relevance and interest to the HIV/AIDS community;
- ensure the informed consent form clearly and accurately explains the protocol to potential volunteers;
- provide a forum for the discussion of clinical trials issues by community representatives;
- improve communications between community representatives and researchers; and
- improve the flow of clinical trial-related information to community groups.

Representation and Community Advisory Board Members

The membership of an organization's Community Advisory Board should represent the interests of people who might participate in clinical trials. For example, HIV research is of interest to a wide range of HIV-positive people, including people from different parts of the country, people representing different risk groups (i.e. women, hemophiliacs, gay men, native peoples, IV drug users, etc), people representing different language groups, and people from a variety of backgrounds in terms of their education and experiences. In general, a scientific background is not required to join a community advisory board. A keen interest in treatment, a passion for human rights and an eye for detail are the only pre-requisites. This manual, along with practical, on-the-job experience should make any community member eligible to serve on such a board. A connection to and familiarity with a community group or collective will help you bring a broader perspective to the table, although not all boards would require such affiliations.



Chapter 1: Human Experimentation & Ethics

Ethics

What is the field of ethics?

"Ethics" is the study of real life issues that require the application of moral principles to specific cases. The role of the ethicist is to find solutions to problems that most reasonable human beings would commonly agree upon in a specific cultural setting and in a specific time period. Biomedical ethics, or bioethics, deals with moral issues that arise in the practice of medicine.

The beginnings of biomedical ethics

Ethical protection for participants in human research exists today as a result of past abuses. In 1947, the Nuremberg Code established ethical guidelines for biomedical research in response to the terrible experiments carried out by Nazi doctors on concentration camp prisoners during World War II. The Nuremberg Code emphasized that research is risky, and that research participants must be protected from coercion and harm.

The most important guideline to come out of the Nuremberg Code is that all scientific research involving humans requires the consent of research participants. Consent is a legal and ethical requirement based on the ethical

principle of autonomy, the participant's right to make decisions about his or her own medical care - without being forced or pressured to participate.

Concepts: The Nuremberg Code

To qualify as ethical, consent must be:

1. Voluntary — the participant must make the decision to participate freely, without force, pressure or manipulation.
2. Informed — the participant must be provided with all available information regarding risks and benefits, including available alternative treatments.
3. Comprehensible — the participant must clearly understand the information provided, and be capable of making a knowledgeable decision.

Process: Declaration of Helsinki

After Nuremberg, many other safeguards were put in place to protect human research participants. In its 1964 Declaration of Helsinki, the World Medical Association stated that experimental procedures involving humans should be clearly explained in a research protocol, a plan that describes in detail what the researcher is studying and how he or she intends to conduct the study.

They also recommended that this protocol be given to an independent committee or research ethics board, to review from an ethical perspective. These boards are based at the local level (i.e. each hospital participating in trials) as local conditions will influence what is considered ethical.

Principles: Belmont Report

In 1979, the Belmont Report, written by the National Commission on Protection of Human Subjects of Biomedical and Behavioral Research,

suggested using three ethical principles to protect the rights and well-being of research participants: beneficence, respect for persons, and justice.

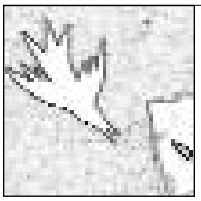
1. Beneficence — Participants should be treated in a way that respects their decisions and looks out for their well-being.
2. Respect for persons — Participants should be treated as individuals who are capable of making their own decisions without force or outside influence. Participants who are incapable of making decisions for themselves are entitled to have someone authorized to make decisions on their behalf. Confidentiality is a vital aspect of the "respect for person" principle. Participants have a right to privacy, as well as a right to control their personal information.
3. Justice — Researchers should divide the benefits and risks of the research equally among participants. No single group or individual should take on more or less of any risk or benefit.

All scientific research involving humans requires the consent of research participants...

The Medical Research Council of Canada recently released their own code of conduct which added the concept of "non-maleficence" to the above three. This flip-side of "beneficence" was added to emphasize that ethical research forbids torture, genocide, and the exploitation of vulnerable groups (e.g. prisoners, children).

These concepts, processes, and principles provide the basic codes and tools available to you when evaluating a protocol. We will examine these and other issues in greater detail later in Chapter 3.

Notes



Chapter 2: Clinical Trials — An Overview

The Basics

What are clinical trials?

A clinical trial is a carefully controlled scientific study used to determine the benefits and risks of a new drug or treatment for a particular disease. Researchers conduct clinical trials to test the safety and effectiveness of new drugs and to understand how much of the drug must be taken and how often.

What is a clinical trial protocol?

Every clinical trial begins with a protocol. A protocol is the written plan of a trial, a researcher's description of why and how the study will be conducted. A protocol outlines:

- who is eligible to take part in the trial
- how the treatment will be given
- the schedule for tests and procedures
- the number of required visits
- dosage amounts of the treatment
- the length of the study
- how the results will be determined

This protocol ensures that, if more than one place is conducting the trial, the exact same procedures are followed by each. By standardizing the procedures, researchers can pool the results from the different sites together, knowing the experiment was conducted the same way in every place.

How is a protocol developed?

A protocol can be initiated by a group of doctors, researchers or representatives of a drug company, or it may be community-initiated. In Canada, clinical trials are usually sponsored (designed and paid for) by a company that has developed a new drug.

The sponsor or trial initiator appoints a principal investigator, the researcher who supervises the trial — usually a doctor with experience running clinical trials. If a trial takes place at several locations across the country, the sponsor or initiator must appoint a site investigator — again, usually a doctor — for each trial site. Each site also needs its own Research Ethics Board to approve the protocol before the study can begin.

Due to issues of confidentiality within the drug industry, members of community advisory boards are often not given the entire protocol. Rather they are given a comprehensive summary of the protocol along with the informed consent form. However, protocols generated by researchers with non-industry funding are usually given in their entirety to a community board.

The four phases of a clinical trial

To get government approval to conduct a clinical trial involving humans, a drug company must show all the information they have obtained on the

experimental drug in previous studies, and demonstrate that the drug is safe enough to be tested in people. The company must also submit a protocol to the Health Protection Branch (HPB) of Health Canada. If the HPB approves the protocol, researchers can begin clinical trials. Once approved, a clinical trial usually goes through four phases, although in HIV/AIDS research, some of the following phases are sometimes combined to speed up the process:

Phase I
Researchers test the drug in a small number of people (people with or without the disease in question) to see if it is safe enough to test more intensively. Researchers give different participants different doses to pinpoint the largest safe dose. Phase I trials are riskier than later phases because little is known of the drug's effects. Phase I trials are short, usually two or three months, or less.

