Research Fundamentals for Activists

CREATE

Consortium to Respond Effectively to the AIDS TB Epidemic

In collaboration with:

TAG

Treatment Action Group

Research Fundamentals for Activists

The goal of the *Research Fundamentals* booklet is to build the research literacy of activists, so they can engage in evidence-based advocacy with:

- an increased understanding of research concepts, processes and results;
- an awareness of the value of research; and
- the ability to use research data to address and inform advocacy priorities.

This booklet is meant to help increase your capacity and comfort with using scientific evidence in informing, supporting and strengthening your activism. We hope to demystify scientific research, provide understandable explanations of some fundamental research concepts, and familiarize you with the language of research. The focus of this booklet is on critical thinking, so there are very few right or wrong answers.

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Please note that the views expressed by our advisory committee and medical editor are not necessarily those of their respective institutions or organizations.

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Module 1: Introduction to Research

Key Terms (see Glossary for definitions)

- **Community advisory board (CAB)**
- **Data**
- **Epidemic**
- **Hypothesis**
- **Qualitative**
- **Quantitative**
- **Study protocol**

1.1 What is research?

Simply put, research is the organized search for knowledge. To put a finer point on it, it is the systematic gathering and study of facts to increase knowledge, and test a theory or educated guess, also known as a **hypothesis**.

Research produces **data**. This is a collection of observations from which conclusions can be drawn. Data can be words, numbers or images which describe a phenomenon or experience or experiment. *Raw data* is the information gathered through an experiment or study, which is then analyzed using proven statistical methods (*more on the statistical methods in the Module 4*) to identify trends or patterns, and to draw conclusions. Once analyzed, data is called *evidence.* Evidence can be used to inform decision-making and/or may lead to more questions. Very few studies are definitive on their own. Therefore policy makers, activists, healthcare providers and patients should rely on strong evidence, drawn from a number of studies when making policy, program, and treatment decisions. The strength of evidence is often determined by the depth or consistency of findings across studies. In other words, do multiple well-designed studies support the recommendation?

1.2 Can anyone conduct research?

Yes! People see and experience things that prompt research all the time. Any time you are comparing one method or product to another, you are conducting research.

For instance, say a person is wondering whether they should drive to work or take the bus, and their main concern is cost. Their hypothesis (or untested, educated guess) may be if they take the bus rather than driving to work to work, then they will save money. To see if this hypothesis is correct, this person may drive their car to work for a week and then during the following week, take the bus to work. At the end of the two weeks they add up the costs associated with each method of transportation, and compare the results. This is a simple example of research.

1.3 Who is conducting scientifically rigorous medical research?

Academia (universities), industry (pharmaceutical companies) non-governmental organizations, public-private development partnerships (collaborations between industry and non-profits), and governments all conduct research. The types of research topics and the studies being conducted varies widely. Industry, foundations, and governments fund most research. Pharmaceutical companies use their profits to fund their own research efforts, while academia

may rely on grants from foundations and governments, and government research institutions use tax dollars to support their research. In fact, the U.S. Government is by far the largest funder of scientific research in the world, and provides resources to research efforts in the U.S. and abroad.

1.3 The difference between science, fiction, and everything else in between

Knowledge is in flux, and today's fiction may become tomorrow's fact. It was long believed that stomach ulcers were caused by excessive stomach acid, mainly due to stress levels. In the 1980's two scientists identified the *H. Pylori* bacterium as the actual cause of most cases. This discovery disproved a widely accepted belief and demonstrated that ulcers could be easily treated with antibiotics. Their hypothesis was met with a great deal of skepticism by the medical and scientific communities, but the strength of their evidence was able to overcome those doubts.

Individual and/or community experiences can be more powerful than the results of a scientifically rigorous trial, regardless of their scientific validity. When ethical scientific research aims to uncover the truth and provide information on how best to address an issue or problem, this may mean upholding a commonly held belief or disproving it.

It is important to remember that personal experiences differ from the objective collection of information. If someone brings up a personal belief that is not supported by scientific evidence but is powerful to him or her, do not dismiss it. Sometimes these beliefs are true and it is a mistake not to be open to this possibility. In the 1990s, some HIV-positive African Americans found that AZT, an anti-HIV medication, caused their skin color to change in spots, but this was often dismissed because it had not been seen during clinical trials. Prompted by these reports, further study showed that the skin discoloration was indeed being caused by the medication. This is but one of many examples where real world experience has led to research which upended the scientific wisdom of the day.

However, even if the belief is not true, and at times harmful, it is important to explore these beliefs. Researchers need to be aware of these beliefs when initiating studies in a community because people in a community may have different ideas about the value and ethics of research.

In the 1850's, there was cholera outbreak in the SoHo section of London. The general belief among the community, including most doctors, was it was caused by pollution or "dirty air", which they called 'miasmas'. However, a local physician named John Snow had his doubts and through careful and systematic interviews with local residents he made a link between a commonly used water pump and the cholera cases. Once he identified the pump as the source of the outbreak it was understood that contaminated water NOT dirty air was to blame. Once the pump was disabled the outbreak subsided. Dr. Snow's groundbreaking work in tracking and characterizing the cholera **epidemic** is considered a pivotal event in modern-day public health.

Interactive exercise:
What are ways to discuss community truths that are not supported by research findings?
What are some beliefs in your community that are considered to be "truths"?
How do they interfere with the health of the community?
How could a research study address the issue?
What questions(s) could research ask?

1.4 Community Advisory Boards

Some research studies will convene a **community advisory board** (also known as CABs) to provide recommendations and advice to study investigators. CABs may look different from study to study. They generally are made up of members of a community (people with the disease being studied, service providers, residents of a study location, etc) and are charged with representing the community's concerns and beliefs. A CAB may help develop culturally appropriate information and education materials or ensure that the **study protocol** does not conflict with community traditions or beliefs. A CAB might also provide meaningful feedback on study design and methods. CAB members often have

different perspectives and priorities from the researchers that can impact the success of the study. For example, CAB members may notice that there are an unrealistic number of lab visits, making it difficult for people with jobs and/or children to participate in the study. In this example, the researchers may be more focused on data collection methods and may overlook real life issues for study volunteers.

1.5 Differing research approaches: quantitative and qualitative

Quantitative research evaluates phenomena (such as presence of disease) or properties (e.g. response to treatment) in numerical values, or asks how much and/or how many. This type of research uses close-ended questions that are often answered with a yes or no, such as is medication X better than medication Y in curing malaria. Quantitative studies also use pre-determined values, such as immune cell counts or blood tests that verify presence of disease such as HIV antibody tests, to measure success.

Qualitative research explores and tries to understand beliefs, experiences, knowledge, attitudes, and behaviors, or may ask what, where, why and how. Qualitative studies often use more-open-ended questions, such as what are the barriers to getting tested for HIV. These questions may prompt a variety of responses that allow for varying interpretations from the researchers.

There are pros and cons for each of these methods. Depending on the question being asked, one approach may be chosen over the other, or both may be used. For example, a study evaluating the effectiveness of an anti-HIV medication may quantify the effect on HIV viral load, and also ask qualitative questions about study volunteers' experience taking the medication, such as its impact on quality of life. Regardless of the approach used, good research should provide useful answers to the study question.

Exercise 1.1: Ask the group to list some pros and cons of each method (see list below to help lead discussion…this is not an exhaustive list, and some qualities may hold true for both categories but are more often associated with one or the other)

Qualitative research

1. May be more subjective and open to interpretation
2. Researcher may not know what they are looking for in advance
3. Study design may emerge as study unfolds
4. Data is often narrative and may be difficult to quantify
5. Data content is richer but may be more time consuming to collect and less able to generalize
6. Danger of researcher not maintaining distance and becoming a part of the data
7. Most commonly used data collection methods are in-depth interviews, focus groups and participant observation.

Quantitative research

1. May be more precise because hypothesis can be tested
2. Researcher always knows in advance what question they are trying to answer
3. All aspects of the study are carefully designed before data collection
4. Collects categorical or numerical data
5. More efficient data collection but may miss contextual data
6. Use statistical models to explain what is being observed
7. Easier for researcher to maintain separation from participant(s), and perhaps objectivity

1.5 What is evidence-based advocacy?

Evidence-based advocacy uses research data to inform better policies, and to develop and implement programs. Scientific evidence is a powerful advocacy tool that HIV activists use very successfully to support their demands, build credibility, and get a seat at the table with policy makers and researchers. Early in the AIDS epidemic, activists in the United States realized that demonstrations and civil disobedience were only a few of the strategies they could use to get their voices heard and their needs met. Because HIV was devastating their communities, highly-motivated activists educated themselves and each other, and reached out to scientists to learn how research could provide a better understanding of HIV disease and how best to treat it. They also worked, sometimes contentiously, with academia, government and industry to influence the design of clinical trials and ensure that questions relevant to their communities were addressed. At times, activists had to demand research that addressed the priorities of their communities. For instance because gay men were the first to present with immune deficiency symptoms, much, if not all, of the early AIDS research largely ignored women-specific opportunistic infections. So in 1990, activists demanded that the National Institutes of Health,

the leading U.S. research institution, initiate a study to understand better how HIV progressed in women. Three years later, the first study tracking the natural history of HIV in women began.

Below is a brief timeline of how HIV activists used science to inform their advocacy agenda and how their work impacted the scientific response to HIV. These are only a few of the many achievements made by HIV activists and researchers. While this timeline focuses on activism from the U.S. and South Africa ends in the early 2000's, activists from all over the world continue to play a vital role in pushing for better research and its application across many diseases and conditions.

1.6 Some historical highlights from HIV activism

- 1985
  - First clinical trials of AZT (the first anti-HIV medication).
  - Project Inform is formed, a HIV treatment education organization run by and for HIV-positive people that provided information on HIV treatments and research efforts.
- 1987
  - ACT UP-New York, a grass roots activist organization that used science-based advocacy in its arsenal of tactics, is formed.
  - After calls by activists to speed up access to medications for people with HIV, the U.S. Food and Drug Administration (FDA) shortens drug approval process by two years.
  - Activists demand that AIDS Treatment Evaluation Units do more clinical trials of anti-HIV medications and expand the number of people with HIV included in these studies.
- 1988
  - FDA protest
- 1989
  - Based on the testimony of AIDS activists, the FDA Advisory Committee finally approves Gancycolvir (only treatment available for cytomegalovirus (CMV), a HIV-related opportunistic infection).
  - At the urging of activists, parallel track drug testing, in which drugs already found to be non-toxic are placed in both clinical trials and released simultaneously to patients who do not qualify for the trials, is launched. Activists included on the panel appointed to write procedural standards for parallel track.
- 1990
  - Activists demonstrate at the Centers for Disease Control (CDC) headquarters protesting the CDC's narrow definition of AIDS
  - The "Storm the NIH (National Institutes of Health)" protest calls for more AIDS treatments
  - ACT UP/NY's Treatment and Data Committee (which would eventually become Treatment Action Group) issues its 1990 Treatment Agenda which outlines the direction the AIDS research community should be taking in the coming year
  - The Treatment and Data Committee releases the "Countdown 18 Months Plan," a set of scientific procedures and demands designed to implement treatment and research for controlling the five most devastating opportunistic infections, at that time

- 1991
    - During the International AIDS Conference in Florence, Italy, scientists join activists in a march on the U.S. Consulate to protest the exclusion of HIV-positive persons from entry to the US
- 1992
    - The Treatment and Data Committee of ACT/NY breaks off to form Treatment Action Group, a science-based activist organization working towards a cure for HIV
- 1993
    - First study tracking the natural history of HIV in women is initiated (this demand was made to NIAID in 1990 by HIV activists)
- Development of protease inhibitors and non-nucleoside reverse transcriptase inhibitors
- Expanded access and accelerated approval
- Establishment of OAR
- Establishment of CPCRA also ACTG
- Formation of TAC
- Approval of ARVs in South Africa
- 2001
    - SMART study

1.7 Study and review questions

1. What are community advisory boards and how can they impact research from a community perspective?
2. Name one potential advantage and one potential disadvantage of quantitative research?
3. Name one potential advantage and one potential disadvantage of qualitative research?
4. Name an event in HIV research activism that has significance to the advocacy work that you are doing and explain its impact

Module 2: Ethics as part of the Research Process

Objectives
Upon completion of this module, activists will be able to:

- Understand key ethics principles relevant to human beings;
- Understand how these ethics principles apply to different aspects of design and implementation of research studies;
- Describe the features of a good informed consent process; and
- Participate in ensuring studies follow ethical principles

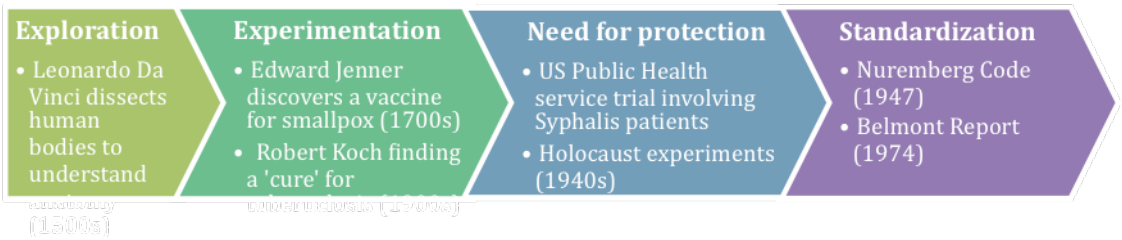
Key Terms

- **Ethical Principles**
- **Beneficence**
- **Respect**
- **Justice**
- **Nuremberg Code**
- **Belmont Report**
- **Institutional Review Board (IRB)**
- **Data and Safety Monitoring Board (DSMB)**
- **Informed Consent**
- **Incentives**
- **Placebo**
- **Adverse Events**

2.1 Introduction

Health research is conducted to improve people's health. Sometimes researchers are seeing whether a new drug works. Sometimes they're figuring out whether a new way to do health education works. In some research studies, the researchers already know a lot about the drug or the new program being tested. In other research studies, it is the first time that the drug is ever given to people, and researchers do not know much about whether the drug will work or how people will react to it. Because research always has **uncertainties,** research often involves risks. Sometimes these risks are large, sometimes they are small. Generally when people decide whether or not to join a new research study, they consider the **benefit-harm balance**. This balance helps potential volunteers decide whether the possible harms posed in the study outweigh the possible benefits of participating. For example, do the risks of this new antiretroviral outweigh the potential benefits of free antiretrovirals and quality medical care? Over time, **ethical principles** have been developed to guide researchers in ways to safeguard, as much as possible, the well-being of people who decide to join research. These ethical principles are meant to help make sure people considering whether to volunteer for a research study understand what will happen if they join, understand the risks and benefits of the research, know they can decide voluntarily whether or not to join, and to make sure they are treated as fairly as possible. It is important to note that these principles are *universal*, meaning that they apply to everyone regardless of skin color, gender, nationality, etc. The three principles you'll learn about in this module are **beneficence, respect for persons**, and **justice**[i].

