Chapter I – Tuberculosis (TB) Research & Development

**CORE INFORMATION**

What is Research?
Research is an organized process of searching for an answer to a question; or testing a hypothesis or educated guess based on observation. Through the process of testing a hypothesis, information (or data) is produced and collected, then analyzed and used as evidence to evaluate whether the original hypothesis has been proven true, or false.

Challenges of Current TB Drug Treatment
TB disease is caused by bacteria called, *Mycobacterium tuberculosis* (*M.tb*). The current (recommended) treatment for drug-sensitive TB, also called “first-line” TB treatment, was developed over 40 years ago and requires that multiple drugs be taken, often daily, for six to nine months. This drug treatment can cure active, drug-sensitive TB, as long as treatment is completed properly, with no interruptions.

Because this course of treatment is so long and burdensome, often with difficult side effects, many individuals with TB do not, or cannot complete treatment properly which leads to a poor outcome. In these cases, the TB infection may not be cured, and disease can recur again (called relapse). A shorter TB drug treatment, with fewer side effects is desperately needed and could help to improve adherence to treatment, improve cure rates, and decrease TB transmission overall.

In addition to the length and burden of treatment, some first-line TB drugs (for drug-sensitive TB) are not compatible with commonly used antiretroviral (ARV) therapies; used to treat HIV. This means that in some cases TB and HIV cannot be treated at the same time. This is very dangerous for individuals who are HIV and TB co-infected. A new drug treatment for TB must be compatible with ARV therapy.

Daily, six to nine month TB treatment with multiple drugs is very difficult. Further complicating TB treatment; when these drugs are not taken properly, when doses are missed, or when treatment is stopped, the TB bacteria become drug-resistant and much more difficult to treat and cure. “Second-line” treatment of multiple drug resistant TB (MDR-TB) is much longer (nine months to two years), has more severe side effects, and is more expensive than first-line treatment. It is more difficult for both the patient and the health care provider to treat MDR-TB.

New Drugs and Drug Regimens
Drugs used to treat drug-sensitive TB are rifampin, isoniazid, ethambutol, pyrazinamide, and to a lesser extent, streptomycin. These are all antibiotics, and due to the complexity of TB bacteria, must be used in combination to treat and cure TB disease. A given combination of several antibiotics is called a treatment or drug regimen.
Given the burden of current TB drug treatment, a shorter regimen with fewer side effects would help to improve adherence, cure rates, and to decrease the emergence of drug-resistant TB. Studies suggest that there are new antibiotic drugs that could be effective in shortening TB treatment. These new drugs, called “drug candidates,” could replace one or more of the drugs in the current treatment regimen to kill TB bacteria more quickly, if they are proven to be safe and effective in clinical studies.

One hypothesis is that by substituting a new drug candidate for one of the drugs in the current regimen, the duration of treatment can be shortened. For instance, if a regimen consists of drugs A, B, C, and D taken for 6 months and scientists believe that new candidate drug E kills TB more quickly than drug A then a regimen consisting of E, B, C and D may theoretically only take 4 months to cure TB in the patient.

A shorter TB drug regimen could significantly improve patients’ quality of life, increase treatment adherence, and therefore decrease the emergence of multi-drug resistant (MDR) TB and extremely drug resistant (XDR) TB.

Finding a New TB Drug Regimen: TB Drug Research & Development (R&D)
The process of TB drug research and development (R&D), to find a new TB treatment, consists of several stages beginning with a discovery/pre-clinical stage, followed by a clinical stage, which is usually followed by registration and adoption of a new drug, if studies prove to be beneficial.

Each stage of TB drug R&D is designed to find the best possible drug candidates that are safe and effective against TB. It can take several years to move a new drug candidate through research and development, as each stage of research must meet extremely strict safety and efficacy standards.

Challenges of TB Drug R&D
The process of developing any new drug candidate is very challenging. To find just one new drug that is safe and effective researchers must first begin with hundreds or even a thousand potential drug candidates. A majority of drug candidates will be eliminated very early in the research process; in the discovery and pre-clinical stages (see below). Only the safest, most effective and appropriate drug candidates will graduate to clinical stages of research and development; and still many of these drugs will not make it through the entire development process.

There are several other specific and unique aspects of R&D of new TB drugs which pose significant additional challenges to the research process. A few of these include: the unique biology of the TB bacterium, low levels of funding for TB drug R&D over the past 40 years, and the length of current TB drug regimen which adds to the length of clinical trials.

Biology
The bacterium that causes TB is not currently well understood scientifically, which poses a challenge to TB drug research and development, as studies to understand how the TB bacterium functions are happening at the same time as new TB drug trials.
The TB bacterium is also remarkably adept at developing resistance to drugs, no matter how potent. Therefore, active TB must be fought with combination therapy. Today’s four-drug first-line TB treatment, which is antiquated and inadequate, evolved through the addition and substitution of single new drugs into an existing regimen. Each trial to amend the regimen can take six or more years to complete, thus the development of a fully novel treatment regimen could take decades.

**Funding**

TB is the world’s second leading infectious killer after HIV, claiming the lives of nearly 2 million people every year. Yet only 16% of the world’s investment for poverty-related infectious diseases is devoted to developing new technologies for TB. TB research and development (R&D) has been profoundly underfunded, historically. The difficulty of conducting trials, scientific challenges posed by the TB bacterium, and the disease’s association with poverty all serve as disincentives for the pharmaceutical industry to invest in TB R&D.