Phase II
If a drug is found to be safe enough in Phase I and is approved by the Bureau of Human Prescription Drugs, a Phase II trial can begin. Researchers test the drug in a larger number of people who are living with the disease over a longer period of time to determine the most effective dose, if the drug has any longterm side effects, and if it is working. If researchers find that the drug is not working against the disease at this point, no more trials will take place. Phase II trials normally last from a few months to a few years.

Phase III
If the drug seems to work in Phase II, researchers test the treatment in a much larger group of people over several months or years to see if it is effec-

tive and has any side effects that only show up after a longer period of time. Researchers also compare the new treatment with standard treatments that are already in use. If a drug is successful in Phase III, it may be approved for widespread use. In HIV/AIDS, Phase II and Phase III are often combined in one protocol, with a stepped process.

Phase	Duration	# of Participants	Questions asked about drug
I	2 – 3 months or less	small group	• what is the maximum safe dose? • is it safe enough to test in more people?
II	several months to several years	larger group	• what is most effective dose? • does it work? • are there any side effects?
III	several months to several years	much larger group	• how well does it work long term? • are there any longterm side effects? • is it better than current treatments?
IV	years	drug approved, in widespread use	• are there side effects that only show up years later?

Figure 1: The four phases of clinical trials

Phase IV

Once approved, researchers continue to watch for any side effects or problems that may show up after several years of treatment.

Inclusion/Exclusion Criteria

Most clinical trials restrict entry into the trial to people who meet certain criteria. These criteria are set for two reasons:

1) to ensure that people who may be most likely harmed by potential side effects are excluded from the study;
2) to ensure that volunteers are of similar health status, are taking similar medications outside the study, and in general, reduce the variables that might confuse the results.

Most inclusion/exclusion criteria in HIV/AIDS trials include a particular CD4 and/or viral load range, the presence or absence of a certain illness, the use or absence of certain other drugs, and so on.

Monitoring clinical trials

The Bureau of Human Prescription Drugs must approve a drug in each phase before researchers can move to the next stage of testing. Once researchers have finished testing a drug and it appears to be both safe and effective, the drug company applies to the Health Protection Branch (HPB) for formal approval to promote or sell the drug. The company must provide all the results from the clinical trials. Based on this scientific evidence, the HPB decides whether to allow sale of the new drug.

Just because the federal government approves a new drug does not necessarily mean it is effective or safe for all people at all times. Approval only means that a drug has proven useful in a majority of people and that its known side effects are not considered dangerous.

Stopping a trial early

In the protocol, researchers usually estimate how long the trial will last, anywhere from a few weeks to several years. In many large clinical trials, a group of independent researchers and lay people form a committee called the safety committee. This committee checks regularly on the results of the trial while it is taking place. If they find that one group of patients is doing much better than another group, they can recommend that the trial be stopped earlier than planned so the better treatment can be offered to all participants. They can also recommend that a trial be stopped if one group of trial participants develops serious side effects.

Types of trials

Researchers use a number of terms to describe the general characteristics of a clinical trial. Trials rarely fall into just one of the categories listed below. For instance, you usually won't hear a trial described simply as a comparison trial, whereas it is quite common for a trial to be a controlled, randomized, blinded comparison trial. These terms are defined and discussed below:

Randomized

Researchers randomly divide participants into two or more test groups (like flipping a coin) to prevent bias and give all participants an equal chance of receiving the experimental drug or treatment.

Controlled, comparison

All clinical trials require specific rules to be followed by both researchers and participants to ensure clear and accurate results. These rules include having

an experimental group (with the experimental drug) and a "control" group against which to compare the new drug.

The most common type of clinical trial is a comparison trial, in which researchers compare a new drug with an existing drug to find out which is more effective and/or safer. There are three different types of comparison trials.

Types of comparison trials

1. *New vs. standard treatment*
   One group of participants gets the new treatment, while the other group gets the standard treatment already in use. Researchers then compare the two groups to see which treatment works best.
2. *New + standard treatment vs. standard treatment alone*
   Researchers investigate whether adding a new drug to a commonly-used treatment is more effective than the standard treatment alone.
3. *Different-dose comparison*
   Researchers compare different doses of a drug to see which works most effectively and has the fewest side effects.

Blinded

Single-blind trials are those in which researchers know which treatments participants are getting but the participants do not.

In *double-blind* trials, neither researchers nor participants know who is getting the experimental drug and who is getting the standard treatment.

The purpose of blinding is to make sure that biases do not affect the results of the trial. For example, if a researcher knows which participants are receiving a particular treatment, it may influence the way the researcher views those participants. Without blinding, researcher expectations may affect the outcome of the trial. If a trial is not blinded, it is often because one treatment causes obvious side-effects (such as having a strong taste or turning urine a bright colour).

Clinical trials in HIV infection

What treatments do current HIV/AIDS clinical trials test?

Researchers are conducting clinical trials of HIV treatments that fall into seven categories:

1. Antiretrovirals — drugs that fight HIV at different stages of its lifecycle in order to stop or delay damage to the immune system
2. Immunomodulators or immunostimulators — drugs used to try to improve and strengthen the immune system
3. Prophylaxis — treatments that prevent or delay the onset of various HIV-related opportunistic infections, such as thrush or PCP (Pneumocystis carinii pneumonia)
4. Drugs that treat the various HIV-related opportunistic infections after they have already occurred, such as MAC (*Mycobacterium avium* complex)
5. Drugs that treat cancers, such as Kaposi's sarcoma
6. Vaccines that could prevent or cure HIV infection
7. Gene therapies in which researchers try to find a gene that may be immune to the HIV virus

How do researchers evaluate results?

Often researchers evaluate drugs based on hard clinical evidence such as whether they cure an infection, or whether the volunteers in one group live longer than the volunteers in the other group. However, to speed up the process, researchers sometimes evaluate the effects of HIV drugs using a disease marker – often called a surrogate marker. A surrogate marker is a substitute measure used to predict the eventual effect of a treatment when no other direct measure is immediately available or feasible.

A surrogate marker is a substitute measure used to predict the eventual effect of a treatment...