2.2 Evolution of Ethics as Part of Research



Research for the sake of learning without the intent of applying that knowledge for benefit is unethical. Ideally all investigators should have the welfare of the research volunteers in mind as they are designing the study and implementing procedures. However, history has shown that standards are required in order to ensure these ideals. In order to understand the three principles mentioned above, a look at the history of research can help illustrate how attention to ethical principles became an integral part of the research process.

Basic, human curiosity led to study through experimentation and observation. During the 1500s, the Renaissance in Europe spurred scientific thought and exploration. One of the great scientists of that era, Leonardo Da Vinci, learned how the human body is constructed by dissecting cadavers and drawing what he observed. Later another scientist, Edward Jenner, discovered an inoculation for smallpox by observing a natural pattern of who was able to avoid disease, and experimenting based on his observations. Jenner isolated a protective pathogen from milkmaids, since they appeared to be immune to smallpox. He exposed a person to what he thought was a protective pathogen, before directly exposing them to smallpox. The research participant was protected from smallpox, though Jenner was lucky—smallpox can be a fatal disease, and it is doubtful that the research participant really understood the risks involved or even that they were in an experiment at all.

About 100 years after Jenner, Robert Koch isolated the bacteria that causes tuberculosis and attempted to come up with a way of stopping the disease. Koch came from a school of thought that believed that organisms caused disease before there was scientific evidence to prove it—and it was because of this belief that Koch dedicated his research to finding the organisms that cause disease in the body[ii]. His discovery of the bacteria *Mycobacterium tuberculosis*, and his subsequent experiments, led to a test that is still used today to determine if a person is infected with the bug that causes disease.

Definition of Ethical Principles

Beneficence *requires investigators to do no harm by ensuring the potential risks to a research volunteer not outweigh potential benefits to the individual.*

Respect for persons *says all research volunteers must be treated as free human beings with the right to choose whether or not to participate in the study—and be made aware of the risks involved. Informed consent is a vital tool in ensuring this principle is followed.*

Justice *requires investigators to choose study participants fairly and distribute risks equally*

For more information, visit the Family Health International Research Ethics Training Curriculum

Unfortunately, in some cases scientific experimentation has also involved horrific human exploitation. Evidence of unfair and harmful research practices done by the Nazi regime in Germany was uncovered at the end of World War II. When the world heard of these experiments, the United Nations responded with the **Nuremberg Code**[iii]**,** a document written in 1947 that set out 10 ethical points to be followed when conducting human research. Other events, which you'll read about below, led to the writing of the **Belmont Report** in 1979, which described the three ethical principles of **beneficence, respect for persons,** and **justice.**

The Belmont Report also describes how each of these principles applies to research. [iv] These principles should be incorporated at every point of the research process—from beginning to end.

Exercise 2.2

One of the most well-known violations of ethical principles in research was exposed in the 1970s when the truth of a United States Public Health Service syphilis study was revealed. As you read through the description of the study, think of how the investigators violated the principles of **beneficence, respect,** and **justice.**

The United States Public Health Service Syphilis Study at Tuskegee: In 1932, researchers from the US Public Health Service began an observational study that followed a group of 399 poor African American men with syphilis and 200 African-American men who did not have syphilis. The men were told that they were being treated for 'bad blood' (the name they used for syphilis), and they were never told that they were part of a research study. Since the men in the study were very poor, they were eager to be part of something that they thought was giving them free medical care. The researchers were actually trying to find out what happens when people have syphilis for a very long time, for years and years. This is called a 'natural history study', when researchers keep track of how a disease unfolds in people over time. The men were given free food, medical exams, and burial insurance while the researchers kept track of what was happening with their syphilis. . A decade into the trial, a cure for syphilis became available in the form of penicillin, but the participants were not informed that treatment was available. As a matter of fact, the researchers went to a lot of trouble to make sure the men in the study did *not* get treated so that the researchers could continue to study the progression of the disease without treatment. When left untreated, syphilis can cause serious harm to the body, including damage to the heart, brain, eyes, and bones, and can be fatal. Many of the study participants became disabled, or died because treatment was withheld. By the time the truth of this trial was uncovered in 1972; only 74 of the 399 men who started the study were still alive[v]; 20 died directly of syphilis, while 100 more died of complications due to the disease[vi][vii].

Exercise 2.2 Discussion Questions

- How were the ethical principles of **beneficence, respect**, and **justice** violated by the study investigators?
- What steps could the investigators have taken to ensure these ethical principles were followed?

2.3 Who is Responsible for Following Ethical Principles?

Many different people are involved in making a research project happen. The researchers conduct the study. Private funders or governments pay for the study. Outside ethics boards are required to review the study before it can be done. All of these groups have responsibility for making sure that ethical principles are followed. Study investigators must design and implement research in a way that minimizes harms and chooses study populations fairly, they must recruit volunteers in ways that are respectful and that make sure volunteers understand what the study involves and that they don't have to join it if they don't want to. Funders are responsible for making sure ethics procedures are followed and making sure investigators know that any violation in ethics rules could result in loss of support. Finally, all human research should be reviewed by an external ethics board. In the U.S., these are called **Institutional Review Board (IRB);** in other countries these are often called Research Ethics Committees. IRBs/RECs are responsible for reviewing planned research before it is conducted to make sure all procedures are consistent with the requirements of the three ethical principles. This group is responsible for ensuring 'the rights and welfare of humans participating as subjects in research'[viii]. The IRB approves study processes before the study starts, and keeps track of how the study is doing. Members of IRBs can be ethicists, investigators, and people who know the community in which the study will be conducted.

Another body of people, called the **Data and Safety Monitoring Board (DSMB),** may be responsible for monitoring the study data and safety of all research volunteers. All **adverse events**, which are any unwanted or unexpected medical events that happen to a research volunteer who is taking study medication[ix], must be reported to the DSMB and it is their duty to determine if the study is safe enough to continue as planned. If the DSMB feels that the study is unsafe, it can stop the study. The DSMB can also stop a trial if the intervention has proved to be beneficial, by determining that everyone participating in the trial be given the intervention being studied. Like IRBs, DSMBs should be independent from the researchers to guard against biases and conflicts of interest. See Module 3 for more information on study design.

Study staff should also be trained in *Good Clinical Practice Guidelines*, which were created by the International Conference on Harmonization as an 'international and ethical quality standard'[x] for

researchers who are involving volunteers in their studies. These guidelines help to ensure that staff does not violate any of the study participants' rights, and that the study participants' information is kept confidential. GCP guidelines also require researchers to record their data in very specific ways to maintain the quality of the research project. The whole point of doing research is to learn new things that will help prevent or treat illness or improve their health. If research is not done well, and if details in how data are recorded and kept are not followed carefully, then the research findings could be incorrect due to sloppiness. Finally, community members and public health activists can play a very important role in ensuring that ethical principles are followed. See exercises below and the 'Practicum' section for details.

2.4 Informed Consent

Informed Consent is a process through which researchers tell people interested in a research project what the study is about. The informed consent process tells people details like why the study is being done, why they specifically are being invited to join, what they will have to do if they join, what the possible risks and benefits are, and that joining is completely up to them. The informed consent process should both allow researchers to provide key information that most people would want to know about a research study and also allow potential volunteers the time to ask questions that they might have about the research.

Informed consent as a process can help to ensure that a person who has agreed to be part of a study really understands what he or she has agreed to do. It is not appropriate for another person to read through a document and ask someone else to sign the paper. People should be able to take the informed consent form home with them to review and discuss with others before deciding whether or not to participate in the trial. They should also have plenty of time to ask questions about the study before making their decision. It is important to make sure that the informed consent is a *process* and that the information described in the consent form can be revisited by the patient over the course of the study.

The components of a basic **Informed Consent** document or form include the following[xi]:

- Name of the study and study rationale
- Study Question
- Explanation of study processes
- Known and potential risks and adverse events
- Known and potential benefits for participating in the study
- Explanation of volunteering and what that means for the person participating (i.e. amount of study visits, duration of study, samples needed from the volunteer, and an explanation that no one has to continue to be part of a research study if they do not want to)
- Explanation of how study information will be used
- Description how the information obtained from study participants will be kept confidential

Is the use of an incentive ethical?

Imagine that a community where the average household income is $80 USD per month is chosen as a site for an HIV vaccine trial, and study participants are offered $2,000 for participating in the trial.

Does this incentive cause undue influence? Could it be considered coercive? Why or why not?

What is an appropriate relationship between compensation and risk/benefit ratio in the context of the community that the study is being conducted in?

What would be a fair incentive?

When is the use of a placebo ethical?

Imagine that a research trial is designed to look at a new drug to be added to treatment for HIV. The study provides one group of research volunteers, 3 standard drugs +1 placebo, and gives the other group 3 standard drugs + new drug.

In this case would it be ethical to use a placebo? Why or why not?

- Names and contact information for study investigators; sometimes information to contact the IRB can be included

The form which contains the above information should have the key information someone would need to make the best decision about their individual participation. However, a long and complicated consent form isn't the goal. If a form is too long or too difficult to read, a research volunteer may become intimidated. The goal of the informed consent form is to provide clear and concise information in an understandable way. Activists can help ensure that informed consent forms are clear and concise for the community members they represent.

There is an example of an informed consent form in the practicum section on page 46.

It is important to understand that community can play a key role in making sure that the information contained in the consent form is understandable and relevant to the research volunteers. Community Advisory Boards (CABs) or members of the IRB may find that there is too much emphasis on one component of the informed consent, and not enough on another. For example, a CAB member may find that the study process for a new drug is fully described in the informed consent—but essential information about what the study drug actually does to the body is missing, which would be central to a research volunteer's decision to participate. A CAB can also look for an appropriate informed consent form from the point of view of the research volunteer—such as making sure that it is the first language of the volunteer, that the reading and grammar level are understandable and not full of confusing terms, etc. If CAB members cannot all understand the form well, then it probably means that researchers will need to change it to make it clearer before trying to give it to actual participants.

Incentives are often offered as a way to compensate a study participant for his or her participation. The form of the compensation is determined by the study investigators, but must be approved by the IRB and is often documented as a 'benefit' on an informed consent form, or in a separate section called 'compensation'. The **IRB** and study staff have to carefully evaluate whether the **incentive** causes undue risk to or could be considered to be **coercive** to the participant or cause **undue influence**. In this context

coercive is a term that means that research volunteers feel that they must participate under threat of harm, while *undue influence* means that study volunteers are influenced to be part of something they would not normally do. There are other support mechanisms that some studies offer to enable research volunteers to be part of a trial, such as childcare for parents during their clinic visits, and standard transportation fees so that people can get to and from the study site.

Another potentially hot-button issue in drug trials is the use of a **placebo**, which indicates a harmless pill[1] is given to those who are randomized to be in the control group and not receive a study drug/intervention. A placebo is an important tool for scientists so that they can compare the study drug to standard of care. Module 3 explains the use of a placebo in experimental study designs.

Researchers look for safety and side effects, as well as efficacy (how well the intervention works). In experimental studies, if those involved in a study don't know if they were assigned to get the drug or vaccine in question, or if they are getting a placebo, then the study is called a blinded study. If the investigator is also unaware of who is getting intervention versus placebo, it is called double blinded. Blinding is done to decrease bias amongst the investigators as well as study volunteers. For example, if a large yellow study drug is tested against a small white sugar pill, some study participants might answer questions based on what pill they think they are getting, instead of reporting actual effects, and investigators may focus more on a particular group. It is unethical to use a placebo when a real treatment exists *if* using the placebo would cause serious and/or irreversible harm—for example, you could not test a new regimen for the treatment of HIV against a placebo, because effective treatment for HIV is already available. Instead, you could test the performance of a new regimen against a standard regimen. Research volunteers may not understand or believe that they are receiving a placebo, because it counters how doctors treat people. Extra care and creativity must be used to explain placebos. The **IRB** must approve proposed use of placebo.

In addition to the use of a placebo and incentives, **research imperialism** is an issue that has ethical implications for community members. Research imperialism is the performance of research in a population without the assurance that an intervention found to be effective in the study population will then be made available to that population. For example, if a new HIV drug is tested in Botswana, where HIV prevalence is high, does the study population have the assurance that the new HIV drug will be made available to community if it proves to be better than a standard ARV regimen?

2.5 How can communities participate in following ethical principles?

Activists can play a major part in ensuring that ethical principles are a part of research studies. A first step is to get to know how to evaluate whether the principles of **beneficence, respect for persons,** and **justice have been followed in research studies.** There are some simple questions to ask, including:

- ✓ Has this study been approved by an IRB?
- ✓ Does the study process seem fair?

[1] Placebos can come in other forms, such as a harmless solution that resembles a vaccine

- ✓ Do the risks outweigh the benefits for research volunteers?
- ✓ Are study participants informed about all available treatment options?
- ✓ Do research volunteers understand what the study is about?
- ✓ Do research volunteers understand the possible risks?

Activists can also play a key role in creating demand for an intervention to be continued after the study is over. For example, if a new antiretroviral that has been tested proves to be more effective than the standard of care, activists can demand for the drug to be continually supplied to the research volunteers even once the study has finished.

Exercise 2.5

Take a look at the following three study examples. All have been designed to answer the question of, "Is male circumcision an effective way to prevent HIV transmission?" Answer the questions below for each of the studies.

1. Is the study fairly distributing risks and benefits?
2. Were the people enrolled in the study fairly?
3. Is the incentive provided in the study appropriate for the population?
4. What parts of the study description are related to ethical principles?

Study A	Study A will take place in a rural area in South Africa among men between the ages of 20 - 45. Study participants are randomly divided in to two groups: one will have a routine health assessment, and the other will be offered a free surgery for circumcision. The study participants will be followed for a period of two years, with HIV testing offered every six months along with safe-sex education offered at every session. At the end of the study period, those who were in the group that were not offered circumcision will be offered free surgery if circumcision is proven beneficial. Study investigators will compare the rates of HIV infection in the circumcised and non-circumcised groups.
Study B	Study B will take place in rural South Africa among men between the ages of 12- 45. The young men will be offered free surgery for circumcision and $100 USD. The study participants will be followed for a period of two years. At the end of two years, the study investigators will compare the rates of HIV infection with provincial numbers.
Study C	Study C will take place in rural South Africa among young men between the ages of 12 – 45. Study participants will be chosen based on their age—the young men will be offered free circumcision, and the older men will be referred to a local health clinic. An incentive of $450 USD will be offered for the men to come back to get their blood drawn every six months—the results of the HIV test will not be shared with the men. At the end of the study, the investigators will describe the rates of HIV infection in the men who completed two years of follow-up.

2.6 Regulatory Bodies

A regulatory body is a government agency that regulates, or approves and monitors, biomedical products (e.g. medications or vaccines) and devices (e.g. blood pressure machines), and food. The mandate given to the agency may vary from country to country, as each has its own regulatory body, and there are regional bodies (such as the European Union's EMEA). Each agency has its own set of rules and guidelines. In the U.S., the Food and Drug Administration (FDA) "is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation[xii]."