Governments around the world have made moderate commitments to TB R&D, but not nearly enough to bring new TB drugs to those who desperately need them. Further, their commitments to addressing TB disease in general are distributed between funding for TB control, health system strengthening and R&D. Therefore, an already inadequate commitment of resources is being split several ways.

**Length of TB Treatment**

The length of the current TB drug regimen; 6 months for drug-sensitive TB and up to 2 years for drug-resistant TB, is challenging for participants in TB drug clinical trials, as participants must typically be followed for a full year after drug treatment has been completed. This is done to evaluate participants for relapse of TB infection, which is extremely important, however does add to the length of clinical trials.

**Research and Development of New TB Drugs**

Researchers determine if a new drug candidate is viable for incorporation into an existing treatment regimen in order to make TB treatment shorter by testing the new drug candidate in a series of studies. This process starts with laboratory studies (Discovery), followed by studies in animals (Pre-clinical), and finally studies in humans (Clinical).

**Discovery**

The discovery stage involves testing chemical compounds (potential new drugs) in the laboratory (*in vitro*). This process begins with a large number of chemical compounds that show various levels of activity against TB bacteria. Carefully selected compounds are then tested for chemical potency, to see if they can kill drug-susceptible and/or drug-resistant TB bacteria. Although these early stage tests are conducted outside of an animal or the human body (*in vivo*), these tests try to mimic key conditions in the TB-infected human lung. This is to identify drugs that would be relevant for treating the disease animals or humans.
Pre-Clinical Research
Compounds that perform well in the laboratory (in vitro) are then tested in animals (in vivo), some of which are infected with TB, usually mice. These tests assess the safety of the drug and its ability to kill active bacteria (efficacy). Pre-clinical studies further narrow down the number of potential drug candidates. Once the best drug candidates are selected, further in vivo studies in animals define possible dose ranges, potential drug combinations, and frequency of dosing to ensure safety and efficacy before they are tested into humans.

Clinical Drug Trials
Once a drug candidate is proven safe and effective in laboratory and animal studies, it is then studied in humans in a rigorous series of clinical trials. Clinical drug trials (also called a research studies or medical research) are designed to answer questions about a new drug, or new ways of using a known drug.

Clinical trials are used to find out if a new drug or treatment regimen is safe and effective in people. There are four phases to clinical research trials, and each phase is designed to test the safety and efficacy of the drug candidate in increasing numbers of human subjects. Efficacy refers to the drug’s ability to have an effect against the TB bacteria. All drug candidates, including any proposed TB drug, must go through this strictly defined series of clinical trials in people to ensure safety and efficacy.

Phases of Clinical Drug Trials
Clinical trials are carefully designed to answer questions about a new drug treatment, or a new way of using a known treatment. They occur in a series of four phases. All drug candidates, including any proposed TB drug, must go through this strictly defined series of clinical trials in people to ensure safety and efficacy.

Phase I Clinical Trials:
Phase I clinical trials are the first studies of an experimental drug in humans, and are conducted on a small number of healthy volunteers. The experimental drug is first tested in people who are not infected with TB, to determine the safety and tolerability of the experimental drug, its potential side effects, and what the body does to the drug (pharmacokinetics); how the drug is absorbed in the body, how much of the drug is available to be used by the body once it is absorbed, and how and when it is eliminated from the body after it is taken. Safety and tolerability data are needed before an experimental drug can move on to Phase II clinical trials, and be tested people who are infected with TB.

Phase II Clinical Trials:
Phase II clinical trials are the first studies of an experimental drug (or drugs) in people who are infected with TB, and evaluate the efficacy, safety, side effects, and potential risks of the experimental drug (or drugs). Phase II clinical trials are highly controlled and regulated, and are typically conducted in a slightly larger group of participants than Phase I trials.
Because of the potential for drug resistance, TB must be treated with a combination of multiple drugs to avoid development of resistance to any one drug. In Phase II TB drug trials, experimental drugs might sometimes be tested alone for very short periods of time (up to two weeks), or they might be tested as part of a combination regimen. Typically, Phase II studies can last between two weeks to two months, but are sometimes even shorter than two weeks.

Early Bactericidal Assay (EBA) studies are the first studies conducted in Phase II trials. EBA studies test the short-term potency of an experimental TB drug (or drugs), and also help to find the most appropriate dose for TB patients. EBA studies give a preliminary indication of the efficacy of the experimental drug (or drugs); measuring the rate at which TB bacteria are killed in a patient’s lungs, represented by how many live bacteria remain in the sputum after taking the drug (or drugs) for a short period of time.

Slightly longer studies may be conducted for up to two months. These studies test a TB drug regimen (3 or more TB drugs) in TB patients and aim to evaluate how fast TB bacteria are eliminated from the lungs by measuring the TB bacteria in the sputum and the time it takes for a patient to have a negative sputum sample. Data on the safety and side effects of the combination are also collected in this type of study.

**Phase III Clinical Trials:**

After evidence of the safety (Phase I and Phase II) and efficacy (Phase II) of the experimental drug has been obtained through Phase I and II clinical trials, the experimental drug must then be tested in Phase III clinical trials; the final stage of testing before a new drug treatment can be approved and licensed for registration (use in the general population). Approval from governmental drug regulatory agencies is required before any experimental drug can be marketed to the general population. Phase III trials are much larger than earlier clinical research phases, testing the experimental drug in thousands of TB patients; as opposed to a very small number of healthy volunteers in Phase I studies, or a slightly larger number of TB patients in Phase II studies. In addition to the larger size of Phase III trials, they are also much longer in duration, as participants in Phase III TB drug trials receive a full course of TB treatment, and are usually also followed for up to one year after completing treatment to assess for relapse of infection.