A common surrogate marker used in HIV research is the *CD4 count*, (sometimes called a T-Helper count) a blood test that measures the white blood cells that regulate the immune system. A low or dropping CD4 count is a sign of progressing HIV disease. However, researchers are recognizing the limited usefulness of CD4 counts as a surrogate marker because counts fluctuate throughout the day and the tests to measure CD4 counts are not always reliable.

Viral load, a more reliable measure, is beginning to replace CD4 counts as a surrogate marker. Viral load measures the amount of virus in the blood. A very low or undetectable viral load indicates that HIV is contained or controlled within the body. A rising or high viral load (more than 10,000 copies) indicates that the treatment may not be working.

These measures are often used in the trial's entry criteria to ensure the volunteers are of similar health status.

Notes

Chapter 3: Volunteer Rights & Informed Consent

Informed consent basics

What is informed consent?

Informed consent is a process during which all the benefits, risks and requirements of a trial are clearly explained to a prospective participant so he or she can make an informed decision about whether to participate in the trial.

Importance of informed consent

From the participants' perspective, the informed consent form is the most important part of a protocol because it helps to protect their rights. Participants in clinical trials should not confuse treatment with participation in a clinical trial. In a treatment setting, the doctor's main goal is to look after the interests of the patient. In the clinical trials setting, the researcher's priority is to gain new knowledge about the experimental therapy, although within a carefully controlled environment to minimize any risks to the individual.

When is consent informed?

Consent is considered informed when a participant:

- has all the information needed to make a decision about enrolling in a trial;
- fully understands this information; and
- agrees to participate in the trial based on this knowledge

Participants should be made aware that informed consent is an ongoing process and does not end after they sign the informed consent form...

Once the requirements of informed consent are met, and if the participant meets the inclusion criteria for the trial, they will be asked to sign an informed consent form before being enrolled in the trial.

As part of the informed consent process, participants are usually given an information package that outlines the:

- reasons for doing the trial;
- drugs involved;
- potential risks, discomforts and side effects of these drugs;
- number of visits the participants will be expected to make to the trial site; and
- types of tests that will be performed.

Participants should be made aware that informed consent is an ongoing process and does not end after they sign the informed consent form. Researchers have a responsibility to give participants any new information about the drug or the trial as it arises.

Participants should also be aware that even after they sign an informed consent form, they can change their minds at any time and leave the trial whenever they want for any reason.

Participant rights

Clinical trials participants have certain rights that you should keep in mind when reviewing protocols and informed consent forms.

Participants have the right to be:

- informed of the nature and purpose of the experiment
- given an explanation of the procedures that are to be followed in the medical treatment, and of any drug that is to be used
- informed of any discomforts and risks that can reasonably be expected
- informed of any benefits that can reasonably be expected
- informed that benefits are neither promised nor guaranteed
- informed of any appropriate alternative drugs or therapies that may be advantageous, as well as the risks and benefits associated with these alternatives
- informed of any available medical treatment in case medical complications arise
- given an opportunity to ask questions regarding the study or any of the procedures involved
- provided with a 24-hour emergency contact name and number
- informed that consent to participate can be withdrawn at any time without negatively affecting other treatment options
- provided with a copy of the signed and dated consent form
- given the opportunity to decide to consent or not to consent without intervention, coercion or undue influence

During the review process, board members should ask for clarification on any issues that aren't clear so as to best represent the interests of trial participants.

Potential benefits and risks of participating in clinical trials

Part of being informed means understanding the risks and benefits of human experimentation. HIV/AIDS clinical trials involve both potential benefits, or positive aspects, for participants, and risks, or negative aspects. While each trial may be different, these are a few general risks and benefits that must be understood by potential research volunteers:

Benefits/positives

- getting access to new drugs and treatments before they are widely available; being one of the first to benefit if an experimental drug or treatment proves to be effective;
- receiving the benefits of specialized care and regular health monitoring that are a part of the clinical trial process (remember, providing health care is rarely the primary purpose of the clinical trial);
- participating in a process in which new treatments are developed and medical knowledge is advanced to help others living with the disease; and
- experiencing a sense of empowerment over one's situation by taking action and participating in clinical trials.

Risks/negatives

- having no guarantee of a personal benefit from the trial;
- experiencing potentially dangerous side effects; some longterm side effects are not immediately apparent in the early stages of a trial;

- having to stop taking other medications that are working well because they conflict with the requirements of the trial;
- not being eligible for other trials of the same or similar drugs;
- not knowing if you are receiving the experimental drug or standard treatment (in a randomized study);
- having to make changes in lifestyle, such as taking medication at very regular intervals or not eating certain foods; and
- possibly having to make frequent and lengthy visits to clinical sites for checkups and testing.

Elements of a typical informed consent form

Because no process is perfect, informed consent forms must be carefully reviewed by an independent committee, such as a research ethics board and sometimes a community advisory board. As a community board member, you should check to make sure the form is written in plain language so that participants can easily understand all that is required of them before they sign the form. The goal of an informed consent form is to give the participants information, not to persuade them to give consent.

An ethically acceptable informed consent form should include the following elements or sections. Forms can vary slightly, so the elements may not appear in the same order as listed below, and some elements may appear under different headings.

Introduction

This section usually states the name of the trial, what kind of trial it is, what is being studied and who is doing the research.

Study purpose/background

Researchers explain why they believe the research is important, or what they hope the study will accomplish. For example, they may hope to learn if a certain combination of drugs can reduce the viral load of a particular group.

This section may identify the investigation drugs and include background information on the study. It may also include an evaluation of the safety and effectiveness of the proposed research. Researchers should clarify that the research is experimental and that there are no guarantees of benefits.

Inclusion/exclusion criteria

This section outlines the conditions that potential participants must meet to take part in the study (inclusion criteria) and the conditions by which potential participants will be disqualified. For example, an HIV clinical trial may require participants to have a CD4 count within a specific range. Many trials do not allow pregnant women to join.

Length

Researchers should specify the length (duration) of the study, as well as the time commitment expected of participants. A trial may last two days or several years. Participants may have to make only a few short visits to the trial site, or they may have to make frequent, lengthy visits.

Description of procedures

This section describes the procedures that must be followed by participants if they are accepted into the study. Experimental procedures should be clearly identified. The description may outline the:

- frequency and duration of visits
- amount of blood to be drawn (shown in teaspoons)
- types and dosages of medication to be taken
- form of treatment, i.e., injection, pill, liquid

Description of risks

Because no process is perfect, informed consent forms must be carefully reviewed by an independent committee...