Requirements for approval to market a new medication, treatment, or intervention vary from country to country. Therefore just because a medication has been approved for use in the U.S. does not mean that it is available in Brazil since approval by one regulatory authority does not guarantee approval by another. Therefore when designing a trial, an investigator should make sure that the study design meets the minimum safety and efficacy criteria of the regulatory authority where the study is being conducted.

For example, rifapentine, an anti-TB medication, is approved as part of the continuation phase of treatment of TB in HIV-negative persons in the U.S., but is not approved for use in any other part of the world. This means that in order to get rifapentine approved for use in other countries, the makers of rifapentine must initiate new studies according to their regulatory requirements. However, this does not mean that a drug must be studied in every country in the world to be approved for use in every country in the world. Often if there is enough good scientific evidence to support the use of the medication, then regulatory bodies will accept that and approve the medication. For instance, there is enough good evidence that isoniazid is an effective anti-TB medication that is approved for use in every country to treat TB.

2.7 Study and Review Questions

1. In your own words, describe the three ethical principles of beneficence, respect, and justice.
2. True or false: All studies must be reviewed by a Data and Safety Monitoring Board.
3. How would you describe a placebo?
4. Do you think that special populations, such as orphaned children, deserve extra protection when they are involved in research studies? Why? If so, how would you ensure this?

Module 3: The Study Design

Key Terms

- **Assignment**
- **Bias**
- **Blinding**
- **Case Report**
- **Cases**
- **Causal relationship**
- **Clinical research**
- **Control**
- **Endpoint**
- **Exclusion criteria**
- **Exposure**
- **Hypothesis**
- **Inclusion criteria**
- **Intervention**
- **Noise**
- **Operational research**
- **Preclinical research**
- **Prevalence**
- **Randomization**
- **Scientifically rigorous**
- **Study question**

3.1 Introduction A research study can –and should--only answer the question that is being asked, but it may yield some results that lead to more questions and/or more research. Some trials will include sub-studies to answer different questions, for instance a study evaluating the effectiveness of a medication in preventing the development of active TB disease among people with latent TB infection, may also include a sub-study looking at how well children absorb the medication. It is of utmost importance that researchers are asking questions that are important and they choose a study design that best answers that question (more on that in the following pages). The number and types of research questions are endless, and a study may not lead to a definitive answer but more questions. This does necessarily mean that the study was a failure. It may highlight the complexity of the problem and the need for further examination. Maybe the number of study volunteers was too small to provide a conclusive answer. Data collected for one study may help to provide answers to different study question. The MACS Cohort Study has been tracking the natural history of HIV since the 1980's, and has helped to answer many questions about how HIV was initially spread, but many of the blood samples used were initially collected as part of viral hepatitis study.

It is important to remember that research cannot answer every question and that some research is flawed. Sometimes the investigator does not pick the right population to study or the values used to measure the effectiveness of the experiment were not accurate. So it is best to be critical when considering the question a study is asking. Is the question

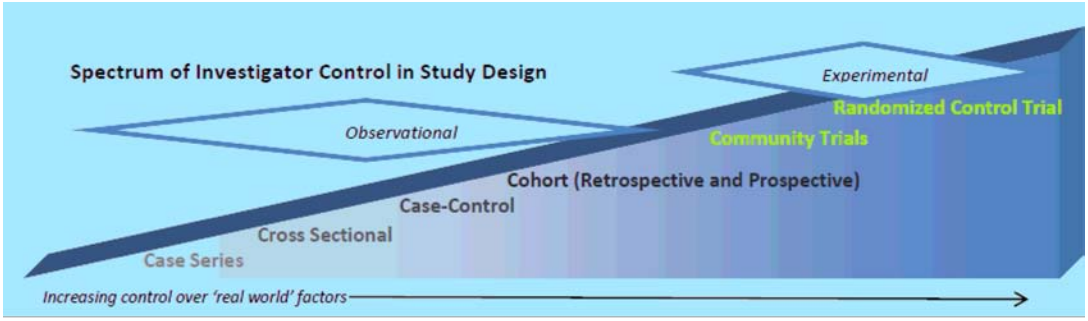
How do we measure success?

An **endpoint** is an outcome measure used in a research study to determine whether the hypothesis is true or not. Studies will often have a *primary endpoint* like cure or death or some biological marker that indicates disease progression or improvement like HIV viral load or termination of symptoms called **surrogate markers**. A study may also want to evaluate a *secondary endpoint* that can impact the primary endpoint such as side effects. Let's take the example from above comparing medication K and medication Z in curing TB, if medication K requires a study volunteer to take just as many pills as medication Z, and the length of treatment is exactly the same BUT medication K has fewer side effects, cure rates may be higher in this study group because more volunteers are able to complete their treatment. In this instance curing TB was not the only value being measured to determine success, fewer side effects was also a desired effect and contributed to achieving the primary endpoint of cure.

important? Has anyone asked the same question? Is this the best way to answer this question? What impact could the answer have on an issue? This last question may be particularly difficult to answer when the research is being conducted in test tubes, rather than in humans, and is therefore far way off from being applicable to the 'real world'.

Once the specific **study question** has been chosen, researchers set up experiments to test their **hypothesis**, hopefully in a way that will prove or disprove the theory. For example, a study may ask "*is medication K better in curing tuberculosis than medication Z?"* The hypothesis or theory to be tested is *"If a person takes medication K, then s/he is more likely to be cured of tuberculosis than a person taking medication Z."*

This module will take a look at how the question that is being asked guides the type of study design used, and the strengths and limitations of these different research methods



3.2 Study Designs

Study designs fall into two categories, observational and experimental. But rather than consider one or the other, it may be more useful to think of study designs as a spectrum of investigator control. One is not better than the other but rather, can elicit different types of information. As one moves along the spectrum of observational to experimental studies, the amount of control that the study investigator has over all factors that may affect the result of an experiment increases (how this is done will be explained in more detail when discussing specific study designs in the following pages).

Observational Studies

Observational study designs allow investigators to ask a question and choose a hypothesis without having to formulate an **intervention**. An intervention is the experimental medication, technique, strategy or device that is being evaluated in a research study is used in experimental studies, and is designed by researchers. However, in observational studies, investigators do not use an intervention. This means that the investigators are looking at what happens in real life without interfering. Many observational studies look at the relationship between disease and **exposure**. People who have disease are referred to as **cases,** and people without disease are referred to as **controls.** The **exposure** is determined by the study investigator as a factor that they want to explore in relationship to the disease. The factor of interest can be anything—exposure to smoking, exposure to HIV, exposure to a bacteria,

exposure to a new treatment, etc. For example, to look at the association between the development of tuberculosis (disease) and HIV infection (exposure) through observational study design, the investigators could look through medical records, and compare the histories of TB patients. Is the patient HIV positive? For how many years? How many of our TB patients are HIV positive, and how many are HIV negative (i.e. comparing the rates of HIV infection)? These are the types of questions that can be asked as part of an observational study. In contrast, an experimental study design might compare the effect of TB preventive therapy in HIV (+) and HIV (-) groups, and determine how development of TB differs based on HIV status.

The strengths of observational studies include the ability to observe natural patterns and draw conclusions on the associations between disease and exposure—and generally the effort required from study volunteers is less than the demands of an experimental trial. The weaknesses have to do with the lack of control over 'real world' factors, and the risk that the sample selected by study investigators may not accurately reflect the overall population. This is called **'bias'** and it is hard to fully account for bias in the study design and in the analysis of the results.

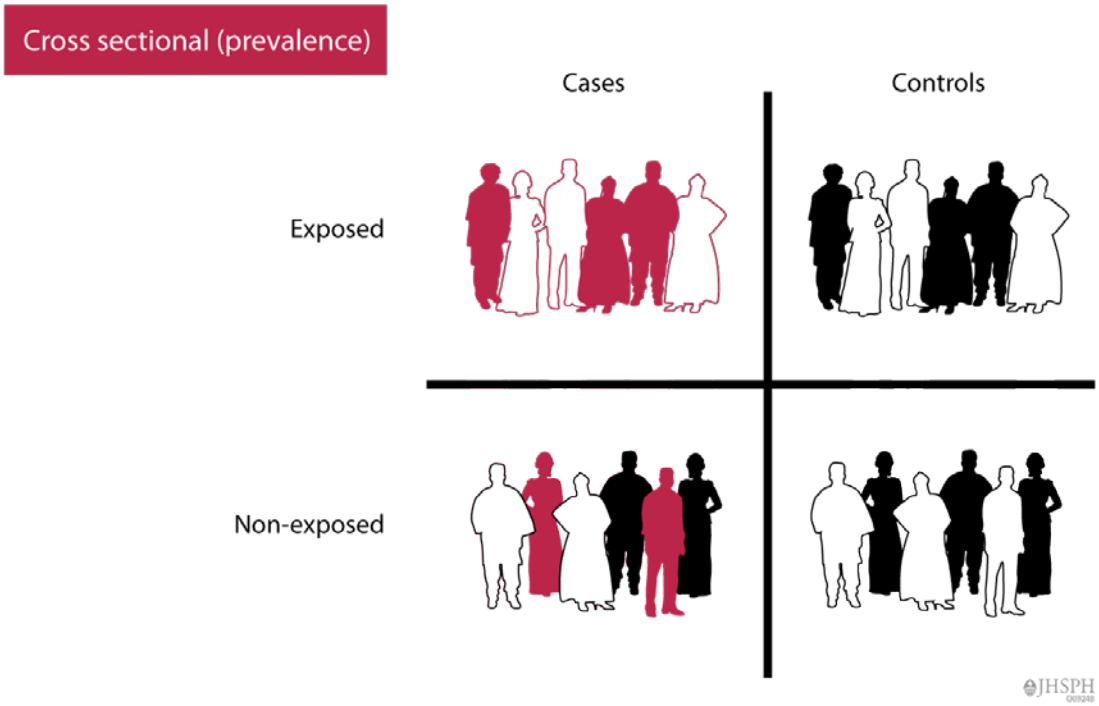
3.4 Study Designs

Described below are the different types of observational study designs.

The case report series is a very useful tool for describing diseases or medical manifestations that are rare or unknown. Case report series are often published in journals as a report on patients, and may lead to a better understanding of underlying causes and characteristics. For example, an investigator (often a physician) may observe an unusual skin presentation of a rare form of cancer in young homosexual men and write up a report on characteristics of the patients, what symptoms of disease are, and if any treatment has been successful. The data in case report series are taken from medical charts. However, the results cannot be extended beyond the patients that are described, and often call for further study. The importance of this type of study can be illustrated by a case report series that helped scientists to identify AIDS in the early 1980s. In 1981, before HIV was identified, the CDC reported an unusual presentation of Kaposi's sarcoma and *Pneumocystis* pneumonia among five men as a case-series, and around the same time eight patients ('cases') with a rare form of cancer were described in the *Lancet* in[xiii],[xiv]. These articles helped to focus attention on young men suffering from rare forms of

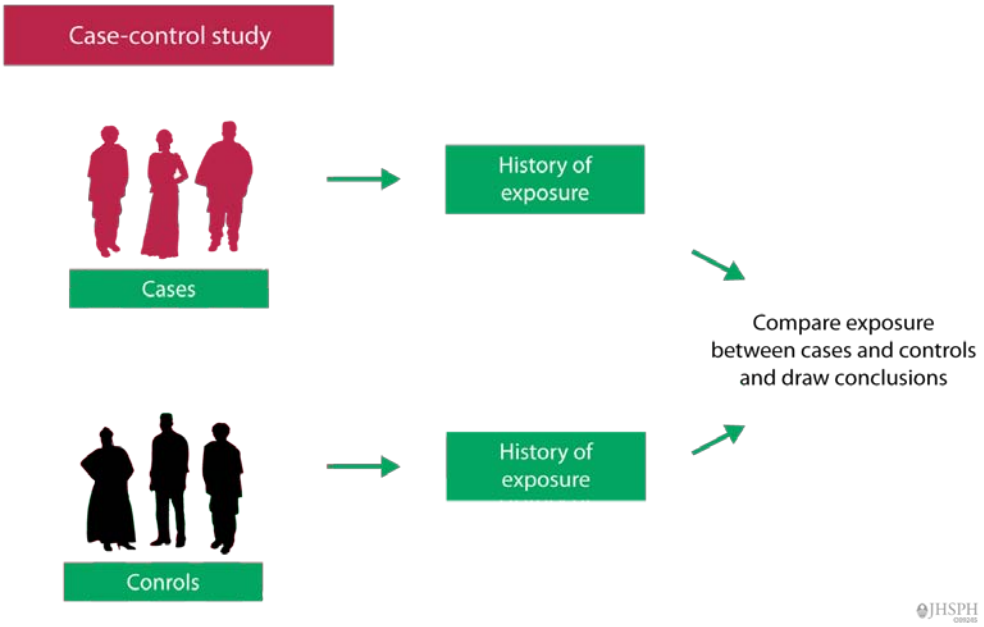
disease, and this and other case report series led to studies that helped scientists to recognize a new illness.

Case Report Series	
Pros:	Simple design; no undue burden on the patient; focuses attention on rare disease or manifestation; can lead to more rigorous study
Cons:	Description and any conclusions are limited to only the patients described; no control over 'real world' factors



Cross prevalence surveys are a snapshot of disease within a predetermined population. Often called prevalence studies, an investigator can get an idea of how much disease or phenomenon (number of cases) is in a population in exposed and non-exposed groups. The investigators can then do an analysis to see if there is any relationship between exposure and disease. For example, a cross prevalence study that led to an important change in policy occurred when scientists evaluated an association between HIV infection and severe cutaneous reactions to thiacetazone, a TB drug that was commonly used in Africa. Because of the association between thiacetazone and HIV infection, the TB regimen was changed to prevent cutaneous reactions. Cross prevalence surveys generally require a large population size, and aren't great for diseases that are rare[xv].