Because TB must be treated with a combination of drugs, the experimental drug must also be tested in combination with other TB medications. In most cases the experimental drug will replace one or more of the standard TB drugs. Current Phase III TB drug trials continue to evaluate trial participants for relapse of TB infection a full year or more beyond the completion of treatment, which significantly adds to the length of the trial, the cost, and to the difficulty of completing such a TB drug trial.

Phase III TB drug trials, as well as earlier phase trials, are designed to answer specific questions about the experimental TB drug being tested for a new treatment regimen; in most cases, will the experimental drug work as well as the standard treatment for TB. In order to answer these questions
the trial must be designed in such a way that tests the experimental treatment in the right “environment”. Guidelines are developed define the type of TB patients that can be involved in the trial; called the inclusion/exclusion criteria.

Following completion of Phase III testing, drug candidates must be evaluated and licensed by regulatory bodies, such as the U.S. Food and Drug Administration (FDA), European Medicines Agency, and national regulatory authorities in the countries where they are to be used, before they can be administered to patients. Drugs are registered on the basis of their performance in clinical testing.

Generally, after a new TB drug is registered it must be adopted as part of a treatment regimen in countries where the drug will be used. Often, the government’s National TB Program (NTP) decides which regimens to use, but in some countries, private doctors or medical associations can also decide what regimen(s) they will prescribe. Adoption requirements for NTPs are complex, with standards often differing greatly from country to country. Considerations include, but are not limited to cost, burden on healthcare providers, and recommendations of intergovernmental bodies like the WHO.

**Phase IV Trials:**
Phase IV studies take place after a drug has been registered and is starting to be used by doctors and patients in real-world settings. These are not controlled clinical trials, but rather observational studies, designed to collect additional data about safety and effectiveness in more “real-life” situations than the controlled conditions of a clinical trial. Phase IV studies can also be used to examine how the drug works in a wider patient population than would typically be included in a clinical trial. Phase IV studies are sometimes optional, but are generally recommended or required by a regulatory body as a condition for approval of the drug for use in the general population.

**The TB Drug Development Process at a Glance:**

- **DISCOVERY/PRECLINICAL:** Identify lead structural series; optimize activity *in vitro*. Perform preclinical (animal) pharmacology, safety and efficacy studies in animals allowing filing of an Investigational New Drug application. Use combination testing in animals to identify the best potential new regimens for clinical development.
- **PHASE I:** Test drug candidates and regimens in small numbers of healthy volunteers for safety, tolerability, and pharmacokinetic properties.
- **PHASE II:** Evaluate single drug candidates and multidrug regimens for safety, tolerability, food effects, pharmacokinetics, dose-ranging and proof-of-concept (efficacy) in TB patients for relatively short time periods (two weeks to two months, in general for TB).
- **PHASE III:** Test multidrug regimens in large numbers of TB patients for efficacy and safety in controlled clinical trials for anticipated complete treatment durations.
- **REGULATORY APPROVAL:** Regulatory authorities license the drug/regimen after reviewing all preclinical and clinical results (also called registration).
- **ADOPTION/AVAILABILITY:** National TB control programs adopt the new drug/regimen, ensuring that it is available to those who need it.
Key Concepts for TB Drug Trials

**EXPERIMENTAL DRUG:** An experimental drug has not been approved by a regulatory authority for use on the market. TB drug trials usually compare an experimental drug treatment with the standard TB drug treatment.

**NON-INFERIORITY:** Non-inferiority means that the new drug treatment being tested is not worse than; meaning it yields equivalent results to the standard (control) TB treatment it is being compared to.

**CONTROL:** The treatment for which the effect is known. In drug-sensitive TB drug trials the control is the standard 6-month TB treatment regimen of isoniazid, pyrazinamide, ethambutol and rifampin.

**PLACEBO:** A harmless, inactive substance that is made to look like a real drug. The use of a placebo in clinical trials allows researchers to isolate the effect of a study drug. Study participants should not know whether they are taking an experimental drug or a placebo as part of their treatment regimen.

**RANDOMIZATION:** The assignment of trial participants to either the experimental or control treatment by random selection. Randomization ensures each treatment group has approximately the same characteristics; size, age, gender, etc; so comparison is possible, and no bias is introduced.

**BIAS:** When individual point of view prevents impartial judgment.

**BLINDING:** Participants do not know which treatment they have been assigned; experimental or control, and will not know until the trial has been completed. Blinding prevents biased interpretation of reactions or side effects from study treatment.

**DOUBLE-BLIND:** Neither the participant nor the researcher knows which treatment the participant is taking until after the clinical trial is complete. This design technique is used to prevent bias during the study process.

**EFFICACY:** Efficacy refers to whether or not the drug achieves its intended effect. In TB drug trials efficacy is measured by the ability of the drug treatment to kill the TB bacteria and/or to produce a stable cure.

**STUDY OBJECTIVES:** Statements outlining clearly why the study is being conducted; what question(s) the study is designed to answer, or for what purpose(s) the study is being performed.

**STUDY ENDPOINTS:** Indicators measured in the study to evaluate the study objectives. Examples of endpoints are: amount of TB bacteria killed, rates of stable cure, safety measures, etc.