This section should describe any known or expected risks or discomforts to the participants, based on information presented in the protocol and previous research studies of the treatment(s) being tested. It may also include a section that pertains to women who may become pregnant during the course of the trial. A sentence should state the specific risk for pregnant women. If the risk is unknown, this should be stated.

Potential drug interactions

This section may appear under Description of Risks, and should include a list of any known side effects that could result from potentially dangerous drug interactions, including over-the-counter medications. For example: "Certain antihistamines such as [give names], when combined with Drug A, can have serious side effects such as [list effects]." If any previous studies revealed side effects, researchers should disclose the percentages of participants who had such reactions. Make sure that the level of detail provided in the protocol is appropriately transcribed onto the informed consent form.

As a reviewer, if you are not familiar with a particular drug, you should ask what the risk is for allergic reactions, side effects and drug interactions. If the drug is unknown and one of the aims of the protocol is to determine its safety, you should check to see if the protocol includes adequate strategies to monitor adverse side effects.

Description of potential benefits

This section should describe any potential benefits for participants or others that may reasonably be expected from the research. These benefits should be clear but not overstated. The following examples are overstated, in other words, coercive:

"Drug A may be helpful in treating HIV disease and may make you feel better."

"You will receive drug A free of charge as long as you are part of the program."

Researchers should also include a sentence that states that no benefits are guaranteed because the research is experimental. The consent form should not include explicit or implicit claims of effectiveness that will bias participants, nor should it include overly optimistic representations, as these can be misleading. If no direct benefit is anticipated, this should be stated.

Disclosure of alternative sources of treatment

Researchers must disclose alternative procedures or sources of treatment that might be of use to participants. This section should not only list other procedures or treatments, it should explain any advantages or disadvantages associated with the alternatives. For example: "Another AIDS treatment is zidovudine, a

drug that fights HIV. Zidovudine, commonly known as AZT, has been approved by the government for use in HIV disease." There should also be a sentence advising participants that they will be told about any other treatments that become available during the course of the study.

Participation in concurrent studies

An optional section, this states that participants should not take part in any other research study without approval from the researchers. It is included to protect participants from possible injury arising due to extra blood drawing, extra x-rays or interaction of research drugs. Participating in other research studies may confuse research results, making the data collected on participants difficult or impossible to evaluate. However, participating in other researchers studies is often an exclusion criteria confirmed at the outset of a trial.

Confidentiality

This section should describe the extent, if any, of the confidentiality (privacy) of records that identify participants. For example, a sentence may state that any data published in scientific journals will not reveal the identity of participants, or that all information collected during the course of the study will be confidential.If government officials from the HPB or FDA (US government) may review the files, this should be stated.

Compensation in case of injury

In research involving more than minimal risk, there should be a description of whether any compensation or medical treatment is available if injury occurs during the course of the trial and, if so, where further information can be obtained. There may also be a section that clarifies whether the

participants' family will be compensated if he or she dies or becomes disabled as a result of participating in the trial. If no compensation is offered, this should be stated.

Patient withdrawal

This section should state that participation in the study is voluntary, and that participants are free to leave the study at any time without any penalty. For example: "You may leave the study at any time with no effect on your future treatment."

Leaving the study early

This section should outline the health consequences of a participant's decision to leave a trial, as well as the procedures involved in leaving a study early. Although it is inappropriate to prescribe a treatment regime after a participant has withdrawn from a study, there may be instances where sudden withdrawal may have harmful effects on the participant's health. In these cases, the informed consent form should clearly explain the details and necessity of any special withdrawal procedures that are required for the participant's safety.

Circumstances under which patients may be asked to leave a trial

This section may state the circumstances under which participants may be asked to leave a trial. Participants should be clearly told that if they fail to follow the instructions given to them by the researcher, they may be asked to leave. For example, participants may be asked to withdraw from the trial if they miss three visits to the trial site in a row.

Contact persons

A standard section on most forms, this provides participants with the name and number of a study coordinator they can contact if they have any questions regarding the trial. Restricting questions during the research undermines the validity of informed consent; the inclusion of this section is usually a good indication that researchers are trying to keep participants informed. The name and number of a 24-hour emergency contact must also be included in this section.

The Contact Persons section may also include the name and number of a person that participants can contact to ask questions about their rights. To avoid conflicts of interest, the contact should not be connected to the research study in any other way.

Disclosure of findings and availability of drugs after the study

This section should explain to participants that researchers will inform them about any new findings regarding the effects of the drug as they arise. This section may also specify whether participants will find out the results of the trial after the study is completed.

As a reviewer, you should check to see if there is anything that states whether any arrangements have been made for participants to receive the experimental drug after the trial has ended, and whether they will have to pay for the drug. Some trial sponsors have not allowed study participants to continue to take the experimental therapy after the trial has ended, even if the drug appeared to be helpful. On the other hand, some sponsors allow participants to continue taking the drug if it appears to be helpful, even if the trial as a whole is a failure.

Signature and copy of informed consent

This is the "bottom line" where the participant signs the informed consent form. Signing the form means that the participant has read and understood the information, and has decided to participate based on the information provided. It should be clear within this section that the consent form is not a contract and the participant does not give up any rights by signing it. A sentence should restate the fact that the participant can leave the study at any time. Researchers should give a copy of the signed informed consent form to participants.

Reviewing informed consent forms — questions to ask

This section discusses some general issues that you should consider when reviewing an informed consent form to ensure that it is written in a way that sufficiently respects the rights of the participants. These general issues, in addition to the specifics outlined above should provide the bases for a comprehensive review.

Invitational phrasing

Does the form use words and phrases that may give participants the impression that taking part in the clinical trial will mean guaranteed benefits and no risks? Until clinical trials have been conducted, there is no scientific proof as to whether the new treatment being tested will be more effective than currently available treatments. In fact, it is possible that the new treatment will be ineffective or do more harm than good. Informed consent forms should avoid invitational phrasing such as the word "invite" because it conveys the impression of an exclusive opportunity from which participants will benefit.

READABILITY

Is the form easily understandable to the average person? Researchers are sometimes under the mistaken impression that because they can understand a consent form and the accompanying information about a study, prospective participants will also understand it. This is not always the case; studies have shown that information about research studies is often written well above participants' educational level. Informed consent forms should be written in plain, clear language. Eighth-grade English (the Canadian average) is appropriate. Technical and scientific words must be adequately explained and common terms substituted for complex scientific terms whenever possible. For example, instead of using the term "hepatic" researchers can use the phrase "relating to the liver."