Cross Sectional Studies	
Pros	Quick and don't require more than a snapshot; can provide some idea of association between exposure and disease; not expensive
Cons	Require a large sample size; subject to bias
Potential Research Q	What is the relationship between exposure A and disease B?
Hypothesis	Exposure to A is associated with disease B



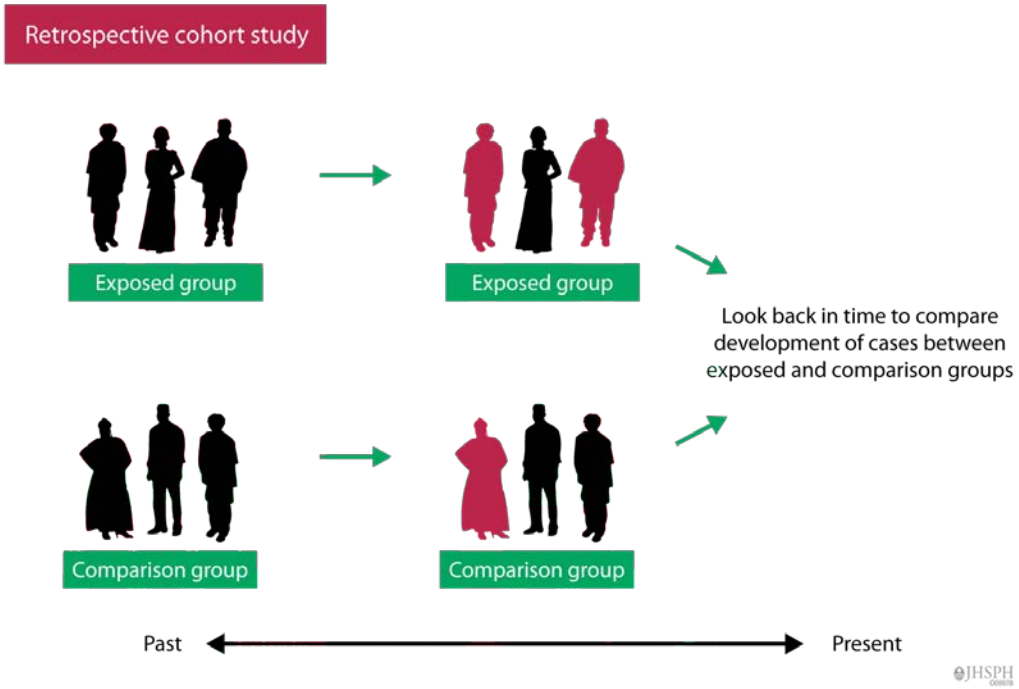
Case-control studies look at the relationship between disease and exposure to factors that might have a **causal relationship** to disease. Most of these studies begin with a disease and non-disease group and compare histories of groups to determine whether exposure to certain factors is linked to development of disease. This is helpful for investigators who are looking at rare disease, because they can start with a group of people who have disease (cases) and match them with people who don't have disease (controls) and take their history of exposure. For example, one recent case control study wanted to look at the relationship between smoking (exposure) and TB (cases). To do so, investigators matched 72 cases (male TB patients, ages 18 – 65 years) to 81 controls (males with no history of TB, ages 18 – 65 years), and looked at the history of smoking between the two groups. The investigators found that 43% of cases (TB patients) had a history of smoking, compared with 25% of controls (men without TB disease). The investigators concluded that smoking increases the risk of TB[xvi].

Case-Control Studies[xvii]	
Pros	Investigators can look at the outcome by groups of interest; not expensive and quick; usually retrospective; good for rare outcomes
Cons	Subject to bias
Potential Research Q	Is Disease A associated with a history of exposure to B?
Hypothesis	Disease A is associated with a history of exposure to B

Cohort Studies

Cohort studies, in comparison to case controls, do not start out with disease and non-disease groups. Instead, these studies look at the relationship to exposure and development of disease *over time.* Cohort studies can be retrospective (looking back in time) or prospective (looking at the present and following research volunteers forward). In contrast to case-control studies, investigators begin the study with a group who has been exposed and look for the development of disease over time. They then compare the development of new cases of disease with the non-exposed group. In prospective cohort studies, this means that the investigators do not know who will develop disease, and follow their research volunteers forward in time. If the investigators want to look at the association between HIV infection and tuberculosis, their 'exposure' group would be HIV (+) persons, and their comparison group would be HIV (-) persons. They would then follow the both groups through time to see how many people develop TB disease. Cohort studies can use medical records, questionnaires, and in prospective studies, serial assessments (prospective studies often include repeated clinical assessments to track direct indicators of health).

	Prospective Cohort Study
Pros	Measures exposure before disease (this helps to establish whether exposure actually causes disease);
Cons	Subject to bias (though less than retrospective); can be very expensive
Potential Research Q	Is an Exposure A associated with Disease B?
Hypothesis	Exposure to A is associated with disease B



Retrospective studies look to the past to determine the relationship to exposure and disease. Retrospective studies can also track how durable the effect of a treatment or intervention is (that is, how long the effect lasts). These studies rely on data that already exists—that is why the only source of information can be medical records, questionnaires, stored samples and other materials that have already been documented in the past (not in-person interviews). With retrospective studies, it is the investigator's job to determine which exposure of interest s/he wants to look at, and then review the history of both groups to see who has developed disease. To look at the relationship between HIV status and TB retrospectively, an investigator would look back in time and choose to follow a group of HIV (+) persons and HIV (-) persons. Using medical records, the investigator could look at who developed TB in the past, and compare the results between the HIV (+) and HIV (-) groups.

	Retrospective Cohort Study
Pros	Investigators can use data that already exists to look for relationships between Exposure A and development of disease B over time
Cons	Subject to bias
Potential Research Q	Is a history of Exposure A associated with Disease B?
Hypothesis	A history of Exposure to A is associated with disease B

Experimental Studies

Experimental studies are comparative studies involving an intervention, such as comparing the use of insecticide-treated bed nets to no bed nets in the reduction of the incidence of malaria. Unlike observational studies that merely observe exposure and disease or outcome, in experimental studies investigators control the exposure, such as bed nets, among the study volunteers.

Many consider experimental studies to be the more **scientifically rigorous** because they allow the investigator more direct control over individual exposures and can therefore more accurately and thoroughly determine cause and effect: If X, then Y; if the intervention is given, then the outcome occurs; or if one sleeps under an insecticide-treated bed net, then one is protected against malaria. Experimental studies can assess change based on the intervention on the individual or the community level. They can be large-scale community interventions, such as comparing malaria infection rates of one community who received insecticide-treated bed nets to another who did not, or tightly controlled clinical studies comparing the effectiveness of two anti-malarial medications among two groups of six individuals.

Components of an experimental study

Before a study is initiated, investigators must establish baseline eligibility criteria in order to limit the proposed intervention to appropriate individuals and/or communities, ensure the impact of the intervention can be assessed among the study volunteers, and to exclude those for whom the intervention may be harmful. For instance, it might be inappropriate and unethical to have pregnant women enrolled in a study evaluating birth control methods or procedures that use x-ray (that could harmful to the fetus). The eligibility is defined by the **inclusion** and **exclusion criteria**, and refers to the characteristics or conditions that potential study volunteers must meet in order to be eligible for consideration for participation in the study. For instance, a study may require that all participants be between the ages of 16 and 64 and HIV positive (inclusion criteria), but will not accept anyone who has taken anti-HIV medications (exclusion criteria) because the medication works best in treatment naïve persons (never taken any anti-HIV medication). This is one of the ways that the investigators control the factors that may impact the results of the study.

What makes a study a "true experiment" is **randomization**. This refers to the assignment of study volunteers to different study groups based on chance. The goal of randomization is to ensure that the groups being compared are equivalent to one another, in age, gender, disease stage and other characteristics, so that comparisons can be drawn. It would be impossible to make the groups exactly the same but randomization limits the variation between the study groups so that even when study volunteers are randomly assigned, the study groups do not differ significantly from one another.

In order to reduce **bias**, or the inclination to report more favorably about treatment and side effects particularly if one is in the intervention arm, study volunteers and perhaps the investigators do not know who is in the intervention arm and who is in the control arm. This technique is called **blinding**, and is done because a volunteer may be biased towards showing that the intervention works, particularly if they are receiving the experiment. Many studies will also keep the investigator in the dark and this is referred to as *double blind.*

In studies evaluating medications, a **placebo**, or 'fake' pill, is given to volunteers in the control arm in order to blind the volunteer, and perhaps the investigator, to the fact that they are not receiving the experimental treatment. The pill is made to look exactly like the real thing. The use of placebos is only ethical if there is not a standard of care to use as a control OR if the placebo is being dosed along with the standard of care. For instance, it would not be ethical to do a randomized control trial of anti-HIV medications vs. placebo among a group of people whose CD4 cell count is very low because we know

From bench to bedside

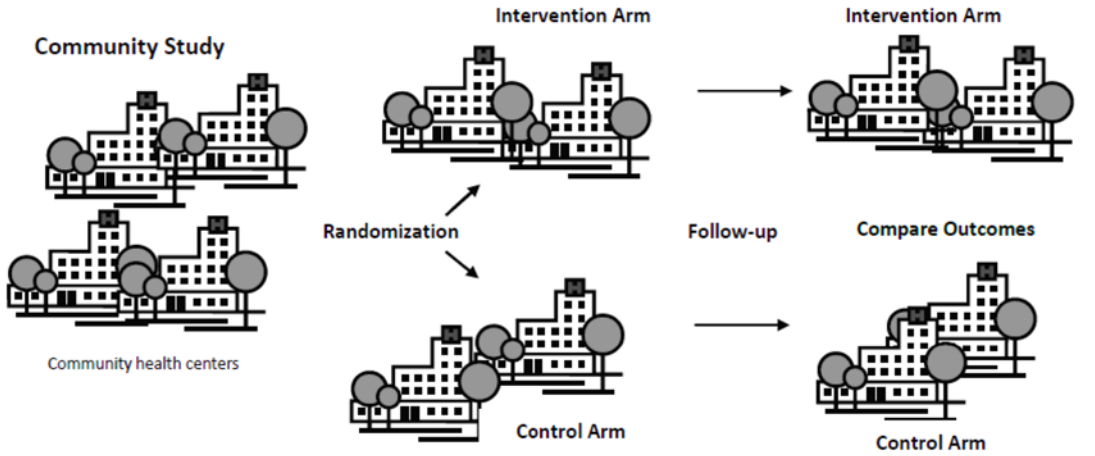
It can take decades for a discovery in a lab to ever find its way into a clinic or as part of policy. In fact for every one effective medication, there are thousands that were deemed ineffective or unsafe. The journey of many scientific breakthroughs begin in **preclinical research** which involves experimentation **in vitro** (in the test tube) and then in animals, it includes *basic science* which investigates underlying mechanisms of life and disease and, *applied research* which seeks to discover new technologies (drugs, diagnostics and vaccines). In **Clinical research,** investigators take the findings from pre-clinical studies and test them **in vivo** (in bodies) on people to see the effect of an experimental intervention on a given condition or disease. **Operational research** allows the findings of clinical research, and of good common sense, to be applied to 'real life systems'. An investigator may test thousands of different molecules in the laboratory to figure out which compound is effective in killing mosquitoes that transmit malaria (*pre-clinical*). After finding an insecticide that is a fast and effective killer of mosquitoes in the laboratory, the insecticide is then tested in humans for safety, toxicity, and efficacy in protecting them against mosquitoes that transmit malaria (*clinical)*. In this scenario, the insecticide is found to be highly protective but is difficult to convince participants to apply the insecticide daily, therefore a study is done comparing the malaria rates in a community that is given bed nets treated with the insecticide to those in a community using the daily skin application and non-treated bed nets to determine if a different delivery system for the insecticide is more efficient in providing protection (*operational).*

the risks for death and illness in this population if they are not given access to optimal anti-HIV medication.

Community Trials

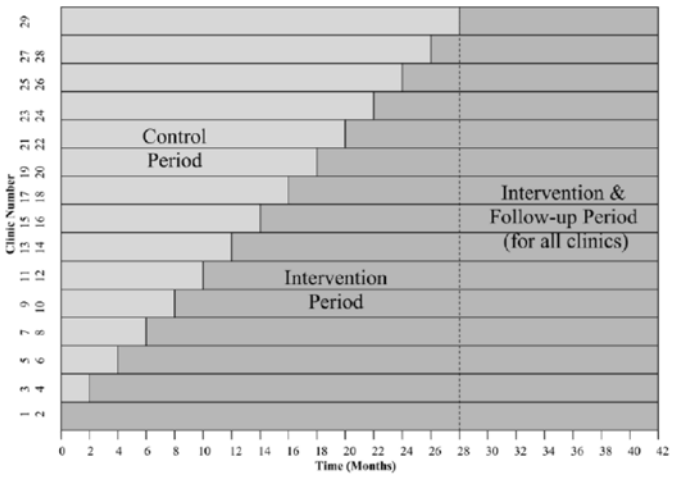
These studies often evaluate operational research. It is applying scientific methods to come up with solutions to problems or issues that have a strong social component. For instance, the most commonly

used anti-TB treatment regimen has a 95% cure rate when taken correctly, however, in some countries the cure rate of TB is below 50%, or more than half of those on treatment do not get cured. The most commonly used treatment strategy requires TB patients to go to the local hospital or clinic daily to get their medication and be watched as they take their medications. This is labor intensive for the staff and patient, and can feel demeaning to some patients. Therefore some researchers have developed research studies to evaluate community-based TB treatment where community health workers deliver the medications and TB education to the patients in their home, and have found it to be more cost-effective and achieving greater treatment success as compared to the traditional hospital-based treatment program. This is community-based operational research.



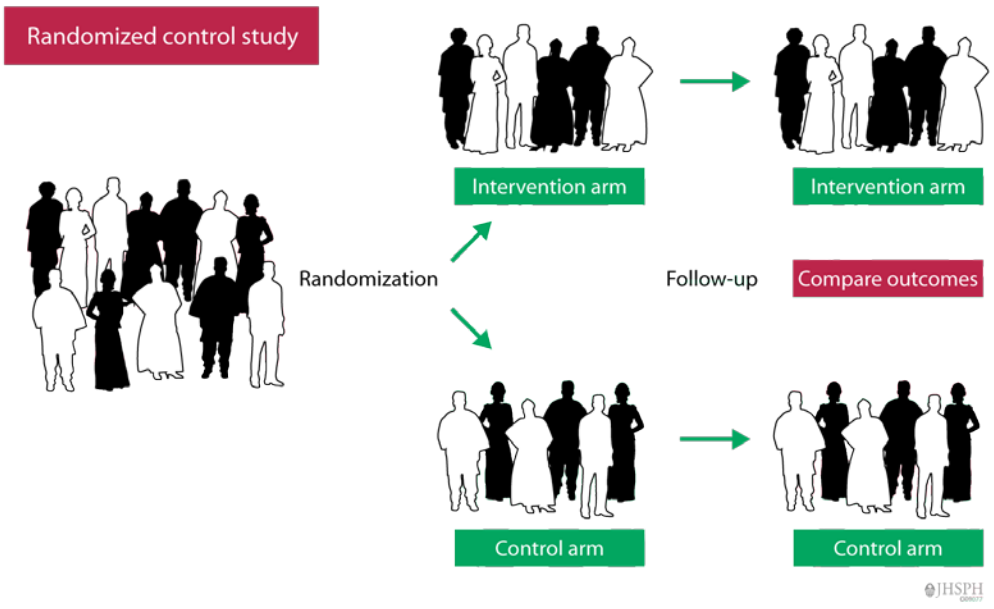
Communities may be villages, clinics, hospitals, schools, offices, or any kind of social, educational or occupational site. These sites are randomized to the experimental arm(s) (to receive the intervention) or to the control arm (no intervention). It is often impossible to blind the community study sites as it is obvious when the intervention is being delivered to any site. For instance, a study evaluating the impact of community-wide treatment for TB infection among gold miners in South Africa randomized by mine shaft. Meaning that study participants in the same mine shaft all either received the intervention (TB screening and mass treatment for TB infection) or no intervention (treatment for TB infection only in confirmed cases). However, all miners no matter which mine shaft they work in, live in the same quarters and would therefore be able to determine who was receiving the intervention.