**REFERENCES FOR FURTHER INFORMATION**

*Research Fundamentals for Activists, TAG*

*Clinical Trials.Gov [http://clinicaltrials.gov/]*
<table>
<thead>
<tr>
<th>Session 1</th>
<th>The Need for New TB Drugs</th>
<th>[Chapter I]</th>
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<tr>
<td><strong>OBJECTIVES:</strong></td>
<td>By the end of this session participants will be able to:</td>
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<td></td>
<td>• Describe why new TB drugs are needed.</td>
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<td>• Argue the case for TB drug research and development.</td>
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<td><strong>METHOD:</strong></td>
<td>Group discussion and brainstorm. Facilitator will lead a discussion about the need for new TB drugs, and participants will suggest good ways to explain rationale for TB drug R&amp;D to others.</td>
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<td><strong>PREPARATION:</strong></td>
<td>Facilitator should perform the following steps BEFORE conducting this session. Note that these steps are not part of the exercise delivery.</td>
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<td>• Read through the CORE INFORMATION section in Chapter I (pp. 24-30) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member from your trial site.</td>
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<td>• Gather four sets of flip charts and markers.</td>
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<td><strong>EXERCISE DELIVERY:</strong></td>
<td>Estimated session time: <strong>45 minutes</strong></td>
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<td>STEP ONE: Briefly explain the purpose of the session and how it will be conducted.</td>
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<td>STEP TWO: Lead a group discussion about the currently available TB treatment, using the CORE INFORMATION pages as a guide. Try to get participants to lead the discussion as much as possible, even if they are a beginner level. Questions you can use to prompt discussion include:</td>
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<td>• What types of drugs are currently used to treat TB?</td>
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<td>• What does taking TB drugs entail? (number of pills, how often drugs must be taken, side effects, etc.)</td>
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<td>• We all know people who have been infected with TB and who have been on treatment. Is treatment easy? Do you think people usually complete their entire course of treatment properly?</td>
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<td></td>
<td>• What are some of the obstacles to completing treatment properly?</td>
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<td></td>
<td>• What are TB patients’ experiences with accessing treatment? Is it easy? What obstacles exist? How can patients ensure their treatment is prescribed correctly?</td>
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<td></td>
<td>• What can happen if someone does not complete their entire course of treatment?</td>
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<td>As you discuss, write participants’ responses on the flip chart, highlighting the drawbacks to currently available TB treatment.</td>
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STEP THREE: Lead a follow up discussion about the need for a new TB drug treatment; again using the CORE INFORMATION pages as a guide. Questions you can use to prompt discussion include:

- Do we need new drugs to treat TB?
- What would make TB treatment better? (shorter treatment, higher cure rates, fewer side effects, etc.)
- Has anyone heard of any new TB drugs being developed and tested?

Explain the way a new TB drug would be developed, using the information on discovery, pre-clinical, and clinical trials in the CORE INFORMATION section of this chapter.

Emphasize the following key fact:
Researchers determine if a new, “experimental” drug would make TB treatment more effective, through a series of studies. This process is called TB drug research and development (R&D). TB drug R&D starts with laboratory research, then animal testing, and finally human trials. This is a long process that involves research and many trials all over the world.

STEP FOUR: Divide participants into four groups, and give each group flip chart paper and markers.

Ask each group to brainstorm for about 20 minutes about how they would explain the need for new TB drugs to a member of their community. They should be creative and develop relevant analogies or metaphors to help explain how a new drug could be a better tool to treat TB. For example: A car with a stronger engine can get to destinations more quickly and with fewer problems along the way.

STEP FIVE: Bring the groups back together and ask each to share their explanation. Invite feedback from all participants as each group presents.

CLOSING: Close the session by emphasizing again the need for new TB drugs and that the process of research and development is very long, involving years of research and trials all over the world.

TEST QUESTIONS: Use or adapt the following questions for training session pre- and post-test.
1. Which of the following represents a challenge with the currently recommended TB treatment?
   a. The duration of treatment is very long; at least six to nine months
   b. Poor adherence can cause drug-resistance, and prolonged illness
   c. Current drugs cause difficult side effects for many patients
d. Patients generally begin to lose symptoms after starting treatment, and therefore stop taking their medication

e. All of the above represent challenges

2. TRUE/FALSE: New, more effective TB treatments are being developed and tested by replacing one or more of the drugs in existing treatment regimens.

TEST ANSWERS: 1. e; 2. TRUE

Trainer’s Notes:
Session 2   Key Concepts in TB Drug Development and Clinical Trials

[Chapter I]

OBJECTIVES: By the end of the session, participants will be able to:

- Describe key concepts in TB drug development and clinical trials.
- Demonstrate the ability to explain these concepts to others.

METHOD: Pairing-up exercise. Participants will match terms and definitions, and then present concepts to the full group.

PREPARATION: Facilitator should perform the following steps BEFORE conducting this session. Note that these steps are not part of the exercise delivery.

- Read through the CORE INFORMATION section in Chapter I (pp. 24-30) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.
- Photocopy the TERMS and DEFINITIONS pages (pp. 38-40). Cut the terms and definitions along the lines for individual distribution.

- OR –
  - Handwrite each term and definition on individual index cards or slips of paper.
  - Gather a flip chart and markers

NOTE You are not restricted to using the terms and definitions contained in this exercise. Feel free to change the list of terms/definitions based on the most relevant concepts for your trainee group.

- Make enough photocopies of the EXERCISE SOLUTION chart (p.37) to handout to all trainees. Change the chart as necessary if you have revised the terms/definitions list.