Informed consent forms should be written in plain, clear language. Eighth-grade English (the Canadian average) is appropriate.

Informed consent forms must also be written in a language that is understandable to the participant or his or her representative. It is unethical to enroll a participant who may not understand the information provided due to a language barrier. When a study population includes non-English speaking people, researchers must provide translated copies of the informed consent form. If the interview is conducted in English, consent should also be in English. If it is conducted in another language, consent must also be in that language.

Those who speak and understand English, but do not read and write it, can enroll in a study by "making their mark" on the consent document. An impartial person should witness the explanation of the study to the participant.

Discriminatory inclusion/exclusion criteria

Are any of the inclusion or exclusion criteria discriminatory? Individuals cannot be excluded from a trial because of race, religion, ethnicity, national origin, sex, age, sexual orientation, disability, other medical condition (such as hemophilia) or history of drug use (without reasonable explanation).

Some forms of discrimination are obvious, such as trials that explicitly exclude women, but subtler forms also exist. For example, some women may not be able to participate in a study due to domestic or child-rearing responsibilities. As a reviewer you may want to find out whether the trial provides day care or travel cost subsidies. Or, the protocol may exclude people whom the investigators perceive to be "unreliable" such as drug users. Instead, the protocol should indicate how many appointments can be missed before someone is involuntarily withdrawn from the study.

Conflict of interest

Are conflicts of interest evident in the form? As a clinician, the physician has only the best interests of the patient in mind. However, as a researcher, the physician is primarily interested in studying the effectiveness of an experimental drug or treatment, and may lose sight of the participants' needs. Is a third party (someone other than the investigator) available to discuss the trial with the participant?

Overstatement of benefits

Does the form contain any unjustifiable assurances or claims of effectiveness, implicit or explicit, that may make participants overly optimistic? Researchers

should not overstate potential benefits associated with participating in a clinical trial. Even the statement "results are fairly positive" is questionable if it cannot be proven.

You should advise participants to be skeptical about a clinical trial that claims to have no possible risks, as this is rarely true of any treatment, much less an experimental one.

As reviewer, you can ask that participants be provided with written information outlining all the known information about the experimental drug that they can take home to read at their leisure.

Paternalism

Does the form use condescending language? Words or phrases that imply that the researcher knows better than the participant what is in the participant's best interests are inappropriate. Researchers should not treat participants as if they are children who do not understand the nature of their illness or the treatment options available.

Insulting language

Does the form use alarmist or judgmental language? For example, using the term "devastating" when discussing the results of an experiment could be viewed as alarmist and insulting to the reader. An example of judgmental language is using the term "intravenous drug abuser" rather than the more neutral "intravenous drug user."

Alternative sources of treatment

Does the form mention alternative sources of treatment? Participants considering enrolling in a clinical trial as a way of obtaining a new drug should make sure they are not missing out on other, improved treatments in order to take part in a trial whose benefits are unclear. Participants need to know that joining a clinical trial is not the only way to gain access to experimental drugs or treatments.

Researchers are ethically required to mention other ways of getting these drugs or treatments. Two alternative sources of treatment are: compassionate access or open label trials; and the Emergency Drug Release Program (EDRP).

Compassionate access or open label programs

Is the experimental drug or treatment available through a compassionate access or open label program? A drug company sponsoring a clinical trial may also release a limited amount of the experimental drug through one of these programs. Such programs allow participants to use experimental drugs but, unlike clinical trials, data is usually not collected and the experimental drug is not tested against a standard therapy.

Compassionate access or open label programs are usually limited to people who do not meet the normal entry requirements or who do not wish to participate in a trial. However, participants may still have to meet certain requirements, such as having a CD4 count below a certain level or a viral load above a certain level.

Emergency drug release program (EDRP)

Is the experimental drug or treatment available through the EDRP? The Directorate of Health Canada runs the EDRP to make unapproved drugs (including clinical trial drugs) available on an individual emergency basis for people with life-threatening diseases. To receive a drug listed in the EDRP, a PWA must have his/her doctor contact the Bureau of Human Prescription Drugs of Canada.

Just because a drug is listed in the EDRP does not mean it is safe. As the name says, the EDRP is an emergency program. Drug companies are not required to provide experimental drugs through the EDRP, and may charge a fee for the drug, or even its full future retail cost. The requests are reviewed on an individual basis although EDRP procedures are currently under review and new policies may be developed.

Unnecessary burden/cost to participants

Are participants responsible for any trial expenses such as drugs or lab tests? Normally, provincial health insurance and the drug manufacturer cover the costs of drugs and lab tests; it is illegal to sell a drug that has not been approved by the Health Protection Branch.

Does the trial cover any other expenses? It is unethical to offer payment incentives for clinical trials in Canada, but some trials will cover child care costs or transportation.

Notes

Chapter 4: Exercise — Sample Consent Form

This chapter is a hands-on opportunity to practice what you have learned in this manual. In this chapter, you can review an informed consent form taken from an actual combination therapy protocol, and then check your work against the original community review of that protocol.

You will find a checklist after the sample consent form, that you can use for your own review. The original community review, performed by the CTN's Community Advisory Committee, is at the end of the chapter.

- **Sample Informed Consent Form**
- **Checklist**
- **Sample Review**

Notes

Notes

Checklist for Reviewing Informed Consent Forms

General questions

- ❑ 1) Does the form use plain language (Grade 8 equivalent) through out in the original or in any translated version?
- ❑ 2) Is the type of language respectful and appropriate (e.g. referring to participants or volunteers, not subjects)?
- ❑ 3) Are all acronyms explained and used consistently?
- ❑ 4) Because the form may have been adapted from a US study, does it refer to Canadian issues and institutions instead of American ones?
- ❑ 5) Are all drugs involved in the trial referred to by both generic and brand names when first mentioned?

Specific items to look for

Overview of study

- ❑ 6) Is it clearly stated that the study involves experimental research?

- ❑ 7) Does it state the study's purpose, rationale and design in plain language?
- ❑ 8) Are the study's inclusion/exclusion criteria clearly explained?
- ❑ 9) Are any of the inclusion/exclusion criteria arbitrary or discriminatory (e.g. specifying a certain age without justification)?
- ❑ 10) Are the various arms of the study fully discussed, including the use of placebo (if applicable)?
- ❑ 11) Is the probability of assignment to each group stated? Is the total number of volunteers being sought included?
- ❑ 12) If the study is double-blinded, are the procedures for double-blinding explained, including procedures for breaking the double-blind?
- ❑ 13) Does it state in plain language the route of administration of the drugs? (e.g. by mouth, by shot or pills and needles etc.)
- ❑ 14) Is it explained that the trial will be monitored by a data safety monitoring board that could stop the study if deemed necessary?
- ❑ 15) Does the form explain who is responsible for costs related to travel and childcare?

Procedures to be followed by volunteers

- ❑ 16) Does it state the volunteer's expected duration of participation in the study?
- ❑ 17) Does it clearly state the frequency of physician visits and the duration of the visits to be made by volunteer?
- ❑ 18) Does it clearly state when and how the study medication must be taken?
- ❑ 19) Does it state if and how adherence to the protocol will be assessed and does it provide a justification for this assessment (e.g. pill counts, interviews, etc.)?
- ❑ 20) Does it give a brief description of the procedures to be performed to monitor the volunteer during the study (e.g. x-rays, blood tests etc.) and the frequency of these procedures? If blood is to be drawn, does it indicate how much (in milliliters and tablespoons)?

Overview of study drugs

- ❑ 21) Does it clearly state which drugs, treatments or delivery techniques are experimental?

- ❑ 22) Does it clearly and fully explain the risks and side effects (including percentage frequency) of all drugs and tests in the study? Does it state that some side effects may not yet be known?

- ❑ 23) Does it state that volunteers will be advised of new information about the study drugs as it becomes available?

- ❑ 24) If applicable, does it clearly explain how and why future treatment options may be compromised by participation in the study (e.g. resistance to other drugs in the same class)?

- ❑ 25) Are drug interactions (including alcohol, over-the-counter medications and street drugs) fully explained?

- ❑ 26) Are issues related to diet and the study drugs clearly explained (e.g. drinking water to prevent kidney stones or eating certain foods at certain times to encourage absorption)?

- ❑ 27) Is it indicated whether the volunteer will continue to receive any or all study drug(s) free-of-charge after withdrawing from the study or after the study is concluded? If so, does it say for how long (e.g. 90 days or until on provincial formularies)?

Alternatives to study participation

- ❑ 28) Is it clearly stated that the decision to participate in the study is completely voluntary and that the volunteer can withdraw at anytime without consequences to his/her healthcare?

- ❑ 29) Does the form clearly state what treatment alternatives exist outside of participation in this trial?

- ❑ 30) Is it stated that participation in this trial may adversely impact a person's eligibility for future trials?

Rights of volunteer

- ❑ 31) In the section called "Benefits" or "Risks and Benefits", does it avoid claims about the experimental treatment that can't be supported (e.g. may shrink tumours or may reduce viral load below detectable levels)?

- ❑ 32) Is it clearly stated whether information collected during this study will remain confidential? Does it indicate which agencies may access this information (e.g. the pharmaceutical company, the HPB, the FDA etc.)? Does it indicate whether a name or just a number will be linked to the information?

- ❑ 33) Does it state if compensation for study-related injury will be provided by the institution, company or insurer?

- ❑ 34) Are the names and phone numbers of (1) a physician and (2) a contact for the ethical review board provided?

- ❑ 35) Does it state the specific circumstances under which the volunteer may be withdrawn from the study without their consent (e.g. missed appointments, non-adherence to protocol, changing health status etc.)?

- ❑ 36) Does it state that significant new findings relating to treatment options will be discussed with the volunteer?

- ❑ 37) Does it state that the volunteer should feel free to ask for clarification or new information at any time during the study?

- ❑ 38) Will viral load and other surrogate markers be made available in real time to study participants?

- ❑ 39) Does it state when the trial results are expected and how they will be communicated to the volunteer?

- ❑ 40) Is it indicated that the volunteer will receive his/her own copy of this form to take away?

- ❑ 41) Does it state that signing this form does not waive the volunteer's legal rights or release the investigators, sponsors, or involved institutions from their legal and professional responsibilities?

Birth control issues

- ❑ 42) Are women of child bearing potential fairly warned of the risk of pregnancy without being unnecessarily forced to use certain forms of birth control?

- ❑ 43) Are women of child bearing potential provided with options in deciding whether to participate in the study?

- ❑ 44) If specific forms of birth control or pregnancy tests are required, does it provide a clear rationale as to why?

- ❑ 45) Are volunteers warned if the experimental drug's effect on sperm is unknown?

Issues for follow-up with study sponsor

- ❑ 46) Is the study drug available through expanded or compassionate release to all Canadians living with HIV?

- ❑ 47) Can volunteers continue to receive the drug if they are withdrawn from the study or when the study is over? For how long? (at least 90 days, or preferably until they are on provincial formularies)

- ❑ 48) Will viral load and other surrogate markers be made available in real time to study participants?

- ❑ 49) Are daycare and travel costs paid for by the study sponsor?

Sample community review

Keep in mind when you look at the points listed below that your review does not have to match the original community review point for point. This is not a math test; there are no absolutes. Political and medical issues change as time passes, and a point that reviewers felt was particularly important or unacceptable then may not be as relevant now. However, you may find this sample review a useful introduction to the actual review process.

Requirements and Recommendations of Community Advisory Committee

CTN 113: A Phase III Randomized Double-blind, Multicentre Study to Evaluate the Safety and Efficacy of 3TC/ZDV/1592U89 and 3TC/ZDV/IND in HIV-1 Infection Antiretroviral Therapy Naive Subjects

This protocol was approved by the Community Advisory Committee with the following required and recommended changes.

Required Modifications to the Informed Consent

1. The section "Duration of Study" on P.1 be simplified to reduce the use of terms such as "randomized, blinded study therapy" and be inserted after "The Study" section and before "Clinic Visits and Procedures" on page 3.

2. On page 2 the chart be corrected to show 200 mg for each capsule of IDV.

3. That on page 2, the first sentence of the last paragraph, the instructions for taking IDV or the IDV placebo be corrected to "you must take this drug on an empty

stomach, either 1 hour before or 2 hours after a meal."

4. That the reason for drinking water with the drug be indicated (kidney stones).

5. Change the sentence "if you become pregnant during the study you would have to discontinue the study medication" to "if you become pregnant during the study you must withdraw. However, you can access other antiretrovirals through your Provincial Drug Program".

6. That the section "Interactions with concurrent medications" be expanded to include cautions about interactions of specific over the counter, street, and prescription drugs, including brand and common names where applicable. Volunteers should be encouraged to contact CATIE for more information on the interaction of street drugs (such as ecstasy).

7. That the percentages associated with side effects be included in the informed consent.

Recommended Modifications to the Informed Consent

1. That the informed consent form on page 3 require only women who are heterosexually active be required to have pregnancy tests and that reference be made to the effect of IDV on the efficacy of birth control pills.

2. That the term "caution" when drinking alcohol be more fully explained (p. 4).

3. That the first paragraph on page 6 be deleted.

4. That the last sentence in the 2nd paragraph on p. 6 not use the term “subjects”.

5. That the benefits section be amended to indicate that you may not benefit and could even worsen your condition.

6. That the first paragraph “compensation” be removed as it does not apply to Canada and that the compensation issue be removed from the page.

7. That the first paragraph under “statement of subject rights” be updated to indicate that Indinavir is available by prescription in Canada.

8. That on page 5 re: blood drawing that tsp or tbsp equivalents be added.

9. That the term “Doctor” in this section be amended to read “Study Doctor”.

10. That ZDV be replaced by AZT and that the term Crixivan also be used with IDV/Indinavir throughout the form.

11. That if travel and daycare expenses are not covered, participants be informed they would be responsible for them.

12. That the reason for concern about resistance be specified and that a warning be included about restrictions of participation in future studies.

The committee commended the checklist/questionnaire at the end of the consent form on page 8 and felt it would be a useful addition to any such form.
November 1, 1997

Appendix I: HIV/AIDS Treatment Information

The Canadian HIV Trials Network (CTN) is a federally-funded organization mandated to develop treatments, vaccines and a cure for HIV disease and AIDS through the conduct of scientifically sound, ethical clinical trials. The CTN publish a regular newsletter as well as a continuously updated list of HIV/AIDS clinical trials in Canada. It operates a toll-free information line at 1-800-661-4664 and a website on clinical trials: www.hivnet.ubc.ca/ctn.html

The Canadian AIDS Treatment Information Exchange (CATIE) provides information on HIV/AIDS treatments, clinical trials, and related issues. You can contact their Treatment Information Network toll-free at 1-800-263-1638 and their website at www.catie.ca.

Many local community groups have superb treatment projects that are available as a resource to HIV positive people. Please enquire at your local group to find out what information and/or counselling is available.

The following national organizations and programs provide information on treatments and clinical trials:

Canadian HIV Trials Network

620-1081 Burrard Street
Vancouver, BC
V6Z 1Y6
Tel 1-800-661-4661 (locally 806-8327)
ctn@hivnet.ubc.ca
www.hivnet.ubc.ca/ctn.html

Canadian AIDS Treatment Information Exchange (CATIE)

The Network
555-505 Richmond Street West, Box 1104
Toronto, ON
M5V 3B1
Tel 1-800-263-1638 or 416-203-7122
info@catie.ca
www.catie.ca

Community Research Initiative of Toronto (CRIT)

617-2 Carlton Street
Toronto, ON
M5B 1J3
Tel (416) 408-1041

Special Access Programme

Therapeutic Products Programme
Finance Building 2nd Floor
Tunney's Pasture, A.L. 0202C1
Ottawa, ON
K1A 1B9
Tel (613) 941-210 8 or(613) 941-3061 (after hours)
EDR_Drugs-BPA@hc-sc.gc.ca

Canadian HIV/ AIDS Clearinghouse

1565 Carling Avenue
Suite 400
Ottawa, ON
K1Z 8R1
Tel (613) 725-3434 or 1-877-999-7740
Fax (613) 725-1205
aidssida@cpha.ca
www.clearinghouse.cpha.ca

Notes

Appendix II: Related Literature

This appendix is a resource that you can use to look for further information regarding clinical trials and research ethics.

Entries are organized alphabetically, by author or by organization. If the publication is a book or article with a credited author, the entry will begin with the author(s) name, followed by the title of the piece and, in the case of articles, the journal or magazine in which it appeared. Entries for publications with no author begin with the organization that published the piece. Wherever possible, publication information is included. This is a sampling only. It by no means attempts to list the huge volume of information available on these subjects.

AIDS Action NOW!. *Confronting the HIV Research Crisis: Treatment Activists' Perceptions of the Canadian AIDS Research Effort.*

AIDS Treatment Data Network. *Should I Join an AIDS Drug Trial?.*

AIDS Treatment Data Network. *Editorial: Time to End the Death Trials.*

AIDS Vancouver. *Contact: An AIDS Resource Guide For BC.*

American Foundation for AIDS Research: *AmFAR Treatment Directory*

Canadian HIV Trials Network and the Canadian AIDS Society. *Clinical Trials: What You Need To Know*.

Claessens, M.T., Bernat, J.L., Baron, J.A. "Ethical Issues in Clinical Trials" *British Journal Of Urology* 1995, 76. 29 – 36.

Community AIDS Treatment Information Exchange. *HIV-Related Clinical Trials.*

Etchells et al. "Bioethics For Clinicians 1." *Consent in Canadian Medical Association Journal* July 15, 1996, 177 – 180.

"Issues in Biomedical Ethics." *Disease-a-Month* December 1993, Vol. 39 (12). 878 – 885.

James, J.S. "Comment: Workable Clinical Trials For AIDS, 'Confirmatory' Trials: What's Wrong, and How to Move Forward Today" *AIDS Treatment News* August 4, 1995.

Levine, C.L., MA, Neveloff Dubler, N., LLB, and Levine, R.J., MD. "Building a New Consensus: Ethical Principles and Policies for Clinical Research on HIV/AIDS," *AIDS Patient Care* Vol. 6(2) April 1992, 67 – 85.

Lo, Bernard. "HIV/AIDS Ethics and Policy Updates" *Journal of the American Medical Association*.

Loue, Sana, J.D., PhD. *Legal and Ethical Aspects of HIV-Related Research*, 1995.

NAM, UK. *HIV and AIDS Treatment Directory*

Roy, David, Williams, John R., Dickens, Bernard M. *Bioethics in Canada*. Scarborough: Prentice-Hall Canada Inc., 1994.

Sutherland, H.J., Meslin, E.M., Till, J.E. "What's Missing from Current Clinical Trial Guidelines? A Framework for Integrating Science, Ethics, and the Community Context" *The Journal Of Clinical Ethics* Vol. 5, Number 4, 297 – 303.

Tannsjo, Torbjorn. "The Morality of Clinical Research — A Case Study." *The Journal of Medicine and Philosophy* Vol. 19, No. 1, 1994.

Notes

Appendix III: Glossary

ADVERSE EVENT
In a clinical trial, an unwanted effect detected in participants. The term is applied whether or not the effect can be attributed to the treatment under study.

ADVERSE REACTION
See side effects

ARM
A group of participants in a clinical trial, all of whom receive the same treatment or placebo.

ASYMPTOMATIC
Without symptoms. In AIDS literature, a person who tests positive for HIV antibodies, but who shows no clinical symptoms of the disease.

BASELINE
1) Information gathered at the beginning of a study from which variations found in the study are measured. 2) A known value or quantity against which an unknown is compared when measured or assessed.

BLINDED STUDY

A clinical trial in which participants do not know if they are in the experimental group (receiving the experimental drug) or the control group (receiving the standard treatment) of the study. See also: double-blind study and single-blind study.

CD4+ CELLS

Usually referred to simply as CD4 cells, these are the preferred target of the HIV virus. CD4 cells are white blood cells that normally orchestrate the immune response by signaling other cells in the immune system to perform their special functions. The destruction of CD4 cells is the major cause of the immunodeficiency observed in AIDS. Also called a t-helper cell.

CLINICAL TRIAL

An investigational study of the effects of a drug or treatment in human subjects. Researchers attempt to determine the drug or treatment's efficacy (its effectiveness) and, in the case of a drug, its pharmacological effects — toxicity, side effects, incompatibility (possible conflicts with other drugs), and interactions (ability to work better when combined with other drugs).

COMMUNITY ADVISORY BOARD

An independent committee that reviews and makes recommendations regarding the informed consent section of a clinical trial protocol. CABs exist primarily to inject a community perspective into the clinical trials process, and to improve communication between researchers and community representatives.

COMPARISON TRIAL
A study in which an experimental drug or treatment is tested against a drug or treatment already in use.

COMPASSIONATE ACCESS OR OPEN LABEL PROGRAM
A clinical trial arm in which unlicensed experimental drugs are provided to very sick patients who cannot or do not wish to participate in the trial, or who have no other treatment options. Most programs are restricted (e.g., participants must have a CD4 count below a specified amount or be intolerant to standard treatments), and are often granted on a case-by-case basis by the Food and Drug Administration.

CONCOMITANT MEDICATIONS
Drugs that are taken together. Certain concomitant medications can have adverse (harmful) reactions.

CONTROLLED TRIAL
A clinical trial in which an experimental drug is compared against another experimental drug or a standard treatment. Participants are usually blinded, i.e., they do not know which treatment they are receiving.

CROSSOVER TRIAL
A clinical trial in which all participants receive both treatments, but at different times. Halfway through the study, one group is switched from the experimental treatment to the control treatment (standard treatment), and the other group is switched from the control to the experimental treatment.

DOSE
The measured amount of a drug to be taken at one time.

DOUBLE-BLIND STUDY
A clinical trial in which neither researchers nor participants know which participants are receiving the experimental treatment and which are receiving the standard treatment. Blinding prevents biases that may affect study results.

EFFICACY
How well a drug or treatment works, i.e., how effective it is.

ENDPOINT
An event used by clinical trial researchers to evaluate whether a therapy is working. For example, developing AIDS or a low CD4 count may be the endpoint of a trial for people who had no previous symptoms.

EXPANDED ACCESS
A general term for methods of distributing experimental drugs to patients who are unable to participate in ongoing clinical trials and have no other treatment options.

EXPERIMENTAL AGENT
A substance (drug) being studied in a clinical trial.

Food and Drug Administration (FDA)

The main US Public Health Service agency responsible for ensuring the safety and efficacy of drugs and medical devices used in the diagnosis, treatment and prevention of HIV infection, AIDS and AIDS-related opportunistic infections.

inclusion/exclusion criteria

The reasons why a person may or may not be allowed to enter a trial. For example, some trials only include people with a lowered CD4 cell count, while others exclude people who have already developed a specific infection. Most trials do not allow pregnant women to join.

informed consent

A process in which the risks, benefits and requirements of a trial are explained to potential participants so they can decide whether they want to enroll in the study. Before enrolling in a trial, a participant should sign an informed consent form that contains, in writing, the risks, potential benefits and basic structure of the trial.

investigational new drug (IND)

The status of an experimental drug after the Food and Drug Administration agrees that it can be tested in people.

open label

A clinical trial in which researchers and participants know who is receiving the experimental drug.

PLACEBO

An inactive substance against which and experimental drug is compared. A placebo can be either a pill or liquid that looks and tastes like the drug for which it is being substituted.

PROTOCOL

The detailed plan for a clinical trial that states the trial's rationale, purpose, drug dosages, length of treatment, how the drug is given, who may participate (inclusion/exclusion criteria), criteria for determining the trial's success or failure, and the methods of data analysis and interpretation. Research Ethics Boards and the Health Protection Branch must approve the protocol before a clinical trial can begin.

RANDOMIZED TRIAL

A study in which a computer randomly assigns participants to receive either the experimental treatment or the standard treatment. This ensures that other factors that might affect how people respond to treatment are equally distributed in the control and test groups.

RESEARCH ETHICS BOARD (REB)

An independent committee established to protect the rights and interests of clinical trials participants. REBs are sometimes called Institutional Review Boards (IRBs), Ethics Review Boards or just Ethics Boards. Every institution or hospital that conducts human research must have its own REB.

SCREENING

The process whereby potential volunteers are assessed as to whether or not they meet the entry criteria of the trial. Screening generally precedes enrollment into the trial.

SIDE EFFECTS

Resulting actions or effects of a drug that are other than that desired. Usually refers to undesirable or negative effects. Experimental drugs must be evaluated for both immediate and longterm side effects.

SURROGATE MARKERS

A surrogate is a substitute. If something under study is not readily measurable because it takes a long time to show up, researchers may use a surrogate marker to predict the eventual measurement. Surrogate markers in HIV research are important because the effectiveness of drugs in slowing down HIV disease progression or increasing survival may not be obvious for many years. HIV surrogate markers measure CD4 counts and viral load.

THERAPY

Any treatment or drug intended to relieve or cure a disease or illness.

TOXICITY

The extent or ways in which a drug is poisonous to the body.

TREATMENT

A form of therapy, often a drug, used to relieve or cure an illness or disease.

TREATMENT ARM
See arm.

VIRAL LOAD
Also called *viral burden*. The amount of HIV virus in the blood. The higher the viral load, the sicker the person may be.