It is important to note that many community trials will eventually offer the intervention to all of the study sites. These studies are phased implementation studies, meaning that the intervention is provided to all sites eventually. A study of the 29 government HIV clinics in Rio de Janeiro compared the outcomes of patients treated at clinics where the staff has been trained



on the use of treatment for TB infection and screening to those treated at clinics that have not received training. The training of healthcare staff was the intervention and the investigators felt that it was important to provide training to the staff at all 29 sites, so over the course of the study, the number of clinics receiving the training increased and the number of clinics in the control arm (no training) decreased.

	Community Trials
Pros	Can improve service delivery; increase service uptake; evidence can support the need for new policies; can increase community awareness of issue/problem
Cons	Often require a large study population to show significance; can be costly to implement;
Potential Research Q	Does providing education about the signs and symptoms of TB to school children increase the rate of people seeking TB screening?
Hypothesis	Providing school age children with information about the how to recognize TB will raise awareness of TB, and therefore increase the number of people being screened for TB.



Randomized control trials (sometimes referred to as RCTs) are considered to be the gold standard of research studies. Because the investigator has the most control over factors that can impact the outcome, there is a greater degree of certainty that the outcome is the result either from the study intervention or from chance rather than other measured or unmeasured factors. These studies are conducted in human volunteers and are referred to as clinical trials.

Clinical trials refer to the evaluation of new medications or treatments (e.g. vaccines, medical procedures) in humans. The safety, efficacy and tolerability of these new treatments in preventing, treating or curing conditions or illness must be established before they can be marketed, particularly in comparison to the current standard of care. This is done in steps, called **phases,** and each phase has a different focus.

In Vitro versus In Vivo

Before reaching the phases of Clinical trials, there are processes that all experimental drugs and vaccines must go through.

***In Vitro**: experiment is done outside of any organism/body (In Vitro means 'in glass', and can be pictured as being done in a test tube).*

***In Vivo:** experiment done inside an organism. In Vivo experiments can be carried out any living organism. Many experimental agents must be tested on animals before they can be used in studies involving human research volunteers.*

Phases of clinical trials[xviii]

Phase I Trial: is the first time that the new medication or treatment is being evaluated in human beings. They are small (typically 10-80 people) and short term, and often start in healthy volunteers before moving into people with the illness or condition in question. These studies look primarily at safety, tolerability, and establish safe dosing range.

Phase II Trial: continues to look at safety, and also evaluates efficacy of different doses of the medication or treatment in volunteers with the disease or condition being studied. These studies are larger (typically 100-300 people) and last longer than phase I trials.

Phase III Trial: continues to collect information about safety, monitors side effects and confirms the effectiveness of the new medication or treatment as compared to the standard-of-care (commonly used treatments) in a large group of volunteers (typically 1,000-3,000 people). Phase III studies are also called *registration trials,* since they provide the data that companies submit to regulatory authorities for marketing approval.

Phase IV Trial: is also known as *post-marketing studies,* and is large trials designed to evaluate the long-term safety and effectiveness of a medication after regulators have approved it, and sponsors have marketed it. These studies may also look at the safety, effectiveness and toxicity of a drug in different populations who tend to be underrepresented in registration trials, such as children and women and/or other groups who were excluded based on the eligibility criteria.

	Randomized Controlled Trials
Pros	Can accurately describe causal relationship
Cons	Can be more difficult to apply to real world, may not be as applicable to 'real life' settings, because they are tightly controlled by investigators
Potential Research Q	Is medication Y more effective at curing hepatitis C than medication J?
Hypothesis	Persons who take medication Y are more likely to be cured of hepatitis C than persons who take medication J.

Advocacy Opportunity

Although activists continue to fight for inclusion of diverse populations in *pre-marketing studies* (phases I-III), the eligibility criteria set out by sponsors of research may exclude some important groups in the initial evaluations. In the 1960's when the oral contraceptives were being studied, women (even female rats) were excluded in early clinical trials because it was thought that the menstrual cycle may throw off the data. This, despite the fact, that females were the final end users of this new treatment.

Post-marketing studies are not always done promptly because the medication or treatment has already been given approval by the regulatory authority AND they are expensive because they require a large population and are time consuming. However, they can provide some vital information about how the new medication or treatment is tolerated in the general population. In the late 1990's efavirenz, a potent anti-HIV medication was approved and marketed to the general populations in the U.S. A few months after being widely prescribed, patients and healthcare providers were reporting severe emotional side effects, ranging from dizziness to suicidal thoughts. It was not until post-marketing studies were done that the makers of efavirenz changed its safety data and recommendations for coping with these, sometimes, severe side effects.

Some medications and treatments for life-threatening conditions, like HIV, are eligible for *accelerated approval.* This means that regulatory authorities may provide approval with limited data, potentially only 24 weeks, so that people have access to the drugs but unanswered questions remain, hence the need for post-marketing studies in such cases.

Review questions

1. What is the importance of case-series reports, despite their simple design?
2. If an investigator wanted to determine how many cases of lung cancer are in smoking and non-smoking populations at a certain time, what type of study would be best?
3. What is the primary difference between prospective and retrospective cohort studies?
4. For a rare disease such as Ebola, what would be the best type of study design to look at the relationship between exposure and disease?
5. Why would an investigator blind a study?
6. What is randomization and why is it significant?
7. How do observational and experimental studies differ from one another?

Module 4: Interpreting Study Results

Objectives
Upon completion of this module, activists will be able to:

- Discuss study results, including strengths and limitations; and
- Evaluate abstracts to determine the usefulness in informing advocacy

Key Terms

- **Background**
- **Methods**
- **Results**
- **Discussion**
- **Research Question**
- **Study population and setting**
- **Sample Size**
- **Intent to Treat**
- **As Treated**
- **Measures of Effect**
- **Measures of Precision**
- **Statistical Significance**
- **P-Value**
- **Confidence Intervals**
- **Risks**
- **Ratio**

4.1 Why research results matter for activists

Data from research can be a powerful advocacy tool. Activists who understand research and its findings can use these to support their advocacy efforts, and press for important studies—AIDS activists have successfully used research results to advocate for open access to antiretrovirals around the world. TB activists are currently lobbying governments in sub-Saharan Africa to have a proven prevention for TB made available to their community members. Malaria activists are using research data to put the spotlight on who is most vulnerable to disease[xix].

There are some fundamental pieces of information that are crucial for interpreting data from studies. These include how the study is designed, where the study takes place, who is being studied, and most importantly, how to interpret the results.

When interpreting studies, it can be easy to become overwhelmed with terms and jargon. The purpose of *Research Fundamentals* is to explain these, so that you can evaluate research methods and results. Most activists have little if any formal scientific training. Activists can, and have equipped themselves and each other with tools to

Usual structure of a presentation/abstract/manuscript

Background: *Provides information on why the study was done in the first place, for example, number of people with a certain disease and limitations of prevention or treatment, and summarizes research that has already helped to answer the question at hand or raised the question that the study is addressing*

Methods: *Describe how the study has been designed, including information on study participants, and each step of the study process (see Module 3 of this booklet for more)*

Results: *Specify the outcomes of the study, usually without any interpretation.*

Discussion: *Describes study results in more detail, interprets outcomes, and*

understand the information presented at conferences and lectures, as well as in abstracts and manuscripts.

This module explores some basic statistical terms and methods used to describe study results, and applies them in practice exercises. The sections are structured in the same order and format that scientists use to describe their studies in manuscripts and abstracts**: background, methods, results**, and **discussion**.

Background

In an abstract or manuscript, the **background** (sometimes called introduction or rationale) sets the stage for the research question that the paper is addressing. Researchers will often describe the problem that led to their specific research question and present results from previous studies. Prior study results that are described in the **background** section provide justification for the current study, which may be evaluating a new research question, confirming an earlier study or exploring a research question in a different study setting an/or in a different population. For example, the fact that TB is a leading cause of death for people living with HIV has been well established. However, a researcher could ask the more specific question, "How many deaths among people living with HIV in Rio de Janeiro can be attributed to TB?" As part of the **background**, the researcher may describe TB and HIV statistics, and the situation in Rio de Janeiro. Take a look at the following example[xx]—what types of background information are described, leading to the research question?

THE TUBERCULOSIS (TB) epidemic is fueled worldwide by human immunodeficiency virus (HIV) infection, and HIV poses the greatest threat to TB control.[1] The World Health Organization (WHO) estimated that there were 8.9 million new cases of TB in 2005. Of these, 741 000 were among HIV-infected adults. TB may have caused 1.7 million deaths in 2004 and 248 000 in TB-HIV co-infected individuals.[2] The Joint United Nations Program on HIV/AIDS (acquired immune-deficiency syndrome) estimated that 2.9 million AIDS deaths would occur in 2006, 65 000 of which in Latin America.[3]

Brazil has an estimated 600 000 HIV-infected individuals aged between 15 and 49 years.[4] According to the Brazilian Ministry of Health, 85 000 new TB cases occur annually, causing 6000 deaths.[5]

AIDS-related mortality decreased in Rio de Janeiro City (RJC) in the 2 years following the introduction (in 1997) of highly-active antiretroviral treatment (HAART), which is widely available free of charge. Since 1999, AIDS-related mortality has been stable.[6] More than 26 000 AIDS cases have been reported since the beginning of the epidemic,[7] and approximately 8000 TB cases are reported annually.[8] Among TB patients seeking care in primary health units in RJC, one study showed that approximately 10% were infected with HIV.[9]

To determine the role played by TB among Brazil's HIV-positive population, we investigated the frequency of TB as the primary cause of death among HIV-positive subjects in RJC. We also looked at the use of HAART by co-infected patients, aiming to use that as a proxy of access to care and to assess relationships between HAART and survival.

The sentence "To determine the role played by TB among Brazil's HIV population…" leads to the research question, "What is the primary cause of death for HIV (+) people living in Rio de Janeiro, Brazil?"

Another important consideration while reading through the background section is the **references,** which are studies and publications that the study investigator is incorporating in to their writing as a support for their research. Researchers are not perfect, and may not cite their references correctly. It is helpful to take a look at the reference list at the end of the paper. This list also can highlight research that has been done on the topic of interest—by going through the list of references, activists can find other articles that can inform their advocacy efforts.

In any presentation, poster, abstract, or published paper, a few good questions to ask are:

1. What is the problem that the study investigators are addressing?
2. Have the study investigators described research that has already been done?
3. What is the research question?
4. Have the study investigators made a good case for conducting another study?

Exercise 4.2

Below is the Introduction section of a paper published on an education intervention to reduce risky sexual behavior for youth in Namibia. As you read through it, ask yourself the **background** questions listed above:

Introduction

The epidemic of AIDS in sub-Saharan Africa calls for urgent interventions. With approximately three-quarters of the global burden of HIV [1], sub-Saharan Africa has many cities where the seroprevalence among young adults exceeds 30% [2]. One such country is Namibia, which is located in south-western Africa. With a population of 1.6 million (including 11 ethnic groups), it is among the world's most sparsely populated nations. As of 1996, the national seroprevalence of HIV was estimated to be 15% among antenatal patients, with rates as high as 25% in some districts [3]. With an average annual per capita gross national product of US$2000 [4], biomedical prevention and treatment methods are simply not affordable to most citizens or to the government [5,6]. However, as of the time that the study described in the present paper was completed, HIV prevention efforts in Namibia were largely limited to clinic-based posters (personal communication, UNICEF, Namibia).

There is an abundance of literature indicating that behavioural interventions in Western settings that share certain common features (such as being based on a theory of behavioural change and including training and practice in specific skills such as the acquisition and use of condoms) can change self-reported risk behaviours among targeted audiences, including adolescents [7–10]. Although there is growing evidence that such interventions (after they have been adapted to the local culture) can also alter adolescent risk and protective perceptions and knowledge in sub-Saharan settings [11] (A.M. Fitzgerald *et al.*, in preparation), to date evidence is lacking regarding their effectiveness in increasing rates of protected sex among older adolescents. Accordingly, in 1996, the Government of Namibia (GON) in partnership with UNICEF and the University of Maryland (UMD), elected to adapt an adolescent AIDS risk-reduction curriculum that had been successful in the United States [12]. The resulting curriculum, 'My Future is My Choice' (MFMC), includes 14 sessions, each 2 h in length, to be administered over 7 weeks (A.M. Fitzgerald *et al.*, in preparation).

Methods

Module 3, 'Study Process,' included a description of the many ways that study investigators can structure their research. In the **methods** section, all of this information is described. Taken piece by piece, the methods section can be a fun way to try to understand how and why a research study was conducted in a specific way. And, most importantly, the methods section includes clues to help the reader decide if the researchers picked the best method to answer their question.

Study population and Setting should fully describe the people who were included in the research, and where the research took place. Age, sex, and other demographic characteristics of study participants that may influence study results should be described here. Unique aspects of the study setting should be described in detail. For example, does the study take place in a rural or urban environment; in a hospital or in a community; in a high or low-income setting; etc?

Sample size is also important to note. Sometimes the findings are very significant, but the sample size is very small. Small sample sizes may not reflect the larger population. This does not mean the findings are not important, but that the study question may require further investigation before being extrapolated to other populations. The letter ***n*** is used to denote the number of people involved in the study (i.e. n=539 would mean that 539 people were enrolled in the study). Sometimes a study can sound very convincing although the number of people involved is too small to draw any conclusions from. If results detailed later are overwhelmingly convincing, it may be helpful to return to the sample size—was it very small? How would this study work in a different setting or with more people?

Data Sources and/or **Study Procedure** should always include a description of the most important parts of the study process. If the study involves a medical chart review, it should describe how many charts are reviewed, what information is collected from the charts, and why certain charts were selected. This section may include definitions used by the study investigators. For example, if the study is about an intervention for people trying to lose weight, study investigators might set the definition of 'overweight' as weighing more than 90 kilos. If an intervention has been part of the study, it should be described here.

Ethical Approval is not always detailed as a separate section and may only be described in one or two sentences, mentioning IRB approval and the informed consent process. This section may also mention that a CAB was involved.