EXERCISE DELIVERY: Estimated session time: **45 minutes**

STEP ONE: Briefly explain the purpose of the session and how it will be conducted.

STEP TWO: For a beginner level audience – participants who have had little to no exposure to the information in this session – start with a brief overview of the concepts to be covered. Use relevant information from the CORE INFORMATION section as a guide.
Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member.

For an intermediate/advanced audience, the overview can be skipped. Rather, facilitate a more in-depth, interactive discussion about concepts during STEP FIVE.

STEP THREE: Distribute the prepared slips of paper or index cards randomly to all participants.

<table>
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<tr>
<th>TRAINING TIP</th>
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<tr>
<td>This session can be conducted with any number of participants. If there are more terms and definitions than participants, each participant should take more than one paper/card until all are distributed. Participants will need to find the match for the term or definition they received. If there are more participants than terms and definitions, assign the appropriate number of people to one term or repeat terms/definitions as necessary. Make sure that if a term is repeated, its definition is also repeated.</td>
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STEP FOUR: Ask participants to walk around the room and find their “pairs” by matching terms and definitions. As each one does, the pair should raise their hands and you should check to make sure the match is correct. If it is, the pairs should briefly discuss how they are going to explain their concept to the large group. This step should take **10 to 15 minutes**.

STEP FIVE: After all matches have been made, have each pair briefly explain its concept to the group. Follow with any needed explanation and ask for questions.

For beginner audiences, build this step around the overview at the beginning of the session. For intermediate/advanced audiences, ask participants to give an in-depth explanation of their concept and to offer an analogy or other effective way they would explain this concept to a community member.

STEP SIX: Distribute the EXERCISE SOLUTION charts to all participants as a take-home reference.

**CLOSING:** Address any of the participants’ outstanding questions about the terms discussed. Emphasize that it is important to have a strong understanding of these terms when talking about TB drug trials with others.
TEST QUESTIONS: Use the following questions in training session pre- and post-test.

1. In a TB drug trial, a placebo is:
   a. A place where the new drug is being tested in animals
   b. A substance given to trial volunteers to reduce potential side effects
   c. A harmless, inactive substance that resembles the active drug in appearance
   d. A chemical substance used to determine if someone is infected with TB

2. Randomization in a TB drug trial is:
   a. A random process in which participants get assigned to receive either the experimental drug treatment or the standard drug treatment
   b. A random process of choosing countries where the trial will be conducted
   c. A random process of selecting people from the population to be part of the trial
   d. When a participant makes a choice to belong to one arm of the trial

TEST ANSWERS 1. c; 2. a

Trainer’s Notes:
<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
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<tr>
<td>safety</td>
<td>Establishing that a product (drug, vaccine, etc.) does not cause severe or serious side effects in trial volunteers.</td>
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<tr>
<td>adverse event/reaction</td>
<td>Any unfavourable event or physical condition that an individual experiences during participation in a clinical trial.</td>
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<td>bias</td>
<td>Any unfair judgment; in clinical research, this is avoided by conducting randomized, blinded or double-blinded studies.</td>
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<tr>
<td>endpoint</td>
<td>Medical outcomes that the trial protocol is designed to evaluate, e.g. severe toxicity, disease progression, cure, failure to relapse.</td>
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<td>efficacy</td>
<td>The ability of an experimental product to have the intended effect, e.g. a new drug regimen having the ability to cure disease.</td>
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<tr>
<td>placebo</td>
<td>A harmless, inactive substance that has no treatment value; given to some trial volunteers instead of the experimental product.</td>
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<tr>
<td>control group</td>
<td>The standard by which an experimental product is evaluated; generally either a standard, comparable intervention or a placebo.</td>
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<td>randomization</td>
<td>The process of assigning volunteers by chance to a certain arm of a clinical trial.</td>
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<td>inclusion/exclusion criteria</td>
<td>Medical or social standards determining whether a person may or may not be allowed to enter a clinical trial.</td>
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<tr>
<td>blinding</td>
<td>Refers to the fact that participants do not know which arm of the trial they have been assigned to, i.e. they do not know if they will receive the control or experimental drug regimen.</td>
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<tr>
<td>toxicity</td>
<td>An adverse effect produced by a drug that is detrimental to one’s health.</td>
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<td>experimental product</td>
<td>A product (vaccine, drug, etc.) that has not completed all the phases of clinical trials and has not been approved by a regulatory authority.</td>
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<td>non-inferiority</td>
<td>Refers to the experimental treatment yielding at least equivalent results as the standard treatment.</td>
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<td>licensed product</td>
<td>A product (vaccine, drug, etc.) that has completed clinical trials and has been approved by regulatory authorities for use in the general population.</td>
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<tr>
<td>sample size</td>
<td>The number of patients required to participate in a clinical trial in order to obtain desired data.</td>
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<tr>
<td>informed consent</td>
<td>The process of a potential trial participant understanding trial participation and making a voluntary decision to participate.</td>
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**TERMS**

* Trainer: Cut this handout along the dotted lines for distribution of individual terms to trainees

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<tr>
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DEFINITIONS

*Trainer: Cut this handout along the dotted lines for distribution of individual definitions to trainees*

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Establishing that a product (drug, vaccine, etc.) does not cause severe or serious side effects in trial volunteers.

---

Any unfavourable event or physical condition that an individual experiences during participation in a clinical trial.

---

Any unfair judgment; in clinical research, this is avoided by conducting randomized, blinded or double-blinded studies.

---

Medical outcomes that the trial protocol is designed to evaluate, e.g. severe toxicity, disease progression, cure, failure to relapse.