Statistical Analysis can be explained in a few sentences, or in great detail. A few common types of descriptions in the statistical analysis section are **intent to treat** and **as treated.** At the start of a study, research volunteers are often assigned to groups. At the end of the study, the groups can be evaluated **by intent to treat**, which means that no matter what happened during the trial (such as research volunteers moving away or not returning for visits), their data will be used according to the group they were assigned to. Another way that results are reported is **as**

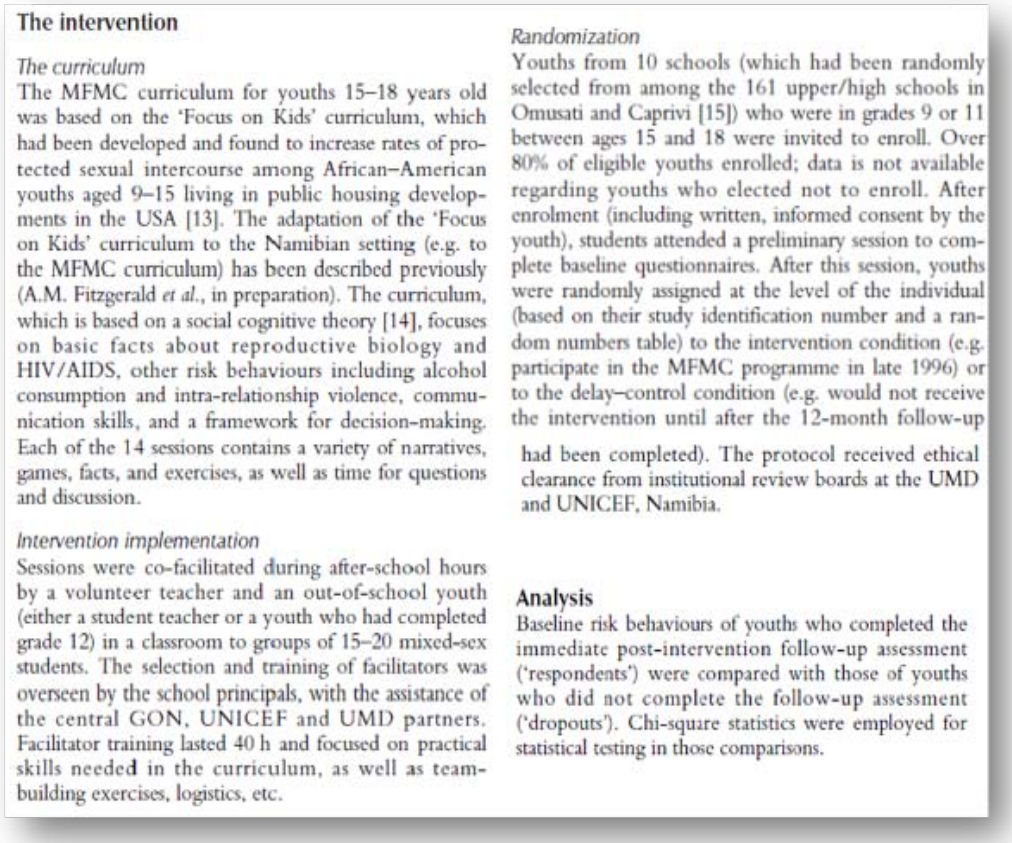
treated, meaning that only those research volunteers who complete the study in the group they were assigned to will have their data used accordingly.

Definitions are often explained in the methods section—and this is very important to the rest of the publication/presentation. For example, TB symptoms may be defined as "chronic cough" for a study that is screening children for TB. The results of this study would be very different if the definition of TB symptoms were more specific, to include, "chronic cough for more than two weeks; night sweats; fever; weight loss; blood in sputum" etc.

Exercise 4.3

Take a look at the **methods** section from a recently published article. The study is the same one used in the exercise above for the Introduction, and is following a group of young people in Namibia who have been randomized to a behavioral intervention. After you've read through the **methods,** see if you can answer the questions below:

1. What is the study design?
2. What is the study setting?
3. Who is the study population?
4. Does this methods section describe the intervention or the procedure that is being evaluated?
5. Are any ethical safeguards described?



The intervention

The curriculum

The MFMC curriculum for youths 15–18 years old was based on the 'Focus on Kids' curriculum, which had been developed and found to increase rates of protected sexual intercourse among African–American youths aged 9–15 living in public housing developments in the USA [13]. The adaptation of the 'Focus on Kids' curriculum to the Namibian setting (e.g. to the MFMC curriculum) has been described previously (A.M. Fitzgerald *et al.*, in preparation). The curriculum, which is based on a social cognitive theory [14], focuses on basic facts about reproductive biology and HIV/AIDS, other risk behaviours including alcohol consumption and intra-relationship violence, communication skills, and a framework for decision-making. Each of the 14 sessions contains a variety of narratives, games, facts, and exercises, as well as time for questions and discussion.

Intervention implementation

Sessions were co-facilitated during after-school hours by a volunteer teacher and an out-of-school youth (either a student teacher or a youth who had completed grade 12) in a classroom to groups of 15–20 mixed-sex students. The selection and training of facilitators was overseen by the school principals, with the assistance of the central GON, UNICEF and UMD partners. Facilitator training lasted 40 h and focused on practical skills needed in the curriculum, as well as team-building exercises, logistics, etc.

Randomization

Youths from 10 schools (which had been randomly selected from among the 161 upper/high schools in Omusati and Caprivi [15]) who were in grades 9 or 11 between ages 15 and 18 were invited to enroll. Over 80% of eligible youths enrolled; data is not available regarding youths who elected not to enroll. After enrolment (including written, informed consent by the youth), students attended a preliminary session to complete baseline questionnaires. After this session, youths were randomly assigned at the level of the individual (based on their study identification number and a random numbers table) to the intervention condition (e.g. participate in the MFMC programme in late 1996) or to the delay–control condition (e.g. would not receive the intervention until after the 12-month follow-up had been completed). The protocol received ethical clearance from institutional review boards at the UMD and UNICEF, Namibia.

Analysis

Baseline risk behaviours of youths who completed the immediate post-intervention follow-up assessment ('respondents') were compared with those of youths who did not complete the follow-up assessment ('dropouts'). Chi-square statistics were employed for statistical testing in those comparisons.

4.4 Results

The **results** section gets right to the point. Study investigators do not get to explain the results—they generally only present the data. It is likely that some of it may be hard to interpret, especially if the statistics terms that are presented are unfamiliar. Some of the most common statistics terms will be described here. Check the glossary for a broader description of terms that are used to describe the results.

When research is disease-specific, the **prevalence** and **incidence** of that disease in a certain area are often presented. This information may have been described in the background data, or may have been an outcome of interest in the study results. The **prevalence** refers to the percentage of the described population that has the disease. This term refers to the *existing* cases at a certain time. For example, if the **prevalence** of HIV in South Africa is 18.1% among 15 – 49 year olds, that means that 18.1 out of every 100 people are HIV positive[xxi]. **Incidence** is a similar measure, but indicates the percentage of the population that has a *new* case of the disease within a specific time frame. If the **incidence** of HIV in South Africa is 2.4% among 15 – 49 year olds in 2005, that means 2.4 out of every 100 people are *newly* HIV positive in 2005[xxii]. Usually incidence rates are time-bound, meaning that the number of new cases of disease is measured over a specific time period. For example, if the incidence of tuberculosis in a population is 200/100,000, it means that for every 100,000 people, there are 200 *new* cases of TB.

Take a look at this **results** section[xxii]—what is the prevalence and incidence data?

> Individuals who were sexually active in the past 12 months recorded an HIV prevalence of 18.7% (95% CI: 17.0 - 20.6) and an HIV incidence of 2.4% (95% CI: 1.5 - 3.3). Interestingly, a substantial rate of recent HIV infections was also recorded in survey participants who reported that they never had sex (1.5%, 95% CI: 0.0 - 3.0) or no sex in the past 12 months (2.4%, 95% CI: 0.8 - 4.1), illustrating contradictions between biological test results and self-reported sexual behaviour. Currently pregnant women were found to have among the highest prevalence and incidence rates, 37.0% (95% CI: 24.9 - 51.0) and 5.2% (95% CI: 0.0 - 12.9), respectively. Individuals who reported only one sexual partner in the past year were less likely to be HIV positive in comparison with those who reported two or more partners, with a figure of 18.4% (95% CI: 16.7 - 20.4) versus 21.3% (95% CI: 15.9 - 28.0), and similarly had a lower HIV incidence, 2.1% (95% CI: 1.3 - 3.0) versus 3.1% (95% CI: 0.0 - 6.4).

The investigators describe the prevalence and incidence rates of five groups: individuals who have been sexually active over the past 12 months, individuals who have not been sexually active over the past twelve months, pregnant women, individuals with one sexual partner over the past twelve months, and individuals with more than one sexual partner. To explain the prevalence among pregnant women, 37 out of every 100 women are HIV (+), and 5.2 out of every 100 pregnant women are *newly* HIV positive.

Remember that prevalence and incidence may be presented in the first section of the paper in the background section. Wherever it is described, understanding these rates and how they apply to countries and communities can play a key role in advocacy efforts, because they describe how the disease is affecting a population overall.

Measures of Effect

Researchers report the results of their study using measures of effect. Measures of effect do not equal truth, meaning that the results do not come with a guarantee to always be the same, no matter what. This is because researchers can never guarantee that their study will yield the same results in every population at every point in time—the world is not a test tube, and the millions of variables that are out of the researcher's control will limit what the results mean. Researchers try to get as close as possible to the true result or 'truth' (but never will!). They can

measure the effect that variables have on the unique make up of each individual's body and mind, but will never be able to control them.

Instead, researchers use rigorous methods to get as close to the 'truth' of what happens to most study volunteers most of the time. For example, the ultimate goal of a treatment study is to find a drug or regimen that works for most people, most of the time. However, no treatment is going to work for *every* person *all* of the time. This is why we say that researchers can never describe the 'true' effect of a study. To get as close as possible they use measures and estimates to indicate their best effort at getting to the 'truth'. These measures include **rates** and **ratios.**[xxiii]

Ratios are a way of comparing two specific things. For example, to compare the number of women who work and take care of children to the number of men who work and take care of children, the investigators could gather the number of men in a village who work and take care of children (n = 100) and compare it to the number of women in that same village who work and take care of children (n= 300). The **ratio** would be 3:1, meaning that for every one man who works and takes care of children, there are three women who do the same.

Ratios are useful because they allow investigators to explain their results in specific terms that are understandable. When interpreting **ratios**, keep in mind that the unit of measurement should be the same in the comparison groups. If there are 10,000 people living with HIV who have TB, and there are only 1,000 non-infected people who have TB in that same city, what would the ratio be? 10,000/1,000 means that the ratio would be 10. For every one person who is non-infected and has TB, there are 10 people living with HIV who have TB.

Odds/Rate Ratios[xxiv]

Odds Ratios (OR) is a ratio of odds, or a ratio of ratios. Odds ratios express the odds of getting disease between the 'exposed' and 'non-exposed groups'. Exposure can indicate an intervention group, or a group of people who have disease. An odds ratio of 1 indicates that the study outcome is just as likely for each of the comparison groups. An odds ratio[2] of > 1 indicates that the outcome is more likely in the 'exposed' group, while an odds ratio of <1 indicates the outcome is less likely in the 'exposed' group. The same rules apply for any rate ratios.

It is important to remember these calculations are all based on a sample size and method of statistical analysis that was calculated before the study started. While the sample size is determined by the investigators, keep in mind that no matter how large a sample, it may not accurately reflect a population. A trial can include 100,000 people living in Nairobi as a sample meant to represent all Kenyans. However, if most of those 100,000 people are middle class and have access to private health care, this sample would be biased and would not reflect the conditions of poor and rural Kenya. Therefore, the results could be used as an advocacy tool for the specific population they represent, but should not be applied too quickly to the broader Kenyan population. Activists could use this data to say, "This is what every citizen should expect—we need research to see if the outcomes among people with low socioeconomic status are the same."

Difference between Odds Ratio (RR) and Relative Risk

Odds Ratios & Relative Risks *are very common measures of probability used to explain study results and are quite similar. What is the difference between the two?*

The ***Relative Risk*** *compares the probability for disease among the exposed and unexposed.*

The ***Odds Ratio*** *compares the odds of disease among the exposed and unexposed.*

Take this example. The table below shows the probability of TB for people who are living with HIV, and those who are non-infected. The probability of disease for those who are HIV(+) is 50/100, compared to those who are HIV(-), or 10/100 (probability of 0.5 compared 0.1)

	TB	***No TB***
HIV (+)	*50*	*50*
HIV (-)	*10*	*90*

The relative risk states the risk for TB by comparing the probability of TB between those who are HIV (+) and those who are HIV (-). For the example above, the RR would be 0.5/0.1, so RR = 5.

The odds ratio states the odds for TB by comparing the odds of TB among those who are HIV (+) to the odds of TB among those who are HIV (-). From the example above (see footnote for odds ratio), the OR would be (0.5/0.5)/ (0.1/0.9), so OR = 9.

Even though the relative risk and the odds ratio describe similar types of information, the numbers, and thus the interpretation, are different.

Measures of Precision

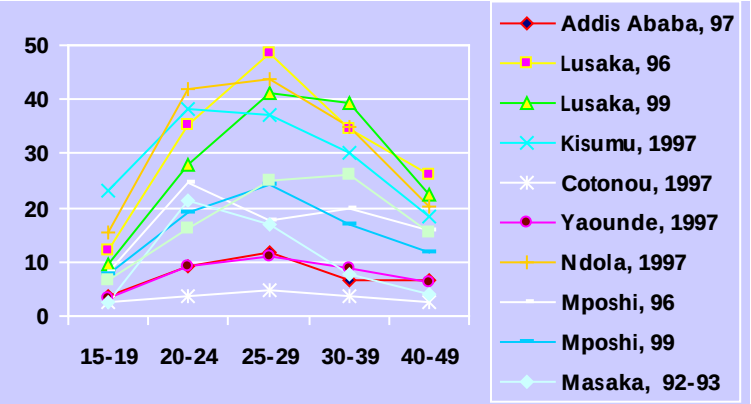
Measures of effect can be accompanied by measures of precision. To understand measures of precision, it is helpful to understand how data are distributed within a sample population.

Characterizing the study population

Research volunteers can be characterized as a group, meaning that their individual information, such as height, weight, etc. are presented as a whole. For example, when talking about the development of TB in a group of 100 people living with

[2] Odds Ratio = [Probability (disease|exposed) / (1 – Probability (disease|exposed)] / [Probability (disease|unexposed) / (1 – Probability (disease|unexposed)].

HIV, the researchers may state that 56/100 study participants are women, 35/100 are between the ages of 15 – 24, and 15/100 have no formal education. A helpful way to describe this is in a distribution curve that shows the character of the study population. The figure below[xxv] represents a distribution curve. A distribution curve is often used in biostatistics to describe the data in a visual way, and is helpful in understanding a population.



This chart shows the HIV prevalence among women in the cities listed based on the year the data was collected. The **mean**, or the average prevalence figure, would be taken by finding the average prevalence in all age groups (in this chart, the mean is an HIV prevalence rate of 25% among all women in the cities listed). The **median** is the central value—here, the median age group is 25 – 29 years of age. The **mode** is the peak of the curve; in this chart, the mode would be 49%, or the highest HIV prevalence shown.

It is important to note that these figures represent the sample, not the overall population. So the chart is representative only of women in the cities listed, and of the year that data was captured.

One measure often used to express the precision of study results is **confidence interval (CI).** The confidence interval characterizes all possible values of a population characteristic that are compatible with study data and results. CIs indicate the range of values for a result within a certain bound area, and that is often set at 95%. Looking at the distribution curve above, a possible 95% confidence interval for the true mean HIV prevalence among women in the cities listed is 2 - 48%. This can be interpreted as, 'if we sampled [x] women in 100 separate samples, 95% of the time the confidence interval formed in this way would include the true HIV prevalence for the women living in the cities listed'.

For the confidence intervals around ratios, it is important to note that anytime a confidence interval of a ratio overlaps 1, that ratio is not statistically significant. These same rules apply to the relative risk[3].

[3] Relative Risk = Probability(disease|exposed) / [Probability(disease|unexposed)

Another measure of precision that is very important and can be difficult to understand is the statistics that researchers use to define **statistical significance.**

Statistical significance is a way of measuring whether an intervention had a true effect and helps the investigators to decide how close to the truth their results are. If an HIV education intervention shows increased use of condoms in the intervention arm compared to the control arm in absolute number (i.e. if 15/20 men in the intervention arm used condoms compared to 10/20 in the control group), should the study investigators say their intervention worked? The answer to this question, yes or no, would depend on how the investigators measured statistical significance to determine if the 15/20 compared to 10/20 shows that the intervention was successful or if these numbers occurred in this way simply by chance.

Probability helps investigators decide the likelihood of a study result occurring by chance, not because there was a real difference between the comparison groups (i.e. treatment and placebo groups). The ***P*-value** is a statistical value that is usually interpreted as follows: if there were no difference in the values being compared and you performed the same sample 100 times, then you would expect to see a more extreme difference only 100% of the time. Note of caution: The *P*-value is often misinterpreted. It is *not* the probability that the difference is due to chance or that the difference is a "true difference". A small *P*-value does not mean that the evidence is necessarily strong or that the difference is important or clinically meaningful. A small *P*-value means only this: if there is truly no difference, then the observed difference is largely due to chance factors. If chance is ruled out, then the assumption that "there is truly no difference" is logically ruled out as well, implying that there must actually be a true difference. The *P*-value helps the investigators to ask questions about the results and decide whether statistically large differences are due to chance or to actual differences. A ***P*-value of <0.05** is usually interpreted as 'scientific significance'. This means that if an experiment was done 100 times and there were truly no difference between compared values, then a larger difference would be expected in only about 5 of these 100 repeated experiments.

Exercise 4.4

In this exercise, we are going to be looking at a very simple chart that shows the results of a small study in South Africa. Take a look at the chart below, and see if you can answer the questions.

Example

Study Outcome	Intervention (%)	Control (%)	Odds Ratio (OR)	P value
HIV tested	72/352 (20.2%)	26/402 (6.5%)	3.7	0.009

This chart comes from a study that tested whether or not training nurses on HIV testing helped to increase the percentage of TB patients counseled and tested for HIV. The intervention trained nurses to offer HIV counseling and testing to their new TB patients for HIV. The proportion of TB patients tested for HIV from the intervention clinics was compared with the proportion of TB patients who were HIV tested from the control clinics.

1. What is the percentage of patients who were HIV tested in the intervention arm?
2. What is the percentage of patients who were HIV tested in the control arm?
3. What are the odds that patients in the intervention arm were HIV tested, when compared to the control group?
4. Are the results significant?
5. What is the probability that the results happened by chance?

From the chart we can see that 20% of patients in the intervention clinics were tested for HIV, compared to 6.5% in the clinics that did not have the training. The odds ratio (OR) for HIV testing is 3.7. That means that patients in the intervention clinic were **3.7 times** more likely to test for HIV than those in the control clinics. And we use the *P*-value of 0.009 to say that these results are **significant**, because the *P*-value is less than 0.05. If there were truly no difference in study outcome between persons with and without HIV, then with this study design repeated many times, we would expect an OR of 3.7 or more in less than 1% of those repeated samples.

No matter what the study, some important questions to ask for the 'Results' section are:

1. Is any prevalence or incidence information presented?
2. What are the results describing?
3. Are there any differences between the comparison groups?
4. Are these differences statistically significant?

4.5 Discussion

After making it through the results section, the **discussion** may seem like a walk in the park. This is the section where study investigators *interpret* their results. A good discussion section should provide context for the results to be interpreted. Often a separate conclusion section will describe the limitations of the study, the answer to the original research question, and an argument for further research that should be done. Often researchers anticipate critiques of their methods, or the data and try to address them in the discussion section. Sometimes study investigators will make recommendations in the discussion section for policy measures that their data support.

Reading through the discussion requires some critical thinking. Activists can use their skills to decide what the strengths and limitations of the study are. Research can be flawed, and often the results may be limited to the study setting and population. The most important thing to know is that help is out there and available—often researchers are eager to discuss their work; they will answer questions directly through email, and during and after presentations. Don't hesitate to approach the investigators with questions and concerns.

Module 5 Practicum

Ethics Learning Objectives

Upon completion, activists should be able to:

- Identify key components of an informed consent
- Evaluate informed consent from a perspective to ensure information is being communicated appropriately to potential research volunteers
- Describe informed consent as a process rather than a form (role play) should be an exchange

1. *Using the consent form below, evaluate whether or not enough information is contained for a research volunteer to evaluate the benefits and risks of participating.*

Principal Investigator: JOE SCHMOE, M.D.

1. *What should you know about his study?*

   You are being asked to be in a research study. This consent form explains the research study. Please read this form and ask about anything you have questions about. If you don't have questions now, you can ask later.

2. *Why is this research being done?*

   The purpose of this research study by doctors at SMRT University is to learn more about preventing tuberculosis (TB). TB is caused by a germ that can lead to serious illness, including lung problems and death. The risk of TB is very high for people with HIV. The purpose of this study is to compare different treatments to prevent TB in people with HIV infection who have been exposed to the TB germ but who do not have the disease TB. People with HIV who have the TB germ in their body, but do not have TB disease may join this study. Studies have proven that a medicine called isoniazid (or INH) for 2 months can lower their chance of getting TB. This study will try to find out if three different treatments are as good as or better than INH treatment for 6 months. The study will compare 6 months INH treatment with INH given for up to 4 years; with a new drug called rifapentine that can be given once a week for 3 months with INH, and with another TB medicine called rifampin given twice a week with INH for 3 months. Rifapentine has been tested as a cure for TB disease in South Africa and tests show that it works to treat TB disease and is safe. It hasn't been tested a cure for TB infection. Rifampin and INH given twice a week is used to treat TB disease and has been shown to work for preventing TB in one other study. This study will help us find out if any of the treatments is better or easier to take than INH for 6 months. We will enroll about 1200 people in this study.

3. *What will happen if I join this study?*

If you agree to be part of this research study, you will be given one of four treatments to prevent TB germ from making you sick. In order to know if the new treatment works, it is important to compare them with the standard treatment of IH once a day for 6 months. You will be treated with one of the four treatments.

- *INH once a day for 6 months*
- *INH once a day for a long as the study lasts (for up to 4 years)*
- *Rifapentine and INH once a week for 12 weeks*
- *Rifampin and INH twice a week for 12 weeks*

Your treatment will be chosen randomly, like flipping a coin. You will be asked to come to a clinic to take your medicines if you are in the rifapentine or rifampin groups. If you are taking INH, you will be given one month of pills at a time. At the beginning of the study, a nurse will ask you questions and you will have an x-ray to be sure that you don't have TB disease. You will have blood taken every month, which will be about 2 teaspoons worth. Doctors and nurses will ask you questions every time you come back to the clinic for your medicines. If you have problems that might be due to the medicine, you may have blood tests done to look for liver and other problems.

4. *What are the risks or discomfort of this study?*

Rifapentine and rifampin can cause rashes, liver problems and joint aching. These drugs may also interfere with other medicine, such as narcotics and birth control pills. There are no side effects once the medicines are stopped. INH can cause upset stomach, rash, liver problems, and nerve problems like numbness and tingling of the hands and feet. People who have liver problems caused by INH but keep taking the medicine can develop serious trouble including liver failure and even death. It is very important that you stop taking INH right away if you have nausea or vomiting, pain in the abdomen, or notice dark colors urine for more than two days; if any of these problems occur you should come to the clinic and tell the nurse or doctor immediately.

5. *Are there benefits to being in this study?*

If you enter the study, the medicines may lower chances for getting TB in the future, but this cannot be guaranteed. You will get regular checkups during the study to look for signs of TB. The results of this study may help others by providing better information on preventing TB in people with HIV infection.

6. *Will you be paid for this study?*

You will receive $3 to help pay for transportation every time you return for a study visit.

7. *Can you leave the study early?*

If you wish to withdraw please notify study staff immediately. You may withdraw from the study at any time.

8. *Will the study pay if you are injured in this study?*

   If you are physically injured by the study drugs and you have followed directions of the study doctor end other personnel, the study will cover reasonable medical expenses necessary to treat the injury. The researchers have purchased insurance for the costs of treatment that is necessary because of participation in this study. No other compensation will be provided by the researchers.

   If you feel you are injured as a result of being in the study, or think you have not been treated fairly, please contact Dr. Joe Schmoe at (283) 2382-23928.

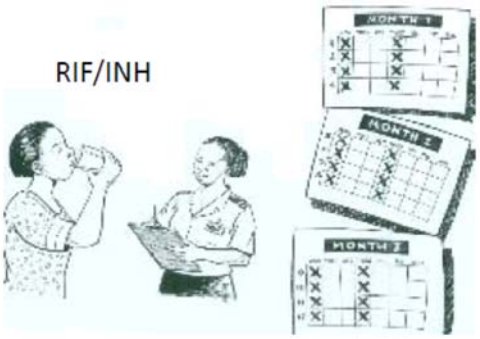
9. *What happened to the data, tissue, blood and samples collected as part of the study?*

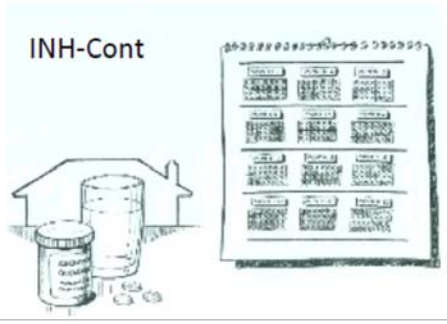
   The study researchers will own any data, tissue, blood and other samples that are collected as part of the study. All of your personal information will be kept private.

- Was all of the information below included?
  a. Name of the study and study rationale
  b. Study Question
  c. Explanation of study processes
  d. Risks and possible adverse events
  e. Possible benefits for participating in the study
  f. Explanation of volunteering and what that means for the person participating
  g. Explanation of how study information will be used
  h. Description how the information obtained from study participants will be kept confidential
  i. Names and contact information for study investigators; sometimes information to contact the IRB can be included
- Is there information that should have been included and was not?
- Can you identify any incentives? Are they appropriate for this study?

2. The following illustrations were developed to further explain the informed consent. Answer the following questions:

   - Are these illustrations useful?
   - Would it be appropriate for volunteers in Antarctica?
   - How would you change/further develop these illustrations?





3. Would you feel confident enrolling in this study?

4. How could this informed consent form be part of an informed consent process?

Study Process Learning Objectives

Upon completion, activists should be able to:

1. Identify what type of trial can best answer a specific research question; and
2. Understand the value of experimental and observational study design.

Activity

For each issue listed below there are 3 different research topics. First, list the research questions that you think are important, and then categorize them by type of study. Then try to answer the 6 questions for at least one of possible research topics per issue.

Example:

Issue: Increase in the incidence of drug resistant malaria in Nigeria

Possible research topics:

- Malaria treatment

Questions to consider:

1. How would you ask the research question? *Is drug x (new drug) better than drug y (standard of care) in curing malaria?*
2. What type of study design do you think would best answer the question? *Randomized, controlled, double-blinded trial comparing malaria cure rates of volunteers on drug x to volunteers on drug y*
3. Who would be your study population? *Mothers and children with a confirmed diagnosis of malaria from areas where there is a high incidence of malaria in Nigeria*
4. Are there any factors that may be considered to be "noise" that could confound the results? *There may be a difference in response to the treatment based on immune status, in other words people who are not as healthy (HIV-positive or those who are malnourished) may not do as well as healthy volunteers. Also unclear if this will be as effective in children.*
5. Would you use a placebo in your study? *No, because it would be unethical to not offer treatment to someone with a confirmed malaria diagnosis*
6. What would be your endpoint that would indicate failure or success? *Blood test indicating whether volunteer was cured of malaria upon completion of treatment.*

1. Issue: Rising rates of HIV infection among women of childbearing age in Asia

Possible research topics:

- HIV preventative vaccine
- Risk factors for HIV infection
- Incidence rate of HIV infection

Questions to consider:

1. How would you ask the research question?
2. What type of study design do you think would best answer the question?

3. Who would be your study population?
4. Would you offer them any type of incentive?
5. Are there any factors that may be considered to be “noise” that could confound the results?
6. Would you use a placebo in your study?
7. What would be your endpoint to indicate failure or success?

2. Issue: Despite being curable, low cure rate for tuberculosis (TB) in East African countries

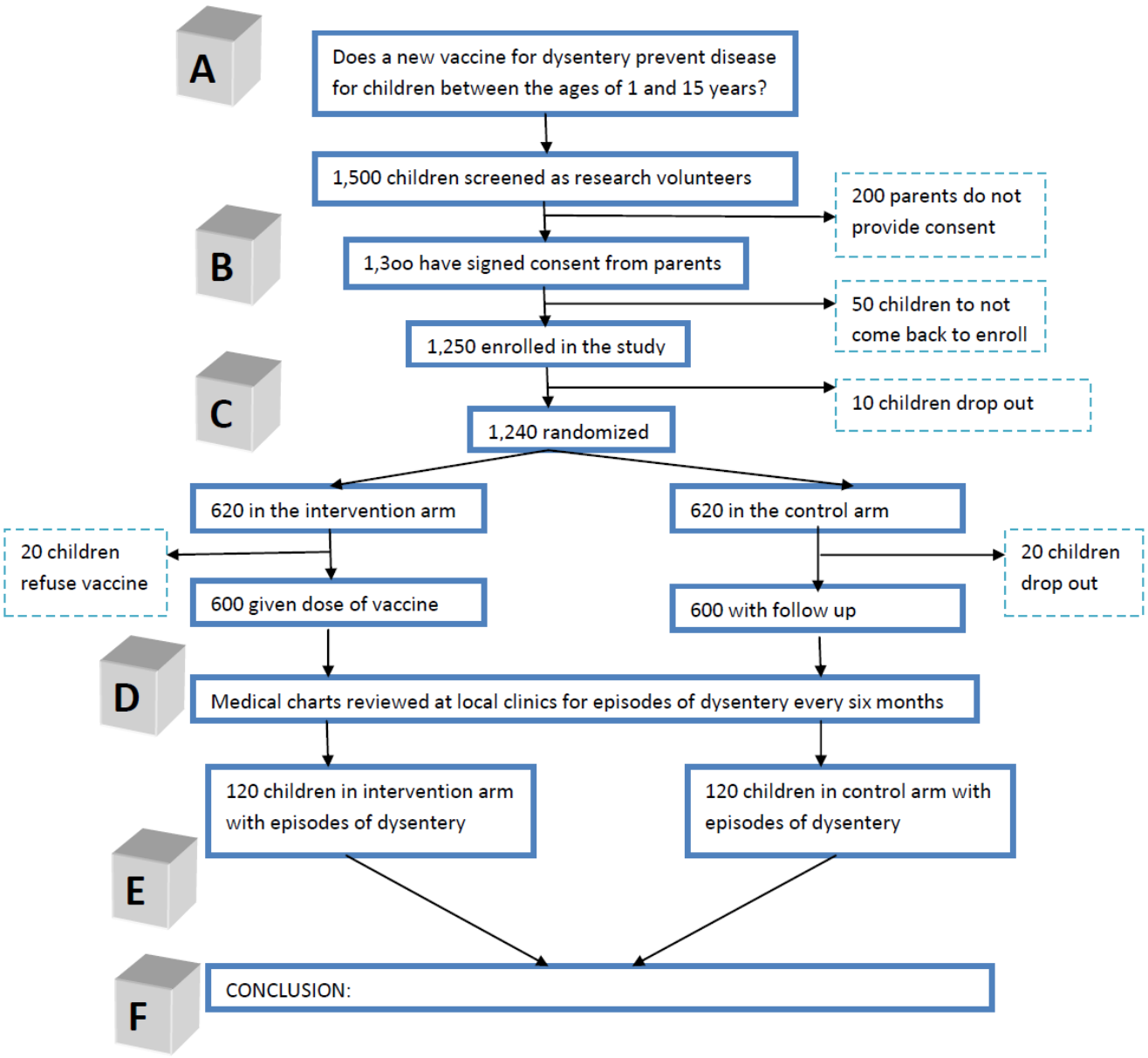
Possible research topics

- Duration of TB treatment
- Community understanding of TB
- Drug resistant TB

Questions to consider:

1. How would you ask the research question?
2. What type of study design do you think would best answer the question?
3. Who would be your study population?
4. Are there any factors that may be considered to be “noise” that could confound the results?
5. Would you use a placebo in your study?
6. What would be your endpoint that would indicate failure or success?

Methods Exercise:



Look through the study described above. This format is a typical format for investigators to show their study design and describe the process. Match the following terms to the boxes A – F:

1. Data Analysis
2. Data Collection
3. Research Question

4. Conclusion
5. Study Design
6. Results

Now answer these questions based on the chart:

1. Is the information in the chart complete enough for you to understand the study process?
2. How would you describe the study intervention?
3. What is the sample size for the study intervention arm? (n =)
4. What is the sample size for the control arm? (n =)
5. Based on the chart, and in the information shown, what would be the conclusion to the research question that is described?

Interpretation Learning Objectives:

Upon completion, activists will be able to:

1. Increase the comfort of reading through research abstracts
2. Evaluate the overall quality of the abstracts
3. Identify the strongest abstract that would support the advocacy priority detailed below

In this practice exercise, read through the three abstracts below. Which of the three best supports the following advocacy priority?

"Infection control is an easy and simple intervention for preventing communicable diseases such as tuberculosis (TB) in primary health care settings"

Abstract A

Background: Infection control is a method that has been used effectively in primary health care clinics in Peru. Cough hygiene education (covering the mouth while coughing) has been part of in-clinic trainings for staff. However, no one has compared how this type of intervention can impact communicable disease in primary health clinics. **Methods:** We conducted a randomized trial of infection control measures in 26 primary health care clinics. Thirteen clinics were randomized to receive a weekly training in cough hygiene for patients in their waiting rooms. At the end of a six month period, rates of communicable diseases for clinic patients and their close contacts were reviewed. **Results:** Patients in the intervention arm had a lower incidence of communicable disease (10 %) when compared to patients in the control clinics (16%), p=0.10. The odds ratio (OR) for communicable disease among the close contacts of patients in the control clinics was 1.7 (95% CI [0.98 – 2.4], p=0.05) compared to the close contacts of patients in the intervention clinics. **Conclusion:** Cough hygiene education in primary health care clinics may

help to reduce transmission of communicable diseases to patients in the waiting rooms and to their close contacts.

Abstract B

Background: Infection control is a method that has been used effectively in primary health care clinics in Nairobi, Kenya as documented by Ntale and colleagues who show that cough hygiene for staff helps to protect health care workers from tuberculosis (TB) infection. Cough hygiene education has been part of in-clinic trainings in Nairobi. However, no one has compared how this type of intervention can impact the spread of TB infection in primary health clinics in rural settings outside of the capital city. **Methods:** We conducted a randomized trial of cough hygiene education in 26 primary health care clinics. At the start of the study, all patients and their close contacts were tested for TB infection. Thirteen clinics were randomized to receive a weekly training in cough hygiene for patients in their waiting rooms. At the end of a one year period, rates of TB infection for clinic patients and their close contacts were reviewed. **Results:** Patients in the intervention arm had a lower incidence of TB infection (10 %) when compared to patients in the control clinics (25%), p=0.03. The odds ratio (OR) for TB infection among the close contacts of patients in the control clinics was 4.0 (95% CI [3.0 – 5.0], p=0.01) compared to the close contacts of patients in the intervention clinics. **Conclusion:** Cough hygiene education in primary health care clinics can reduce the incidence of TB infection among patients and their close contacts.

Abstract C

Background: Infection control is method that has been used effectively in large hospitals in the USA. Cough hygiene education has been part of staff trainings. However, no one has compared how this type of intervention can impact communicable disease in large city clinics. Methods: We conducted a cluster-randomized trial of infection control measures in 5 large city clinics. Three large city clinics were randomized to receive a weekly training in cough hygiene for patients in their waiting rooms. At the end of a three month, rates of communicable diseases for clinic patients and their close contacts were reviewed. Results: Patients in the intervention arm had a lower incidence of communicable disease (10 %) when compared to patients in the control clinics (11%), p=0.5. The odds ratio (OR) for communicable disease among the close contacts of patients in the control clinics was 1 (95% CI [0 – 2], p=0.10) compared to the close contacts of patients in the intervention clinics. Conclusion: Cough hygiene education in large city clinics may help to reduce transmission of communicable diseases to patients in the waiting rooms and to their close contacts.

Exercise Questions:

1. Was previous research cited as part of the abstract?
2. What is the research question?
3. What type of trial is described?
4. What was the intervention?

5. What was the sample size? Equal in both arms?
6. How long was the intervention period?
7. What was the endpoint?
8. Were the results significant?
9. Did the intervention work?
10. Which of these three abstracts best supports the advocacy priority?

Interpretation Exercise:

The following scenario is meant to bring together the skills you've learned in the modules of this booklet. Use your imagination and skill set to answer the questions for Parts I and II below.

Part I:

You are a study investigator and concerned with the health of patients living with HIV. Hepatitis C is very prevalent in the population where your research center is based, and you would like to improve the health of your patients with chronic Hep C infection.

A new drug for Hepatitis C has been approved for a Phase 3 trial that could lead to license of the drug. You have been funded to do a study evaluating DRUG X, which has been shown to result in a sustained viral response. There are some risks involved with taking DRUG X, including a mild rash and itchy skin, and in rare cases, nausea, and high blood pressure.

- What type study needs to be done?
- Would you do an operational or clinical study?
- What would each of the study designs look like, depending on your choice of study type?
- What ethical considerations do you have?
- Would you offer any incentives?
- Who would the study population be?
- Would people on ART be excluded?
- How would the data be collected?

Part II:

The results of your study are now available, after doing sophisticated statistical analysis. DRUG X has shown positive results. What would you conclude based on the following?

	Control (%)	Intervention (%)	p-value
DRUG X	0	45	0.001
Adverse Events (all)	10	23	0.10
CD4 >300	10	15	0.20
CD4<300	10	45	0.002

- What advocacy messages do you take from these results?
- What are your next steps in advocacy and with whom?

Glossary

A

Adverse Event: an unwanted symptom, sign, or clinical event during a clinical trial; *see also side effect*

Anecdote: single event

Arm: a group of study volunteers who receive the same treatment; the treatment arm receives the experimental therapy under study, while control arm receives the standard of care and/or a placebo.

As Treated: a method of analyzing study results where only those who completed the treatment were included in the analysis.

B

Bias: 1) the inclination to report symptoms or outcomes more favorably; 2) in epidemiological studies, it is the presence of confounding factors that may obscure the true relationship between an exposure and a disease (i.e. a study showed an relationship between coffee consumption and lung cancer – further investigation showed the association was due to the bias that smokers were more likely to drink coffee).

Belmont Report: published in 1979, is a document that explains the principles that must underlie all ethical research studies. It was written by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Beneficence: maximizing benefits for the research project while minimizing risks to the research subject

Blinding: a technique used for reducing bias in clinical trials by ensuring that participants do not know who is receiving an experimental therapy or the control treatment and/or a placebo. *Single (study volunteer is unaware of which arm s/he is in), and double (study volunteer and investigator are unaware).*

C

Case Report: a description of a specific clinical case, that is, the development of disease and response to treatment in a single individual.

Causal relationship: connection between cause and effect.

Clinical: refers to the treatment of patient.

Community advisory board (CAB): a group of community members (e.g., people with HIV/AIDS, care providers, advocates) who provide recommendations regarding clinical research.

Confidence Intervals: a statistically derived set of values that is compatible with the observed sample.

Controlled trial: a clinical trial in which a group receiving an experimental drug or other therapy (the experimental arm) is compared with a group not receiving that therapy (the control arm). In a placebo-controlled trial, the control arm receives an inactive substance or fake pill (placebo); in an active control trial, the control group is given an existing standard therapy.

D

Data: descriptions of observations or measurements

Data and Safety Monitoring Board (DSMB): a group of experts that evaluates clinical trials for safety and ethics; DSMBs typically examine interim data as a trial progresses and determine whether it should be stopped or allowed to continue. *(Acronym DSMB)*

E

Endpoint: Outcome measure used in clinical trials; e.g., HIV viral load, cure or death

Epidemic: Infectious disease which is spreading in humans faster than it can be contained

Epidemiology: the study of factors affecting the health and illness of populations, and serves as the foundation and logic of interventions made in the interest of public health and preventive medicine.

Exclusion criteria: are conditions that disqualify a person from participating (e.g., pregnancy, opportunistic illnesses)

Exposure: contact between an agent and an individual; could be a natural exposure (i.e. sunlight) or an exposure introduced through intervention (i.e. exposure to medication).

H

Hypothesis: a theory or educated guess based on the study questions that are to be tested by scientific experiment.

I

In vitro: means in glass; a study done in the test tube.

In vivo: in life; a study done in a living model (animal or human).

Incidence: New occurrence of disease in a specific time frame; there are 9 million incident cases of TB disease each year.

Incentives: a payment or benefit offered to study volunteers to motivate or encourage them to enroll and/or complete a study.

Inclusion criteria: are conditions a potential participant must meet in order to be eligible (e.g., a certain CD4 cell count or HIV viral load)

Informed Consent: a process designed to protect study volunteers in research. Before entering a study, participants must sign a form stating that they have been given and understand important information about the study and voluntarily agree to take part.

Institutional review board (IRB): a committee of physicians, medical experts, researchers, and community members that is responsible for ensuring that clinical trials conducted by a hospital or other research institution are safe and ethical; *acronym IRB*. *(Alternative names may include independent ethics committee (IEC), research ethics board (REB, ethical review committee, and ethical review board).*

Intent to Treat: a method of analyzing the results of a clinical trial in which all participants originally assigned to an arm are analyzed, including those who dropped out or changed treatment due to treatment failure or side effect.

Intervention: is the experimental medication, technique, strategy or device that is being evaluated in a research study.

J

Justice: is one of the ethical principles that underlie all studies as outlined by the Belmont Report, and refers to ensuring reasonable, non-exploitative and well-considered procedures are administered fairly, such s the fair distribution of risks and benefits to *potential* study volunteer.

M

Mean: is the arithmetic average of a set of values.

Median: is the number that separates the larger half of a sample from the lower half. It is the value in the middle.

N

Nuremberg Code: is a set of research ethics principles for human experimentation that were created after the Nuremberg Trials at the end of the Second World War.

O

Observational study: a research study in which no intervention is offered, but study volunteers are observed, retrospectively (looks to past) or prospectively (looks to future).

Operational research: using scientific methods address gaps in health systems or increase the uptake of new strategies or technologies.

P

Placebo: an inactive substance (e.g., a "sugar pill" or “fake pill”) or mock therapy; new experimental therapies are compared with placebos in some clinical trials.

Placebo effect: refers to changes (e.g., improved symptoms) attributable to the treatment process itself as opposed to the therapeutic value of the agents or methods used, likely due to the expectations of the patient or study volunteer.

Preclinical: Stage of research before a new drug or vaccine enters humans; can be in the laboratory (in vitro) or in animal models (in vivo).

Prevalence: Already-existing occurrence of; there are 20 million prevalent TB cases annually.

Protocol: a plan that states the specifics of a clinical trial, such as the hypothesis to be tested, drug(s) to be used, method(s) of administration, length of the trial, endpoints, and eligibility criteria.

***P*-Value:** the probability of obtaining a result at least as extreme as the one that was actually observed, assuming that there is no true difference.

Q

Qualitative: relating to, or expressed in terms of, quality; qualitative research is based on individual, often subjective, analysis

Quantitative: relating to, or expressed in terms of, quantity; quantitative research is based on numerical data

R

Randomization: method of random assignment randomly, e.g., to receive an experimental treatment or a standard one in a clinical trial; a clinical trial in which subjects are assigned by chance to different treatment or control arms; randomization is done in an attempt to cancel out the influence of individual subject characteristics and other factors that are not under study.

Range:

Ratio: is an expression that compares quantities relative to each other.

Respect for persons: is one of the ethical principles that underlies all studies as outlined by the Belmont Report, refers to protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent

S

Sample Size: the number of participants in a research study.

Scientifically rigorous: *or scientific rigor,* the consistent application of accepted standards and the ability, at least in principle, to replicate the study in fine detail.

Standard deviation: is the square root of the variance of a data set.

Statistical significance: a statistical judgment that an observed difference is due to chance-related causes rather than systematic causes; see *P*-value

Study question: is the question that the investigators are aiming to answer through scientific experimentation.

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