---

The ability of an experimental product to have the intended effect, e.g. a new drug regimen having the ability to cure disease.

---

A harmless, inactive substance that has no treatment value; given to some trial volunteers instead of the experimental product.

---

The standard by which an experimental product is evaluated; generally either a standard, comparable intervention or a placebo.

---

The process of assigning volunteers *by chance* to a certain arm of a clinical trial.
Medical or social standards determining whether a person may or may not be allowed to enter a clinical trial.

Refers to the fact that participants do not know which arm of the trial they have been assigned to, i.e. they do not know if they will receive the control or experimental drug regimen.

An adverse effect produced by a drug that is detrimental to one’s health.

A product (vaccine, drug, etc.) that has not completed all the phases of clinical trials and has not been approved by a regulatory authority

Refers to the experimental treatment yielding at least equivalent results as the standard treatment.

A product (vaccine, drug, etc.) that has completed clinical trials and has been approved by regulatory authorities for use in the general population.

The number of patients required to participate in a clinical trial in order to obtain desired data.

The process of a potential trial participant understanding trial participation and making a voluntary decision to participate.
<table>
<thead>
<tr>
<th>Session 3</th>
<th>Stages of TB Drug Research and Development</th>
<th>[Chapter I]</th>
</tr>
</thead>
</table>
| **OBJECTIVES:** | By the end of the session participants will be able to:  
  - Describe and distinguish the stages of TB drug research and development. | |
| **METHOD:** | Categorization and discussion. Participants read characteristics of the stages of research and development and decide which category each belongs to. | |
| **PREPARATION:** | ***Facilitator should perform the following steps BEFORE conducting this session.***  
  **Note that these steps are not part of the exercise delivery**  
  - Read through the INFORMATION section in Chapter I (pp. 24-30) and be sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.  
  - Make three large banners labelled ‘DISCOVERY’, ‘PRE-CLINICAL’, and ‘CLINICAL’.  
  - Cut the CHARACTERISTICS pages below (pp. 44-45) as instructed.  
  - For a group who has never been introduced to these concepts, copy pages 26-29 of the CORE INFORMATION section for all participants as a handout.  
  **IMPORTANT!**  
  Be sure to review the specific details and objectives of ongoing trials at your site, or in your area, with a trial investigator/coordinator if necessary. Remember that the CHARACTERISTICS in this exercise are generic and describe a standard process of TB drug research and development. Write any specific notes you may need in the Trainer’s Notes box below. | |
| **EXERCISE DELIVERY:** | Estimated session time: **45 minutes** | |

**STEP ONE:** Briefly explain the purpose of the session and how it will be conducted.

**STEP TWO:** For a beginner level audience – participants who have had little to no exposure to the information in this session – start with a brief overview of the concepts to be covered. Use relevant information from the CORE INFORMATION section as a guide.

Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member.
For an intermediate/advanced audience, the overview can be skipped. Rather facilitate a more in-depth, interactive discussion about concepts during STEP FOUR.

STEP THREE: Distribute prepared CHARACTERISTIC slips of paper to each participant that describes one stage in the process of TB drug research and development (depending on your number of participants, some may get more than one slip of paper or more than one participant may have to share the same slip of paper). Participants must decide which stage the characteristic falls under and tape it on the corresponding banner in the room.

If necessary, distribute the prepared copies of the INFORMATION section. Give participants about 10 minutes to place their characteristic in the stage they believe it describes. Make sure to tell trainees that several characteristics fit in more than one category. Encourage them to discuss characteristics with other trainees.

STEP FOUR: Once participants are finished, lead a discussion about each R&D stage according to the characteristics assigned to each, using the EXERCISE ANSWERS (p. 46) as a guide. Start with discovery, then pre-clinical trials, then clinical trials. Be sure to make any corrections if characteristics have been placed in the wrong stage. Let trainees lead this discussion as much as possible.

CLOSING: Close by asking if there are any questions or need for clarification. Some closing points should include:

- The process of finding new, more effective TB drug regimens follows a standard process of research and development that is required for any new drug, vaccine, or other product.
- It can take many years to complete the entire research and development process before new drugs can be made available.
- This exercise has discussed generic information about the stages of research and development. Specific details may change according to the type of product being developed, the objectives of the research, or many other factors, and may differ slightly from the information presented in this session.

TEST QUESTIONS: Use or adapt the following question for the training session pre- and post-test.
1. Before a new TB drug can be tested in humans, it goes through all of the following, except:
   a. Pre-clinical testing
b. Phase I clinical trials

c. Discovery phase of testing chemical compounds in a laboratory

d. *In vitro* testing

TEST ANSWER: 1. b

Trainer’s Notes:
**CHARACTERISTICS:** Stages of TB Drug Research and Development

*Facilitator: Cut this handout along the dotted lines for distribution of individual characteristics to participants*

---

The initial stage of research and development of a new product

---

The stage when a new drug is tested in humans

---

The stage when chemical compounds are tested in a laboratory

---

This stage is sometimes referred to as ‘idea generation’

---

No human testing is involved in this stage

---

Includes Phase I, II, III, and IV trials

---

Involves *in vivo* testing

---

Involves *in vitro* testing

---

The final stage of product development

---

Determines safety and efficacy of a new drug (or other product) in animals
Gives an indication of whether the new drug will be safe and effective in humans

Safety of the new drug is studied in this stage

Potency of the new compound or drug is studied in this stage

Includes studies after the new drug has been approved, licensed and distributed in the general population

Efficacy of the new compound or drug is studied in this stage
EXERCISE ANSWERS: Stages of TB Drug Research and Development

Facilitator: Use the key to guide final discussion about each stage

**DISCOVERY**
The initial stage of research and development of a new product
The stage when chemical compounds are tested in a laboratory
This stage is sometimes referred to as ‘idea generation’
No human testing is involved in this stage*
Involves *in vitro* testing
Potency of the new compound or drug is studied in this stage

**PRE-CLINICAL TESTING**
No human testing is involved in this stage*
Involves *in vivo* testing*
Determines safety and efficacy of a new drug (or other product) in animals
Gives an indication of whether the new drug will be safe and effective in humans
Safety of the new drug is studied in this stage*
Efficacy of the new compound or drug is studied in this stage*

**CLINICAL TESTING**
The stage when a new drug is tested in humans
Includes Phase I, II, III, and IV trials
Involves *in vivo* testing*
The final stage of product development
Safety of the new drug is studied in this stage*
Efficacy of the new compound or drug is studied in this stage*
Includes studies after the new drug has been approved, licensed and distributed in the general population
Session 4  Phases of Clinical TB Drug Trials  [Chapter I]

OBJECTIVES: By the end of the session, participants will be able to:
- Describe and distinguish the phases of TB drug trials.

METHOD: Categorization and discussion. Participants read characteristics of the phases of clinical TB drug trials and decide which category each belongs to.

PREPARATION: Facilitator should perform the following steps BEFORE conducting this session. Note that these steps are not part of the exercise delivery.
- Read through the INFORMATION section in Chapter I (pp. 24-30) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.
- Cut the CHARACTERISTICS pages below (pp. 50-51) as instructed.

IMPORTANT!
Be sure to review the specific details and objectives of ongoing trials at your site, or in your area, with a trial investigator/coordinator if necessary. Remember that the CHARACTERISTICS in this exercise are generic and describe a standard process of TB drug trials. Write any specific notes you may need in the Trainer’s Notes box below.

EXERCISE DELIVERY: Estimated session time: 45 minutes

STEP ONE: Briefly explain the purpose of the session and how it will be conducted. Participants will each receive a characteristic that describes a phase of TB drug trials. They must decide which trial phase the characteristic describes.

STEP TWO: For a beginner level audience – participants who have had little to no exposure to the information in this session – start with a brief overview of the concepts to be covered. Use relevant information from the CORE INFORMATION section as a guide.

Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member.
For an intermediate/advanced audience, the overview can be skipped. Rather facilitate a more in-depth, interactive discussion about concepts during STEP FIVE.

STEP THREE: Distribute prepared CHARACTERISTIC slips of paper to each participant (depending on your number of participants, some may get more than one slip of paper or more than one participant may have to share the same slip of paper).

NOTE
Make sure to tell participants that several characteristics describe more than one clinical trial phase.

STEP FOUR: Lead an interactive discussion about each trial phase. Use the EXERCISE ANSWERS (p. 52) as a guide.

For a beginner level audience, i.e. participants who have never been exposed to the information, give a basic description of the trial phase, starting with Phase I. Then, ask participants to stand up if their characteristic describes that trial phase. Ask each participant who stands to read their characteristic aloud and give a brief explanation of its significance to the trial phase. Be sure to make any corrections if any participants stand up for the wrong trial phase.

IMPORTANT!
Be sure to emphasize the characteristics which fall under more than one clinical trial phase, and that participants with those characteristics should stand for every relevant phase announced.

STEP FIVE: Lead an interactive discussion about the following:

- The TB drug clinical trials process, and timeline, may not always follow the step-by-step process described in this exercise. For instance, if an experimental drug in Phase II testing shows promise as a single drug, but is not effective when put into a combination TB drug regimen, scientists may need to go back to testing other potential compounds in discovery, pre-clinical, or Phase I trials to find other experimental drugs appropriate for clinical testing in TB patients.
- Many different experimental new drugs are being tested at the same time. How one new drug is carried forward through clinical testing may be influenced by the outcomes of trials of other new drugs. Do participants know anything about any of the experimental TB drugs in testing?
The TB drug clinical trial process can take many years. It is difficult to estimate exactly how long it will take to license a new TB drug for use in the population. Looking at the characteristics, ask participants to guess at least how long the entire process might take. Make sure to point out that this is not an exact estimate but simply meant to show that the full process is very long and difficult to estimate.

CLOSING: Close the session by emphasizing that this exercise has discussed general information about TB drug clinical trial phases. Specific details are tailored according to the particular drug, the research questions, and many other factors.

TEST QUESTIONS: Use or adapt the following questions for training session pre- and post-test.
1. This phase of clinical TB drug trials involves people who are not infected with TB:
   a. Phase I
   b. Phase II
   c. Phase IV
   d. None of the above

2. Which of the following is true about clinical TB drug trials?
   a. Phase IV trials must be conducted before a new drug can go through regulatory approval, licensure, and distribution.
   b. All clinical trials of new TB drugs are conducted in people who are infected with TB.
   c. Before clinical trials begin, scientists have an indication of safety and efficacy in humans from studies conducted in animals.
   d. Phase III trials involve testing a new TB drug by itself and/or as a part of full combination therapy.

TEST ANSWERS 1. a; 2. c

Trainer’s Notes:
CHARACTERISTICS: Phases of Clinical TB Drug Trials

Facilitator: Cut this handout along dotted lines for distribution of individual characteristics to participants

Follows regulatory approval, licensure, and distribution of a new drug to the target population

Participation in a trial of this phase can last anywhere from two weeks to two months

First time an experimental drug is tested in humans

Participation in this phase generally lasts one year longer than the treatment regimen being tested

Involves trial volunteers who are not infected with TB

Involves volunteers who are infected with TB

Tests the experimental drug only as part of a combination

The final stage of clinical testing before licensure, approval, and distribution of the new drug

Tests the experimental drug only by itself
Safety of the experimental drug is studied in this phase

Efficacy of the experimental drug is studied in this phase

Involves testing of an experimental drug by itself and/or as part of a full combination therapy
EXERCISE ANSWERS: Phases of Clinical TB Drug Trials

Facilitator: Use the answers below to guide the final discussion about each phase of clinical trials.

PHASE I
Involves trial volunteers who are not infected with TB
Safety of the experimental drug is studied in this phase*
Tests the experimental drug only by itself
First time an experimental drug is tested in humans

PHASE II
Participation in a trial of this phase can last anywhere from two weeks to two months
Involves testing of an experimental drug by itself and/or as part of a full combination therapy
Efficacy of the experimental drug is studied in this phase*
Safety of the experimental drug is studied in this phase*
Involves volunteers who are infected with TB*

PHASE III
Participation in this phase generally lasts one year longer than the treatment regimen being tested
Efficacy of the experimental drug is studied in this phase*
Safety of the experimental drug is studied in this phase*
The final stage of clinical testing before licensure, approval, and distribution of the new drug
Tests the experimental drug only as part of a combination
Involves volunteers who are infected with TB*

PHASE IV
Follows regulatory approval, licensure, and distribution of a new drug to the target population
Safety of the experimental drug is studied in this phase*
Involves volunteers who are infected with TB*
<table>
<thead>
<tr>
<th>Session 5</th>
<th>Challenges of TB Drug Research &amp; Development</th>
<th>[Chapter I]</th>
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<tbody>
<tr>
<td><strong>OBJECTIVES:</strong></td>
<td>By the end of this session participants will be able to:</td>
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<td></td>
<td>• Discuss and debate the primary challenges to TB research and development.</td>
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<td><strong>METHOD:</strong></td>
<td>Group discussion and debate. Facilitator will leads a discussion about challenges in TB R&amp;D, and participants will devise arguments around the information.</td>
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<td><strong>PREPARATION:</strong></td>
<td><em>Facilitator should perform the following steps BEFORE conducting this session.</em> Note that these steps are not part of the exercise delivery.</td>
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<td>• Read through the CORE INFORMATION section in Chapter I (pp. 24-30) and make sure you are familiar with all concepts, especially those related to this session. If necessary, discuss any questions with a clinical staff member of your trial site team.</td>
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<td></td>
<td>• Gather a flip chart and markers.</td>
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<td><strong>EXERCISE DELIVERY:</strong></td>
<td>Estimated session time: <strong>30 minutes</strong></td>
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<td>STEP ONE: Briefly explain the purpose of the session and how it will be conducted.</td>
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<td>STEP TWO: For a beginner level audience – participants who have had little to no exposure to the information in this session – start with a brief overview of the concepts to be covered. Use relevant information from the CORE INFORMATION section as a guide.</td>
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<td></td>
<td>Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member.</td>
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<td>For an intermediate/advanced audience, the overview can be skipped.</td>
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<td>STEP THREE: Lead a <strong>10 minute</strong> group discussion about the three major challenges to TB R&amp;D, as described on pp. 25-26 in this chapter’s INFORMATION section. The three challenges are:</td>
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<td></td>
<td>• Unique biology of the TB bacteria</td>
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<td></td>
<td>• History of insufficient funding for TB drug research</td>
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<td></td>
<td>• Long duration of treatment regimen</td>
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Use the flip chart to guide the discussion, outlining key points. Involve the participants as much as possible in the discussion. Ask participants if they can think of any additional challenges, and why. If relevant, add these to the list.

STEP FOUR: Divide participants into groups of 2-4 people, depending on your total number of participants. Ask each group to discuss the challenges, and decide which issue they think is the biggest obstacle to TB drug research and development. Groups should come up with an argument for which challenge they chose. Give them about 10 minutes for group work.

Circulate between groups to see which challenge each has chosen. If all groups choose the same challenge, work with any co-facilitators to prepare arguments for why the other challenges present significant obstacles. You will need this to facilitate STEP FIVE.

STEP FIVE: Bring all groups back together. Ask each group to name the challenge they chose. Then, lead a group debate, where each group presents its arguments for the particular challenge. Facilitate an exchange between groups who have chosen different challenges, having each discuss and debate their rationale.

If all groups have chosen the same challenge, you and any co-facilitators should present your prepared points about why the other challenges are significant. Facilitate a discussion and debate about your points.

CLOSING: Close by repeating the three main challenges (and any additional challenges added by participants). Emphasize that this exercise has shown that each challenge poses significant obstacles; there may be debates about which factor is the biggest, but it is difficult to compare one to another.

TEST QUESTION: Use or adapt the following question for training pre- and post-test.

1. Which of the following describes a challenge to TB drug research and development?
   a. The duration of the treatment regimen is too short to see the effects of the experimental treatment.
   b. It is impossible to find appropriate Phase III trial populations in places where TB is common.
   c. The long length of the TB drug treatment regimen adds length to the process of clinical trials.

TEST ANSWER: 1. c

Trainer’s Notes: