TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB Drug Research Literacy Toolkit

1st Edition, March 2011

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Introduction

Global Threat of TB

Tuberculosis (TB) kills someone every 20 seconds — nearly 5,000 people every day, or approximately 1.8 million in 2008 alone, according to the latest estimates from the World Health Organization (WHO). More than a century after *Mycobacterium tuberculosis (M.tb)*, the bacillus that causes TB, was discovered and a half-century after the discovery of antibiotics to treat the disease, TB is second only to HIV as the leading infectious killer of adults worldwide, is the third largest killer of women in their reproductive years, and the leading infectious cause of death among people with HIV/AIDS. The WHO estimates about one-third of the world's population is infected with *M.tb*.

The Need for New TB Drugs

New drugs are critical to ending the needless burden of TB. The current TB drug regimen, a product of scientific advances made between the 1950s and 1970s, requires treatment for six to nine months for active, drug-susceptible TB. Unfortunately, many patients do not or cannot complete this treatment.

Today's four-drug combination, taken ideally under daily monitoring, is burdensome for patients and care providers alike. Poor adherence and prescribing practices have led to the emergence of multi-, and extensively drug resistant strains of TB (MDR-TB and XDR-TB) that increasingly defy current medicines and are spreading throughout many regions of the globe.

The HIV/AIDS pandemic is still escalating in many countries and the number of patients co-infected with HIV/AIDS and TB is increasing dramatically. An estimated one-third of the 40 million people living with HIV/AIDS worldwide are also infected with *M.tb*, and more than a quarter of those who died from TB in 2007 were HIV-positive. However, the current TB drug regimen is not compatible with certain common antiretroviral therapies used to treat HIV/AIDS.

Driven by its deadly synergy with HIV/AIDS, complicated by drug resistant strains, and amplified by the consequences of poverty, today's epidemic is threatening to destabilize gains in TB control.

Delivering a Better Cure

The promise of TB control efforts will only be fully met when patients and healthcare workers are given the best tools that modern science can deliver.

The Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies used for HIV/AIDS, and improve treatment of latent infection.

Working with public and private partners worldwide, the TB Alliance is leading the development of the most comprehensive portfolio of TB drug candidates in history, paving the way for the first new

treatments in over 40 years. The TB Alliance is committed to ensuring that approved new regimens are affordable and universally adopted so that novel drugs that treat TB more quickly and easily are available to all who need them.

Community Engagement

The TB Alliance is committed to supporting Community Engagement (CE) strategies for clinical trials to serve as a bridge between trial researchers and local TB affected communities. Community Engagement strategies help to ensure that study participants, their families, community leaders, and other community members who may be affected by or at risk of TB infection, have an opportunity to partner with the scientific community in the implementation of research efforts.

Community engagement in TB drug research helps to provide mechanisms to:

- educate communities about TB disease, treatment and the research process;
- obtain community input into clinical trial implementation;
- understand community perceptions and experiences, and identify community concerns so that they are addressed in the research process;
- liaise with community stakeholders to facilitate smooth implementation of clinical programs;
- share and discuss clinical trial and research results; and
- motivate communities to assist with program/policy change

Research Literacy

A first step in community engagement is increasing understanding of basic concepts behind TB drug research and development among interested and/or affected stakeholders. Such stakeholders may include community leaders, policymakers, the media and (ultimately) potential trial participants – all who may not have had previous experience with clinical trials and/or TB drug research. Increasing 'research literacy' among these constituencies can lay the foundation for comprehensive community engagement.

TB Alliance's research literacy efforts rely on information and training resources that are easy to understand and do not require a high level of scientific education; these elements are contained in this TB Drug Research Literacy Toolkit. The Toolkit is meant for use by clinical site staff, often in conjunction with Community Advisory Board members, to reach out to the broader community with basic information and messages.

Research literacy efforts may have the following effects:

- Increasing knowledge and awareness about TB drug research & development in the community surrounding a trial site
- Helping potential trial volunteers to make informed, independent decisions to participate , and to retain volunteers
- Building support among a variety of community stakeholders e.g., the media, political leaders, religious leaders, healthcare providers

Guidelines for Trainers

What is the TB Drug Research Literacy Toolkit?

The *Toolkit* is designed to help members and partners of the TB drug research field conduct training workshops for lay audiences about basic TB drug development and clinical trials concepts. The *Toolkit* contains basic information and interactive exercises that can be used or adapted for training, mobilization, and advocacy initiatives.

The *Toolkit* is divided into several *Chapters* around given topic areas. Each *Chapter* contains the following:

- CORE INFORMATION – basic information about the chapter's topic, written in lay terms.
- REFERENCES FOR FURTHER INFORMATION – additional resources about the chapter's topic that Toolkit users may review.
- TRAINING SESSIONS – interactive exercises to be used in TB drug research literacy training workshops or other community outreach activities. Session components are described in detail below under '*Guide to training sessions.'*

Who should use this Toolkit?

Generally, *Toolkit* users will include staff from TB drug clinical trial sites and trial coordinating organizations (e.g., TB Alliance), but may also be used by individuals or groups involved in outreach and advocacy activities, such as NGO partners of trial sites. Everyone who plans to use the *Toolkit* to train or educate others should have a solid background understanding of TB drug development concepts.

How is this Toolkit used?

The Toolkit is primarily meant to be used to plan TB drug research literacy trainings.

If an individual or group would like to conduct research literacy trainings; generally a "training-of-trainers" (TOT) approach is used. A TOT would be conducted with future trainers to orient them to the *Toolkit*, to cover core content, general training skills, and to practice conducting training sessions contained in the *Toolkit*. After the TOT, the trained group should be empowered to conduct outreach activities and/or training workshops with relevant community groups.

Examples of relevant TB drug research literacy trainee groups include:

- Non-clinical staff at TB drug trial sites
- Community Advisory Board (CAB) members and other community members who conduct outreach around clinical trials. (CAB members may also go through the TOT program to become TB research literacy trainers)
- Civil society groups (NGOs, AIDS service organizations, etc.) in countries and regions where trials are being conducted
- Healthcare providers in communities surrounding clinical trials
- Other stakeholder groups such as media, religious leaders, political leaders, etc.

How should a Research Literacy Trainer plan for a TB drug research literacy workshop?

Trainers may follow sample training agendas included in this Toolkit (see pp. 22-23) to conduct a workshop. However, the format of the Toolkit also allows trainers to create their own agendas by picking sessions according to certain factors, described below.

Knowledge level of trainee group

The level of knowledge, or previous experience with TB drug development concepts should be the primary consideration when planning the agenda for a research literacy workshop.

All training sessions cover relevant content in the CORE INFORMATION section of the respective Chapter. Most training sessions, with a few exceptions, are written for a beginner level audience, i.e. trainees who have had little to no previous exposure to the information. Several sessions, due to their content and/or methodology, would be more appropriate for advanced trainees, e.g. those that have been through previous research literacy trainings or have other previous experience. All sessions include guidance regarding trainee level.

However, when preparing any educational session, trainers must consider participants' knowledge level, and adapt sessions as needed. Some questions that may help trainers determine the background level of the trainee group include:

- Have trainees attended a TB drug research literacy workshop in the past?
- Are trainees involved in clinical TB drug trials?
- Have trainees been involved in advocacy or community mobilization efforts for new TB drugs?
- Do trainees work in the TB field?
- In which sector do trainees work (i.e., civil society, government, healthcare, education, religious, media)?

Length of the workshop

Suggested agendas list the training sessions to be conducted during the workshop. However, trainers should allow additional time for activities such as: pre- and post-workshop tests, introductions and time to establish group norms, coffee/tea and lunch breaks, energizers, and workshop wrap-up.

Trainee level may also influence the overall length of the workshop—beginner level trainees may require a longer (two- or three-day) workshop, whereas intermediate or advanced level trainees may benefit most from a short, "refresher" (half- or one-day) workshop.

Can trainers adapt sessions?

Yes. While each session has been written with specific instructions, trainers should feel free to adapt sessions as needed. Trainers may alter the timing of sessions depending, or adapt the content, as needed, for a trainee group from a given sector.

Trainers should also consider adapting sessions based on the cultural context of trainees. Sessions have been developed with generic content, and where possible, trainers may choose to include culturally-relevant examples, metaphors, or stories as a way to make lessons more relevant to trainees.

Does this Toolkit contain basic information about TB?

No. The *Toolkit* only covers TB drug development and clinical trials. This content overlaps slightly with basic TB information, e.g. regarding the need for new TB drugs, but the *Toolkit* does not contain comprehensive general information about TB.

It is very important for trainers to consider the need for basic education around TB, TB disease, and existing TB treatment when planning a TB research literacy training session. In many cases, participants will need some background information, and at the very least, trainers should be prepared to answer general TB questions. Trainers should reference locally and/or nationally available resources, e.g. National TB Programs or Departments of Health, to prepare relevant information delivery to participants. Trainers may also consider partnering with these groups to provide this information and/or conduct general TB sessions at the beginning of a TB drug research literacy workshop.

Guide to training sessions

Each training session contains the following sections:

- OBJECTIVES – States the outcome(s) that trainees should achieve as a result of participating in the session.
- METHOD – Explains the structure of the session (role-play, lecture, matching game, etc.).
- PREPARATION – Lists everything the trainer should do before the training workshop to prepare the particular session. *It is essential that trainers allow adequate preparation time for any workshop they plan to facilitate.* Steps may include:
    - Reviewing content to be covered in the session – content is contained in the CORE INFORMATION section of each Chapter; additional informational references are also suggested in each Chapter. Trainers should review content with a member of their clinical trial staff, if needed.
    - Making copies of materials to be handed out – many sessions include worksheets and/or other handouts for trainees; these can be photocopied or printed from an electronic copy of the *Toolkit.*
    - Gathering additional materials e.g. flip charts, markers, tape.
    - Coordinating co-facilitators – especially for some of the intermediate or advanced sessions, trainers should identify a co-facilitator to help conduct the session, or to serve as a resource for any questions that may be asked by trainees. This may include an investigator, trial coordinator, or nurse from the trial site staff, or a local expert on the subject (e.g. ethicist).
    - Drafting any additional notes for conducting the session – each session includes a *Trainer's Notes* box for this purpose.

- EXERCISE DELIVERY – Gives a step-by-step outline of how to take trainees through the given session. Includes guidance according to trainees' knowledge level (beginner or intermediate/ advanced) and estimated time it may take to deliver the session. *Trainers must remember that these are general guidelines and they should adapt instructions as necessary for their trainee group.*
- CLOSING – Emphasizes important points or steps to take at the end of the session, most often highlighting the key messages.
- TEST QUESTIONS AND ANSWERS – Suggests questions for use in pre- and post-tests given in training sessions. A key component of conducting training workshops is to measure impact. Trainers should always administer a pre-test and a post-test at any research literacy workshop. Trainers should use or adapt the suggested questions for each session included in the workshop agenda. See also the Knowledge Assessment section.
- WORKSHEETS AND INFO SHEETS – Some sessions contain worksheets to be handed out to participants during the session. Worksheets are to be completed by participants; Info Sheets contain information that may help participants complete the activity. (These sheets are outlined with a dotted-line around the border of the page.)

Additionally, sessions may contain 'Training Tips', 'Discussion Prompts', and other important points to provide extra guidance.

Basic training principles

To ensure a successful workshop, it is important to remember basic training principles. This includes tracking time and making sure that sessions are neither too long nor kept so short that lessons are not learned. It is also important to follow your agenda and timeline for the workshop as closely as possible, while remaining flexible in case participants need more or less time for any given session. Trainers may consider assigning one participant or co-facilitator to act as the timekeeper for the workshop.

It is also important to establish agreed upon ground rules (group norms) with the trainee group. Ground rules may include things such as returning from breaks on time, not interrupting others, and turning mobile phones off while the workshop is in session. Trainers should take a few minutes after the welcome and introductions to establish a list of ground rules with the trainees.

Trainer's checklist

Here is a helpful checklist to ensure adequate preparation for a training workshop. As the trainer, ensure that you have done the following well before the date of the workshop:

⇒ Decide on the dates and times of the training session (at least 4-5 weeks before)
⇒ Determine your target audience for the training session (3-4 weeks before)
⇒ Identify the objectives for your training session (3-4 weeks)
⇒ Send invitations and receive confirmations from participants (3-4 weeks)
⇒ Reserve meeting space and make other logistical arrangements (3-4 weeks)
⇒ Determine your trainees' background knowledge about TB drug development (2-3 weeks)

⇒ Read through each session you plan to conduct (2-3 weeks)
⇒ Gather additional informational resources for trainees, e.g. TB Alliance materials (2-3 weeks)
⇒ Finalize the workshop agenda (1-2 weeks)
⇒ Correspond with any co-facilitators to plan relevant sessions (1-2 weeks)
⇒ Contact any presenters for the workshop (1-2 weeks)
⇒ Make copies of the Pre- and Post-Workshop Test (1 week)
⇒ Make copies of all materials to be handed out to trainees (1 week)
⇒ Send reminder and final agenda to all participants of training session (1 week)
⇒ Gather other materials needed (e.g. flip charts, markers, overhead projector) (1 week)

Recommended Reading

- TB In Our Lives: A book of information sheets for people living with TB, support groups, and clinics. Treatment Action Campaign, 2007. http://www.tac.org.za/community/files/file/TBinOurLives.pdf
- Research Fundamentals for Activists. Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE), in collaboration with Treatment Action Group (TAG). http://www.tbhiv-create.org/sites/default/files/ResearchFundamentals%5Bofficialversion%5D.pdf
- Good Participatory Practice: Guidelines for Biomedical HIV Prevention Trials. AIDS Vaccine Advocacy Coalition (AVAC) and UNAIDS. http://data.unaids.org/pub/manual/2007/jc1364_good_participatory_guidelines_en.pdf
- VaxLit *Core Content*: AIDS Vaccine Literacy Toolkit. International AIDS Vaccine Initiative (IAVI). Found at: http://www.iavi.org/working-with-communities/Pages/vaccine-literacy.aspx
- Family Health International Research Ethics Training Curriculum http://www.fhi.org/NR/rdonlyres/et4ovl5htmkfgojpzjl6xfdgciabw76tkscnezcnqkr3oxvs5fqfxjjrgaznp5kt2vtaz6etfrfi7o/RETC2Full.pdf

Knowledge Assessment

A key component of conducting educational workshops is measuring how much knowledge is gained by the participants of the training. At the beginning and the end of any research literacy training workshop, trainers should always administer a pre and post knowledge assessment (test), to measure the group's baseline knowledge of the content, and their post training understanding – this will help trainers to measure the "impact" of their session on the group. Sample pre- and post-tests are included below. These may be used as they are, or adapted according to the following guidelines.

Guidelines for adapting Pre- and Post Test

Section I – Demographic information

This section contains questions about the participants' general demographic information. It can be adapted as needed, depending on the baseline factors that trainers or researchers feel may be correlated to knowledge transfer.

Section II – Preliminary knowledge and experience

This section collects information about participants' previous experience with TB drug research-related concepts. It will provide important insight on their level of exposure to information and will supplement the technical questions in Section III. It will also help trainers gain an understanding of the correlation between previous exposure and baseline understanding of technical concepts. These questions may also be adapted in order to collect the information in the most relevant way.

Section III – TB Basics

This section collects information about participants' understanding of basic TB facts, and will provide insight on the baseline knowledge of the trainee group. These questions may be adapted in order to collect information in the most relevant way to the trainee group.

Section IV – TB drug research

This section contains technical questions about TB drug research and development. It is very important that trainers adapt this section according to the following guidelines:

- Test questions should reflect the content covered in research literacy training workshops as closely as possible. Each training module in this Toolkit includes specific test questions and answers which trainers should use or adapt when developing pre- and post-tests. The templates below contain questions from almost all of the training modules, and trainers should be sure not to include the questions from sessions not included in their workshop agenda.
- As per the templates below, pre- and post-tests must contain the same technical questions in order to get the most accurate measurement of knowledge gained during the training as possible.
- It is very important to leave enough time in the workshop agenda for both the pre- and post-tests. See 'Sample Agendas', below, which suggest approximately 20 minutes for each. Trainers should decide if more time will be needed for the trainee group and adjust accordingly.

Other types of knowledge assessment activities

There are many other ways that to assess the knowledge of a trainee group. A written test or quiz may not always be the most appropriate method, and research literacy trainers should be able to adapt their methods in order to obtain the best assessment of their participants.

If written tests will not work for a group, consider facilitating some other types of interactive knowledge assessment activities:

- Group discussions
- Interactive group question and answer sessions
- Oral quizzes or tests

General knowledge of a group can also be assessed through activities such as; brainstorms, role plays, presentations or games about the material being covered in the training session.

Sample Pre-Workshop Test

Name _____ **Date** _____

mm / dd / year

I. Demographic information

Please provide the following information about yourself.

a. *Age*

___ Less than 18 ___ 26 – 35 ___ 46 – 55

___ 18 – 25 ___ 36 – 45 ___ Above 55

b. *Gender* ___ Male ___ Female

c. *Home area* ___ Urban ___ Rural ___ Other

d. *Employment* ___ Employed ___ Unemployed

If employed:

e. My sector of work can be described as

___ Medical/healthcare
___ Religious-affiliated
___ Political/Ministry-related
___ Academic
___ Civil society
___ Other: _____

f. My position/title can best be referred to as

___ Doctor
___ Nurse
___ Community Healthcare Worker
___ DOT Supporter
___ Traditional Healer
___ Educator
___ Social Worker
___ Religious Leader
___ Government Official
___ Elected Community Rep
___ Laborer/Farmer
___ Technician
___ Administrator
___ Community worker
___ Researcher
___ Community Engagement Officer
___ Program officer/manager
___ Lawyer
___ Vendor
___ Other: _____

If not employed:

g. The following describes my day-to-day responsibilities

___ Volunteer
___ Student
___ Stay-at-home parent
___ Retired

___ Other: _____

II. Preliminary knowledge and experience

Have you ever attended a:

a. Training on TB disease? Yes No
b. Training on TB treatment? Yes No
c. Training on clinical trials? Yes No
d. If yes, which one?_____
e. Other (specify) _____
f. Have you ever heard of research to develop new TB drugs? Yes No
   If yes, please provide detail: _____
   _____
g. Has a clinical TB drug trial ever been conducted in your area? Yes No Don't Know
h. Is a clinical TB drug trial currently being conducted in your area? Yes No Don't Know
i. Is a clinical TB drug trial planned to occur in your area in the future? Yes No Don't Know

III. TB basics

Please complete the following questions. Mark one response only for each question.

1) All of the following are signs or symptoms of TB disease, EXCEPT:
   a. Cough lasting 2 weeks or longer
   b. Night sweats
   c. Weakness/fatigue
   d. Weight gain
   e. Sputum/mucus

2) TRUE/FALSE: Most forms of TB are curable with medication.

3) All of the following help to spread TB disease, EXCEPT:
   a. Sharing spoons or cups
   b. Keeping windows closed; poor ventilation
   c. Staying in a small space with others for a long period of time; prolonged exposure
   d. Coughing, sneezing, talking or laughing without covering your mouth
   e. Not completing TB treatment

4) TRUE/FALSE: Having TB makes it easier to get HIV.

5) TB Disease can attack all of the following parts of the body, EXCEPT:
   a. Lungs
   b. Bones
   c. Hair
   d. Brain
   e. Kidney

6) TRUE/FALSE: If TB treatment is not taken properly, or doses are missed, the TB bacteria can become resistant to the drugs; causing a longer, more dangerous and more difficult to treat infection called MDR-TB (multiple drug resistant TB).

7) If you or someone you know starts to show signs of a TB infection you/they should:
   a. Go straight to the doctor for a TB test, and learn about the disease and treatment
   b. Take precautions to prevent spreading the infection to others; cover mouth when coughing, sneezing or talking to others
   c. Tell family members, or others living in the same space to also be tested for TB
   d. Take the full course of treatment, without missing doses, to be cured of the disease
   e. All of the above

IV. TB drug research

Please complete the following questions. Mark one response only for each question.

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 feel better 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.

3) 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 only
   d. A chemical substance used to determine if someone is infected with TB

4) Randomisation in a TB drug trial means:
   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

5) 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

6) This phase of clinical trials for TB drugs involves people who are NOT infected with TB:
   a. Phase I
   b. Phase II
   c. Phase IV
   d. None of the above

7) 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.

8) 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 duration of TB drug treatment adds a lot of time to the process of clinical trials.

9) In order to participate in a typical Phase III TB drug trial for drug-sensitive TB, a person must:
   a. Discuss participation with family and friends and receive their approval to participate
   b. Be HIV-negative
   c. Be newly diagnosed with TB and never have been on a TB treatment regimen
   d. Be infected with drug-sensitive TB
   e. (c) and (d)

10) The following person would be excluded from a standard Phase III TB drug trial:
   a. A married woman who plans, with her husband, to have a baby in the next year
   b. A 17-year old man newly diagnosed with pulmonary TB
   c. Someone who is likely to take a new job and move from the area within the next year
   d. All of the above

11) Which of the following describes the informed consent process in clinical trials?
    a. A group education process that includes signing an agreement with other potential volunteers in the trial
    b. The process of explaining the clinical trial or study to potential volunteers and ensuring that they understand and independently sign an agreement before joining
    c. The process of informing a participant about a trial
    d. The consent given by volunteers to receive information about a specific trial-related issue

12) Which of the following indicates that a volunteer can give informed consent and participate in the trial?
    a. He is counting on the new drug regimen to be more effective than the standard regimen.
    b. She believes it is a good way to convince her husband that she shouldn't get pregnant.
    c. She understands the need for new, better TB drugs, and the benefits and potential risks of participating in the clinical trial.
    d. He is excited to participate, even though there is a chance he could take a job in a different district within the next year.

13) Which of the following practices is NOT part of ensuring ethical conduct of clinical trials?
    a. Benefits for trial volunteers greatly outweigh any risk from participating in the trial.
    b. The trial protocol is reviewed and approved by external bodies before starting the trial.
    c. The drug being tested, once developed and licensed for use should be relevant and accessible to the trial population and surrounding community.
    d. A Community Advisory Board is in place to serve as a liaison between the research institution and the surrounding community.

14) TRUE/FALSE: While community stakeholders (e.g. community based organizations, media, community leaders) do not generally have a defined or official role in clinical trials, their support, partnership, and advocacy can be critical to successful research.

15) TRUE/FALSE: Clinical trials are the only way to determine if a new product (drug, vaccine, etc.) will work in humans.

16) Which of the following is NOT true for Phase III TB drug trials?
    a. Trial volunteers will know if they receive the experimental drug or not during the trial.
    b. An individual's participation lasts about a year longer than the standard course of TB treatment.
    c. The trial is always guided by international ethical standards.
    d. All participants must give written, voluntary, informed consent before enrolling in the trial.

If you finish before the time allocated, please stay in your seat and wait. Take this time to check that you have answered all questions as accurately as possible.

Sample Post-Workshop Test

Name _____ **Date** _____
mm / dd / year

Please complete the following questions. Mark one response only for each question.

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
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   c. Current drugs cause difficult side effects for many patients
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    c. The drug being tested, once developed and licensed for use should be relevant and accessible to the trial population and surrounding community.
    d. A Community Advisory Board is in place to serve as a liaison between the research institution and the surrounding community.

14) TRUE/FALSE: While community stakeholders (e.g. community based organizations, media, community leaders) do not generally have a defined or official role in clinical trials, their support, partnership, and advocacy can be critical to successful research.

15) TRUE/FALSE: Clinical trials are the only way to determine if a new product (drug, vaccine, etc.) will work in humans.

16) Which of the following is NOT true for Phase III TB drug trials?
    a. Trial volunteers will know if they receive the experimental drug or not during the trial.
    b. An individual's participation lasts about a year longer than the standard course of TB treatment.
    c. The trial is always guided by international ethical standards.
    d. All participants must give written, voluntary, informed consent before enrolling in the trial.

If you finish before the time allocated, please stay in your seat and wait. Take this time to check that you have answered all questions as accurately as possible.

Answer Key for Pre- and Post-Test Technical Questions

TB Basics Questions

1. D
2. TRUE
3. A
4. FALSE
5. C
6. TRUE
7. E

TB Drug Research Questions

1. E
2. TRUE
3. C
4. A
5. B
6. A
7. C
8. C
9. E
10. D
11. B
12. C
13. A
14. TRUE
15. TRUE
16. A

Sample Research Literacy Workshop Agendas

The following suggested agendas may be adapted based on the objectives or needs of a particular TB research literacy training.

Sample Agenda #1 / Workshop time: 1 day / Participant level: Beginner

Introductions, expectations, group norms, etc.	20 minutes
Pre-workshop test	20 minutes
Overview of TB basics *[Invite a partner group (DOH, NGO, etc) to give an overview session covering relevant topics not contained in this Toolkit, e.g. TB disease, TB treatment, TB/HIV co-infection.]*	60 minutes
Session 1: The Need for New TB Drugs	45 minutes
– coffee/tea break –	10 minutes
Overview of TB drug research and development [*Invite a member of the clinical trial staff (e.g. trial coordinator, principal investigator) to co-facilitate a session which introduces the concepts you plan to cover in the day's training sessions; use Core Information in Toolkit Chapters as a guide if needed.]*	45 minutes
Session 3: Key Concepts in TB Drug Development and Clinical Trials	45 minutes
– lunch break –	60 minutes
Session 12: Agree or Disagree *[Facilitate this session using 1 debate statement that is not too complex and reflects issues discussed during the morning's sessions.]*	15 minutes
Session 6: Can I Participate?	30 minutes
Update on TB trials in the area [*Invite a member of the clinical trial site staff (e.g. trial coordinator, principal investigator) to give a presentation on relevant TB drug trials in the community, country, or region. If possible, ask the presenter to give a global overview of TB drug research. Try to work with the presenter ahead of time to ensure the presentation is not too technical, and be prepared to help translate technical information into simple terms for trainees. Leave at least 15 minutes for Q & A with the trainees.]*	45 minutes
– coffee/tea break –	15 minutes
Session 9: The Wrong Foot – A Clinical Trial in Your Community	30 minutes
Session 13: Popcorn	20 minutes
Post-workshop test	20 minutes
Wrap-up and Feedback	15 minutes

Sample Agenda #2 / Workshop time: ½ day / Participant level: Beginner

Introductions, expectations, group norms, etc. 20 minutes

Pre-workshop test 20 minutes

Overview of TB basics 30 minutes

[*Invite a partner group to give an overview session covering relevant topics not contained in the* Toolkit*, e.g. TB disease, TB treatment, TB/HIV co-infection.]*

– coffee/tea break – 15 minutes

Overview of TB drug research and development basics 60 minutes

Give several brief overviews of basic concepts, including:

- *The need for new TB drugs*
- *Global and local overview of clinical TB drug trials*
- *Clinical trials concepts – placebo, randomization, non-inferiority, safety, etc. (see Session 2)*
- *Phases of clinical TB drug trials*
- *Participation in a TB drug trial*

Participatory sessions

[Conduct shortened versions of Toolkit training sessions around concepts discussed. Conduct only the participatory activity from sessions and skip any overview or lecture. Limit activities to 20 minutes each, but be sure to allow any needed discussion.] Conduct the following sessions:

- *Session 2: Key Concepts in TB Drug Development and Clinical Trials* 20 minutes
- *Session 4: Phases of Clinical TB Drug Trials* 20 minutes
- *Session 6: Can I Participate?* 20 minutes

Session 12: Agree or Disagree 15 minutes

[Facilitate this session using 1 debate statement that is not too complex and reflects issues discussed during the morning's sessions.]

Post-workshop test 20 minutes

Wrap-up and Feedback 15 minutes

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 improvement 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 <u>not</u> 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 <u>are</u> infected with TB.

Phase II Clinical Trials:

Phase II clinical trials are the first studies of an experimental drug (or drugs) in people who <u>are</u> 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.

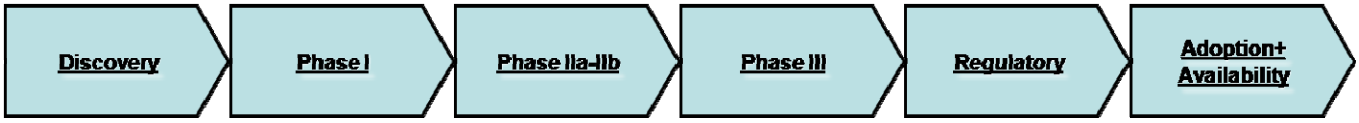
Following completion of Phase III testing, drug candidates must be evaluated and licensed by regulatory bodies, such as the U.S. Food and Drug Administration (FDA), European Medicines Agency, and national regulatory authorities in the countries where they are to be used, before they can be administered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

Session 1	The Need for New TB Drugs	[Chapter I]

OBJECTIVES:

By the end of this session participants will be able to:

- Describe why new TB drugs are needed.
- Argue the case for TB drug research and development.

METHOD:

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&D to others.

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 from your trial site.
- Gather four sets of flip charts and markers.

EXERCISE DELIVERY:

Estimated session time: **45 minutes**

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

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:

- What types of drugs are currently used to treat TB?
- What does taking TB drugs entail? (number of pills, how often drugs must be taken, side effects, etc.)
- 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?
- What are some of the obstacles to completing treatment properly?
- What are TB patients' experiences with accessing treatment? Is it easy? What obstacles exist? How can patients ensure their treatment is prescribed correctly?
- What can happen if someone does not complete their entire course of treatment?

As you discuss, write participants' responses on the flip chart, highlighting the drawbacks to currently available TB treatment.

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 INORMATION 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.

> TRAINING TIP
> 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.

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:

EXERCISE SOLUTION

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

TERMS

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

RANDOMIZATION	BLINDING
EXPERIMENTAL PRODUCT	TOXICITY
LICENSED PRODUCT	ENDPOINT
SAMPLE SIZE	INFORMED CONSENT
CONTROL GROUP	NON-INFERIORITY
ADVERSE EVENT/REACTION	BIAS
PLACEBO	EFFICACY
SAFETY	INCLUSION/EXCLUSION CRITERIA

DEFINITIONS

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

– –

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.

_ _

Session 3 Stages of TB Drug Research and Development [Chapter I]

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 INORMATION 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 INORMATION 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*

Session 5 Challenges of TB Drug Research & Development [Chapter I]

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

- Discuss and debate the primary challenges to TB research and development.

METHOD: Group discussion and debate. Facilitator will leads a discussion about challenges in TB R&D, and participants will devise arguments around the information.

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.
- Gather a flip chart and markers.

EXERCISE DELIVERY: Estimated session time: **30 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 INORMATION 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.

STEP THREE: Lead a **10 minute** group discussion about the three major challenges to TB R&D, as described on pp. 25-26 in this chapter's INFORMATION section. The three challenges are:

- Unique biology of the TB bacteria
- History of insufficient funding for TB drug research
- Long duration of treatment regimen

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:

Chapter II – Clinical TB Drug Trial Participation

CORE INFORMATION

Volunteer trial participants are one of the most valuable and essential components of the clinical research process. Without their willingness to participate, new drug treatments would not make it through clinical testing and reach those in the world who desperately need them. Volunteer participation in clinical TB drug trials is participation in the global effort to bring new, improved TB drug treatments to patients who need them. Clinical research can take a very long time, and it may be several years before new TB drug treatments are available to patients; however, each clinical trial brings us closer and closer to a new, better treatment for TB.

Benefits and Risks

In any clinical drug trial there are potential benefits as well as potential risks to participating. It is the responsibility of the local research team to ensure that every individual screened for potential participation fully understands both of these important aspects of the trial, prior to enrollment.

Some potential benefits of participating in a TB drug trial include:

- Contributing to important medical research that may be beneficial to others and "make a difference" in the fight against TB globally.
- Having consistent, high quality health care from a team of doctors and nurses, while the trial is running. It is well established that the outcomes for patients enrolled in tuberculosis trials are better than for patients in routine care.

Any experimental drug may pose certain risks, and it is essential that participants understand these potential risks prior to enrollment. Risks of participating in a TB drug trial may include:

- The study regimen could be ineffective or less effective than standard treatment against TB.
- There could be different and/or additional side effects to experimental drugs, in comparison to standard TB treatment.

Safety

One of the most important objectives of every phase of research, from discovery through clinical, is to evaluate the safety of the experimental drug being tested. Before a drug candidate is tested in humans (clinical testing), researchers have a good indication of the drug's safety, and efficacy, profile from discovery and pre-clinical (animal) studies. Data from these earlier phase studies provides guidance for how safe it would be to test an experimental drug in humans.

Clinical drug trials are very carefully and strictly designed to protect the safety of human participants. Every clinical trial, no matter how small or where it is conducted, goes through a rigorous process of scientific, regulatory, and ethical review to ensure that volunteers will not be put at undue risk.

Phase I trials are the first trials testing an experimental drug in humans, and are designed to test the drug in a small number of healthy volunteers. Based on safety data from pre-clinical research, scientists have an acceptable level of certainty these healthy volunteers will not experience significant side effects from the experimental drug.

Each phase of clinical testing is conducted in a larger group of patients. The longer the experimental drug is tested, in larger and larger groups of participants, the better researchers understand its effects on the body, and what potential safety issues there is likely to be for humans.

Once a new drug is approved and distributed to the intended population for use, additional safety information continues to be gathered through large-scale Phase IV market studies, often over the course of several years.

Detailed safety information about the experimental drug and potential risks and benefits of participation are outlined in the informed consent document, which is given and explained to every potential trial participant before they give informed consent and enroll in the trial.

Criteria for Participation

Every clinical trial has different guidelines and requirements for enrollment that are approved by the regulatory and ethics authorities before the trial may begin. These requirements are created to ensure participant safety, and also to ensure that the group of participants enrolled in the study have the qualities needed to help researchers prove or disprove their hypothesis. This set of guidelines is called inclusion/exclusion criteria.

Inclusion/Exclusion Criteria

The information below describes example inclusion and exclusion criteria for a Phase III clinical TB drug trial. PLEASE NOTE that this is general information. You should review specific requirements for ongoing trials at your site or in your area.

Trial participants must meet all the inclusion criteria and none of the exclusion criteria.
Example inclusion criteria include:

- Signed written informed consent or witnessed oral consent (in the case of illiteracy), before undertaking any trial related activity
- Infected with active TB disease as determined by sputum samples, and infected with the type of TB that is sensitive to the candidate drug
- Within appropriate age range – most TB drug trials are conducted with adults at least 18 years of age and below an upper age limit; this may vary depending on the purpose/objectives of a given trial, e.g. some trials specifically test pediatric TB drugs
- No previous TB treatment
- Firm home address that is readily accessible for visiting and willingness to inform the study team of any change of address during the treatment and follow-up period

- Agreement to give a sample of blood for HIV testing
- Women – negative pregnancy test and consistent use of barrier form of contraception, surgical sterilization or have an IUD in place
- No significant health problems unrelated to TB, as per specific laboratory parameters (may vary from site to site and/or trial to trial)

General exclusion criteria include:

- Unable to take oral medication
- Previous enrollment in the study
- Receipt of any experimental drug in the past 3 months
- Receipt of any antibiotic against TB in previous 14 days (fluoroquinolones, macrolides, standard anti-TB drugs)
- For trials of first-line treatment drugs (i.e. those to treat drug-sensitive TB) a positive test for multidrug resistant TB (MDR-TB)
- Any condition that could potentially be fatal in the near future
- Pre-existing non-TB diseases or syndromes (e.g. diabetes, blood disorders, liver failure) that may influence the patient's response to TB drugs or general health
- Pregnancy or breast-feeding, or plans to become pregnant during the duration of the trial participation
- Use of antiretrovirals or advanced HIV infection as per CD_4 cell count
- Any condition which may preclude patient from adhering to treatment regimens, e.g. psychiatric illness
- Contraindications or allergy to any study medications or forms of medications
- Low weight, generally less than 35kg

Informed Consent

Informed consent is a cornerstone of ethical research. It is an agreement between researcher and participant, which indicates that the volunteer fully understands and agrees to all aspects of participating in the trial. The agreement is documented when the volunteer signs the informed consent form.

Informed consent document

The informed consent document is the paper that must be signed by every clinical trial volunteer indicating his or her FULL understanding of, and agreement to the following:

- Why the research is being done
- What researchers want to accomplish and who is responsible for the study
- What will be done during the trial and for how long, e.g. number and duration of clinic visits
- Potential safety issues or risks
- Details about the experimental drug
- What is expected of trial participants
- What, if any, benefits can be expected from participation

- The system in place for care and support of participants
- What other interventions are available
- Individuals right to volunteer their participation or to withdraw from the study at any time

Informed consent process

Obtaining true informed consent from each participant is critical for ethical conduct of clinical trials, especially given the complexity and importance of concepts involved. Rather than being a singular event, informed consent should involve a *process* of education and familiarization with trial participation concepts.

The starting point of the process ideally should involve information dissemination by the research team to the broader community, including key stakeholders apart from potential participants (e.g. community/political leaders, civil society, media).

To reach potential participants, research teams often conduct information sessions in the community which are focused mostly on the details of trial participation. When an interested individual comes into the research center for pre-screening, he or she typically receives a one-on-one counseling session to learn about the study in more detail. Finally, some studies require that before signing the informed consent, potential volunteers complete an assessment of understanding, which is usually in the form of a questionnaire containing true/false, multiple choice, narrative questions or combination of these, to test their comprehension of the trial and participation. If the individual is able to show true understanding of the material, then their informed consent, and signature of the document, can be accepted for participation in the trial.

See **Chapter III** for further information about ethical considerations and the process of informed consent.

Experimental versus licensed drugs

An experimental drug is one that has not completed required testing in clinical trials (generally Phases I–III) and has not been approved and licensed by a regulatory authority for use in the general population. This means that researchers, scientists, doctors and regulatory authorities do not yet know if the experimental drug works and/or what the degree of safety of the experimental drug is. Clinical trials must be completed and the collected data must be analyzed and reviewed by researchers and regulatory authorities before the experimental drug can become licensed and made available. Some experimental TB drug candidates may already be approved for general public use to treat other illnesses (i.e. moxifloxacin); however the drug will not be evaluated or licensed for use in TB treatment until clinical studies are completed. Additionally, Phase IV or post-marketing studies continue to look at the safety of approved and licensed drugs after they are widely available in the general population. Licensed drugs are those that have been through the required phases of clinical trials and are approved for use in the general public.

Clinical research versus standard health care

Many different kinds of clinical trials take place all over the world. Often, clinical research trials are seen as a way for community members to gain access to health interventions that they would not normally be able to access, especially in developing countries. However, it is very important to distinguish between treatments given in clinical trials and those given as part of standard health care. Clinical TB drug trials involve experimental drugs whose safety and efficacy for treating TB have not yet been fully proven. In TB drug trials, volunteers will receive some placebo treatments (an inactive substance) and they will not know if they are being given the standard treatment or the experimental treatment because TB drug trials are double-blinded. Researchers who conduct clinical trials are responsible for ensuring that potential trial volunteers understand the difference between experimental drugs that they receive in clinical trials and the drugs they receive as part of standard health care.

REFERENCES FOR FURTHER INFORMATION

International Conference on Harmonisation of Technical Requirements of Registration of Pharmaceuticals for Human Use: Guidance for Good Clinical Practice [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf]

U.S. Food and Drug Administration Regulations for Good Clinical Practice [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm114928.htm]

Session 6 — Can I Participate? — [Chapter II]

OBJECTIVES:

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

- Describe the general eligibility requirements for participation in a TB drug trial.

METHOD:

Quiz. Participants will review personal characteristics of a group of potential trial volunteers and decide if the individual is eligible to be enrolled.

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 II (pp. 55-59) 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.
- Make copies of the WORKSHEET (pp. 62-63) for all participants.

> **NOTE**
> Each clinical trial has different eligibility requirements for participation. It is important to remember that information in this session is meant to be general, and not to describe a specific clinical trial. Make sure to emphasize this point to your session participants.
> You may need to adjust the items on the worksheet to be consistent with local requirements in your country and/or the trial phase you want to address.

EXERCISE DELIVERY

Estimated session time: **30 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 INORMATION 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.

STEP THREE: Distribute the WORKSHEET and ask participants to complete it according to the instructions. They can do this either individually or in small groups.

STEP FOUR: When everyone has completed the worksheet, read through each role aloud, and solicit answers from your group. For each ineligible participant, ask if anyone can explain the reason why the person would not have been eligible for the trial. For example, in the case of Volunteer 1, ask if anyone has an idea of why children below a certain age (usually 18 years old) cannot participate in most TB drug clinical trials. Use the WORKSHEET ANSWER KEY (p. 64) as a guide.

CLOSING: Emphasize the following points:

- TB drug trials have strict eligibility requirements to protect volunteers;
- There are many factors that prevent participation – these are called exclusion criteria.

TEST QUESTIONS: Use or adapt the following questions for training session pre- and post-test.

1. In order to participate in a typical Phase III TB drug trial for drug-sensitive TB, a person must:
   a. Discuss participation with family and friends and receive their approval to participate
   b. Be HIV-negative
   c. Be newly diagnosed with TB and never have been on a TB treatment regimen
   d. Be infected with drug-sensitive TB
   e. (c) and (d)

2. The following person would be excluded from a standard Phase III TB drug trial:
   a. A married woman who plans, with her husband, to have a baby in the next year
   b. A 17-year old man newly diagnosed with pulmonary TB
   c. Someone who is likely to take a new job and move from the area within the next year
   d. All of the above

TEST ANSWERS: 1. e; 2. d

Trainer's Notes:

WORKSHEET: Can I Participate?

Instructions: In this exercise you will practice applying eligibility criteria for potential volunteers in a Phase III TB drug trial (for drug-sensitive TB) calling for participants at least 18 years of age. Below you will find brief profiles of possible trial participants; for each one, decide if the volunteer is eligible to participate, and should be screened and possible enrolment.

Volunteer 1 You are a 17-year-old young man.
You have just been diagnosed with TB and have not started treatment.
You are here of your own free will.
___ Eligible ___ Not eligible

Volunteer 2 You are a 20-year-old man.
You are here of your own free will.
You have been infected with TB for one year during which you started a treatment regimen but did not complete it.
___ Eligible ___ Not eligible

Volunteer 3 You are an 18-year-old woman, unmarried.
You have just been diagnosed with TB and have not started treatment.
Your father (or mother) told you that you must volunteer for this trial even though you don't want to.
You are not pregnant and use a barrier form of contraception.
___ Eligible ___ Not eligible

Volunteer 4 You are a 45-year-old married man.
You have just been diagnosed with TB and have not started treatment.
You have recently accepted a promotion and will be moving out of the area in a few months.
___ Eligible ___ Not eligible

Volunteer 5 You are a 25-year-old married woman.
You have just been diagnosed with TB and would like to start treatment.
You are not pregnant.
Your husband wants to have another child within the year.
___ Eligible ___ Not eligible

Volunteer 6 You are a 45-year-old woman.
You have just been diagnosed with TB and are considering starting treatment.
You are not pregnant and use a barrier form of contraception.
You have a busy daily schedule looking after your five children, and find it hard to take medications regularly.
___ Eligible ___ Not eligible

Volunteer 7 You are a 28-year old woman.
You are newly diagnosed with TB and want to find out about treatment options.
You do not know your HIV status, however you fear taking an HIV test because you are afraid of your husband's reaction if you test positive.
___ Eligible ___ Not eligible

Volunteer 8 You are a 50-year-old man.
You have just been diagnosed with TB and want to start treatment as soon as possible.
You have been HIV-infected for several years and are now on antiretrovirals.
___ Eligible ___ Not eligible

Volunteer 9 You are a 35-year-old woman.
You have just been diagnosed with TB and you want to start treatment.
You have read the informed consent form and are eager to participate because you believe strongly that new TB drugs are necessary.
You are here of your own free will.
___ Eligible ___ Not eligible

Volunteer 10 You are a 24-year-old woman.
You have just been diagnosed with TB and have not started treatment yet.
After discussing the informed consent with your husband, you both agree that you should participate in the trial.
You have just had a baby and are breast-feeding.
___ Eligible ___ Not eligible

WORKSHEET ANSWER KEY

1. Ineligible – too young

2. Ineligible – drug-sensitive TB drug trial patients must be newly diagnosed with TB and, in general, be treatment naïve (never been on any treatment regimen)

3. Ineligible – no volunteer should be at any chance of being forced into a trial, or *coercion*; in this case, the young woman's parents telling her she must participate could be a form of coercion

4. Ineligible—participants should not be planning to leave the trial area for the full course of the trial, which in most cases of Phase III TB drug trials is one year longer than the standard treatment regimen, currently about 18 months

5. Ineligible – female participants should not have plans to become pregnant for the course of the trial

6. Ineligible – participants should be likely to follow the daily course of medication, which often is quite rigorous for TB drug trials; participation also requires frequent visits to the study site, which would be difficult for someone with a very busy daily schedule

7. Ineligible – while participants can choose not to find out their HIV status, they are all required to get tested in order to ensure they receive appropriate medical care; this woman could be put at risk of stigma and/or harm due to HIV testing

8. Ineligible—while HIV infection does not exclude people from volunteering, being on ARVs, or advanced HIV infection (determined by CD4 cell count) is an exclusion criteria in most TB drug trials

9. Eligible

10. Ineligible – female participants cannot be pregnant or breast feeding

Session 7 — Is This Informed Consent? — [Chapter II]

OBJECTIVES:

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

- Determine how informed volunteers are about the trial process.
- Demonstrate the ability to explain various aspects of the trial to volunteers who are poorly or only partially informed.

METHOD:

Questionnaire and role play. Participants will have to decide if certain responses to common questions about a trial indicate the respondent is informed enough to give consent. Participants will then role-play how to inform the respondent.

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 II (pp. 55-59) 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.

- Make copies of the WORKSHEET (pp. 67-68) for all participants.

SESSION DELIVERY:

Estimated session time: **75 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 INORMATION 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.

STEP THREE: Distribute the WORKSHEET, and divide participants into groups of 2-4 people to complete the assignment as explained on the worksheet.

STEP FOUR: After about **30 minutes**, call the groups together and go over the 15 examples soliciting their responses (see Exercise Answer Key, pp. 69-70).

STEP FIVE: Lead a discussion of the key points. Questions you can use to prompt discussion include:

- Why is informed consent so important?
- What can happen if someone who is not informed is enrolled in a trial?
- What are some of the most common misconceptions about TB drugs and trials?
- How can clinical trial teams make sure participants give true informed consent?

STEP SIX: Ask several groups to volunteer to perform the role play they prepared.

CLOSING: Reiterate the point that above all, the purpose of insisting on informed consent is to protect the volunteer.

TEST QUESTIONS: Use one or both of the following questions in training session pre- and post-test.

1. Which of the following describes the process of informed consent in clinical trials?
    a. A group education process that includes signing an agreement with other potential volunteers in the trial
    b. The process of explaining the clinical trial or study to potential volunteers and ensuring that they understand and independently sign an agreement before joining
    c. The process of informing a participant about a trial
    d. The consent given by volunteers to receive information about a specific trial-related issue

2. Which of the following indicates that a volunteer can give informed consent and participate in the trial?
    a. He is counting on the new drug regimen to be more effective than the standard regimen.
    b. She believes it is a good way to convince her husband that she shouldn't get pregnant.
    c. She understands the need for new, better TB drugs.
    d. He is excited to participate, even though there is a chance he could take a job in a different district within the next year.

TEST ANSWERS: 1. b; 2. c

WORKSHEET: Is This Informed Consent?

Instructions: Pretend you are a counsellor or investigator working on TB drug trial. Listed below are questions you might ask a patient who is considering whether or not to enroll in the trial. Read the person's answer to your question and decide if the person truly understands the issue in order to give consent regarding this particular topic. Would you accept this answer? If not, what would you say to better inform the person on this topic?

1. Do you understand why this trial is being done?
   "It has something to do with preventing TB."

2. What do you think this new drug is supposed to do?
   "It will cure my TB faster than the drugs that are available."

3. Do you understand how the trial works?
   "We will be given TB treatment and after a certain amount of time; you'll tell us which treatment was the best."

4. Are you aware of the risks involved in taking this TB drug?
   "I think there are more risks of side effects than if I took the standard drugs."

5. Do you understand how long you will be required to participate in this trial?
   "For about as long as it takes to get through the standard drug regimen."

6. Are you here of your own free will?
   "My husband and I talked and we agreed that I could participate."

7. What do you believe about the medical care we will provide you during the trial?
   "If we get sick, you will take care of us."

8. Do you understand that you are not supposed to get pregnant while you are in this trial?
   "Yes. I am here because my husband wants more children and I do not. This will make him use condoms."

9. Are you aware of any benefits of this trial for you?
   "I don't think there are any benefits."

10. Do you understand what confidentiality means?
    "It means I don't have to tell anybody I am involved in this trial."

11. How would you feel if you tested positive for HIV as part of the screening?
    "I won't because I don't have any symptoms of AIDS, and my husband tested negative."

12. Do you realize you can leave the trial at any time?
"I don't want to leave. I want to stay in."

Once you have finished reading through the questions, you and your partner or group should choose one scenario you found particularly interesting. Develop a role play based on the scenario to present to the whole group when the trainer brings everyone back together, showing how you would further educate the potential participant.

EXERCISE ANSWER KEY

1. No. The volunteer does not understand that the trial is for treatment of TB. Generally, TB drug trials determine if a new drug works as well or better than standard drugs.

2. Maybe. The volunteer understands the concept of comparing the new drug regimen to existing ones to determine if it is more effective or just as effective in a shorter period of time, etc. However, the volunteer should clearly understand that this is NOT YET proven, and in fact is the point of the trial, nor can he/she count on getting the new drug since the trial is randomised and double-blind.

3. Yes.

4. No. The volunteer needs to understand that the chance of side effects from the new drug is unknown, and is in fact one of the points of conducting the trial. He/she should also understand that there are risks of side effects from standard drugs which may or may not be comparable to risks from the new drug.

5. No. The person must know the actual trial length and that he/she will be expected to stay in the trial for a period of time, usually 1 year, after completion of treatment to be followed for relapse.

6. Maybe. The counsellor should find out if the husband is pressuring the volunteer, or if she is truly participating of her own free will.

7. No. A volunteer should have a full understanding of the care that will be provided to him/her during the trial. This volunteer should have a better understanding of issues such as the conditions that apply to receiving healthcare, and the amount of time the site is liable to provide care.

8. No. This person should not use trial participation as an incentive for her husband to use contraception. She cannot guarantee that her husband will agree to use condoms and that she can avoid pregnancy for the duration of the trial.

9. No. Volunteers should have a full understanding of both the risks and benefits of participating, and they should not feel coerced into participating based on the benefits. Volunteers should identify with some motivation to participate, whether altruistic or not.

10. No. While it is true that volunteers do not have to disclose their participation, confidentiality also means that this information will be strictly protected by the trial staff as well.

11. No. A person with HIV infection can be asymptomatic, often for a long time, before showing any signs of AIDS. Further, knowing a partner's status does not guarantee the individual's status. The volunteer should be prepared for either a positive or negative result before getting an HIV test as part of screening for the trial.

12. No. Some volunteers may think they will never have a reason to leave the trial, but they should understand that such a situation may arise. Volunteers should have a good understanding of the possible reasons for leaving, and of the right to leave the trial at any point.

Trainer's Notes:

Chapter III – Ethical Conduct and the Role of Community in TB Drug Research

CORE INFORMATION

Brief History of Research Ethics

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, and then analyzed and used as evidence to evaluate whether the original hypothesis has been proven true, or false.

Research is conducted in a variety of different settings, and with a variety of different subjects; laboratories, communities, hospitals, test tubes, animals, and in humans. (See Chapter I for further information.)

Today, clinical research on humans is highly regulated and reviewed, all over the world, to ensure the safety and protection of trial participants. This, however, was not always the case. Ethical principles for clinical research have developed over time; in part due to several past cases of severe human exploitation in clinical research (see Research Fundamentals for Activists (TAG), Module 2).

In 1947 the United Nations developed the Nuremburg Code, which set out 10 ethical points to be followed when conducting human research. The Belmont Report, another document outlining ethical standards for clinical trials, was written in 1979. Today, any clinical trial conducted anywhere in the world is strictly reviewed to ensure it follows the principles outlined in these two documents.

Principles of Research Ethics

Researchers and ethical authorities work to ensure that research is conducted according to high ethical standards. The following principles form a basis for ethical conduct of all clinical trials.

- Value – the trial should answer a question that will enhance health or provide useful knowledge in the health field.
- Validity – the trial should have an appropriate, careful and practical design and methodology.
- Beneficence/favorable risk-to-benefit ratio – investigators are to do no harm by ensuring there is a fair risk-to-benefit ratio for participating in a trial (see below for further explanation).
- Respect for persons – all research volunteers must be treated as free human beings with the right to choose whether or not to participate in the study, selected for participation in a fair matter, aware of risks involved, able to give voluntary, informed consent, and protected throughout the entire research process from recruitment to follow-up and results dissemination.
- Justice –investigators must choose study participants fairly and to distribute risks and benefits equally among volunteers.

- Independent review – ethical and regulatory committees that are independent of the research team must review and give approval for the study prior to patient enrollment.

Risks versus benefits of participation

Participating in any clinical trial involves both risks and benefits. When someone is deciding whether or not to participate in a trial, that person must fully understand the risks and benefits involved in order to make an informed decision as to whether the benefits outweigh the risks of participation for him or herself personally.

When researchers plan a study, they must make sure that the risks and benefits of participation are balanced. If the relative balance of risks and benefits is not reasonable, the trial will not be considered fair or ethical. If there are too many risks, it is unfair to ask people to participate. If there are too many benefits, people may participate for the wrong reasons, and the study could be considered coercive.

Review of Clinical Trials

Many different groups have a responsibility for ensuring the ethical conduct of clinical trials. All clinical trials, no matter where in the world they are conducted, must be reviewed by external groups. It is important for all review groups to be independent from researchers to guard against bias and conflicts of interest.

Ethical Review Committees/Institutional Review Boards

To ensure that trials are conducted according to ethical standards, a locally based ethics committee must review and approve the proposed protocol, informed consent document and other study-related materials before clinical trials can begin. These committees are generally referred to as ethical review committees (ERC) or, institutional review boards (IRB). The main concerns of the ERC or IRB are the safety and respect of human rights of trial participants and the ethical conduct of the trial. The Committee or Board must approve the study processes before the study can start, and will follow the study as it is conducted.

Committees are made up of scientists, ethicists, community members and other experts who are independent of the trial sponsors and investigators and who are trained in evaluating research proposals. This combination of people provides an unbiased, fair and well-rounded evaluation of the study proposal. In addition to the ethics review, the ERC, IRB, or related committee usually also conducts a regulatory or scientific review.

Regulatory or Scientific Review

Regulatory/scientific review ensures that the trial is asking valid scientific questions and that the study is well-designed to answer these questions.

A national regulatory authority (NRA) generally reviews the technical and scientific information about the experimental product (e.g., candidate drug) or regimen and the trial protocol that gives detailed

information about how the study will be conducted. The NRA, therefore, is responsible to approve both the experimental product being tested and the specific study before it starts. Every six months or year, a report on the progress and results of the trial is sent to the NRA.

Regulatory approval must be obtained from authorities in each country where a study is conducted. Each country has different regulatory procedures. For example, in Europe, a body known as the European Medicines Agency (EMA) establishes overall regulations for NRAs and reviews products at the time of licensure; in South Africa this body is called the Medical Control Council (MCC), and in the United States it is the Food and Drug Administration (FDA).

Data Safety and Monitoring Board

A Data and Safety Monitoring Board (DSMB) is responsible for monitoring study data and the safety of volunteers in a clinical trial, and serves as a primary reviewer of the study while it is still being conducted. Any adverse events that occur during the trial must be reported to the DSMB, and if the board determines that the study is unsafe if continued, it can stop the study.

Materials reviewed by committees

The Committees detailed above review trial-related materials to make certain that all information, provided to volunteers, including informational materials, can be easily understood and that none could be considered coercive.

The following documents must be submitted to one or more committees for review and approval:

- Trial protocol, which explains in extensive detail every aspect of clinical trial conduct, including:
    - Information about the experimental product being tested (drug, regimen), its safety and efficacy data based on phase I and II studies.
    - Study design and objectives, inclusion and exclusion criteria, details about volunteer participation, information to be collected and how data will be analyzed and detailed instructions for the care if injuries or adverse events occur.
- Advertisements (flyers, newspaper, radio, or television ads) that may be used to recruit volunteers
- Informed consent document
- Any documents given to or seen by potential trial participants, e.g. community outreach strategies, recruitment strategies, informational documents or videos
- Plans for volunteer reimbursement
- Investigator's brochure (most, but not all, cases)

Review committees may request additional information.

Informed Consent Process

Informed consent is a cornerstone of ethical research. The agreement, between researcher and trial volunteer, indicates that the volunteer fully understands and agrees to all aspects of participating in the clinical trial.

This agreement is documented when a volunteer signs the informed consent form (described below), however researchers cannot rely on this document alone to ensure that the individual truly understands the clinical trial. In most cases, ensuring volunteers' understanding involves a broader process of education and familiarization with trial participation concepts.

Researchers recognize the importance of obtaining true informed consent. Social and contextual factors must always be considered, such as community members' familiarity with clinical research, and any social pressure or stigma that may be associated with trial participation or the medical treatment being tested. Research teams must ensure that potential volunteers fully understand key aspects of trial participation, including the potential risks and benefits, before they sign the informed consent form. Thus, the informed consent *process* ideally involves two levels of outreach, one to the broader community and one to the individual.

Outreach to the individual may begin with community information sessions about the trial where community members learn more specific details about trial participation. Next, when an individual comes into the research center for pre-screening, he or she typically receives one-on-one counseling to learn about the study in more detail. Finally, some studies require that before signing the informed consent, potential volunteers complete an assessment of understanding, which is usually in the form of a questionnaire containing true/false, multiple choice, narrative questions or combination of these, to test their comprehension of the trial and participation.

Although informed consent is not the only factor in ensuring the ethical conduct of a trial, it is an essential factor. Research teams must ensure potential participants understand key factors about the trial, such as:

- Trial purpose
- Details of the candidate drug
- Number and duration of clinic visits required
- Possible benefits and harms
- Right to voluntary participation and to withdraw from the study at any time

While informed consent reflects an individual agreement between the researcher and participant, ethical involvement of community members often begins with a broader process of community engagement in a trial. Outreach to the broader community extends beyond the scope of trial recruitment. It involves engaging leaders and other stakeholders well in advance of the study as an important channel for building understanding and support among the community at large. Having the

support of key leaders and groups also minimizes stigma that may be attached to community members who participate or who even ask for information about the trial.

Many clinical trial centers set up structures called Community Advisory Boards (CABs). A CAB is made up of key members of community stakeholder groups who as a group act as a liaison between the research team and the broader community. See below for further information about the role of the CAB.

While not a requirement, comprehensive community engagement is increasingly becoming a priority in clinical trials worldwide, as reflected by the development of *Good Participatory Practice* guidelines. See below for further information.

Informed Consent Document

The informed consent document is the paper signed by each volunteer for a trial or other clinical study that indicates his or her understanding of, and agreement to the following:

- Why the research is being done
- What researchers want to accomplish and who is responsible for the study
- What will be done during the trial and for how long
- What risks are involved
- What is expected of trial participants
- What, if any, benefits can be expected from participation
- The system in place for care and support of participants
- What other interventions are available
- The participant's right to leave the trial at any time

Guidelines for Clinical Trials

Trial review committees follow internationally agreed-upon guidelines that provide a detailed definition of requirements for ethical research. These guidelines create uniform ethical and scientific standards for all human trials, wherever they take place.

There are several sets of guidelines that outline regulations and recommend policy for conducting clinical trials.

International Conference on Harmonisation (ICH)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project designed to bring together regulatory authorities from a specific group of countries, to create consensus on regulations for conduct of clinical research and for eventual licensure of pharmaceutical products in those countries. By achieving consensus, the project aims to reduce duplication of effort and therefore avoid delay in development of new drugs while maintaining international high standards and safeguards.

Good Clinical Practice (GCP)

Official guidelines for good clinical practice (GCP) were established by the United States Food and Drug Administration, in agreement with the ICH. The purpose of the guidelines is to establish standards for designing, conducting, recording and reporting clinical trials. These guidelines establish the requirements needed for effective review and approval of proposed clinical studies.

Good Participatory Practice (GPP)

In 2007, UNAIDS and the AIDS Vaccine Advocacy Coalition (AVAC) issued a document titled *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. The document aims to provide internationally recognized standards for community engagement in HIV prevention trials, and is applicable to clinical trials generally. While not an official part of any regulatory approval process, the guidelines provide a universal reference for researchers, funders, trial communities, civil society, etc. in striving for relevant community involvement. They are meant to be put into practice similarly to GCP standards.

The guidelines were drafted and updated with input from a wide variety of stakeholder groups from all over the world, including research staff, community advocates and civil society groups. They are considered a living document to be updated as perspectives on community engagement evolve.

Role of the Community Advisory Board (CAB)

Many clinical research centers have active community advisory boards (CABs), which are an important form of outreach to the broader community. These groups act as liaisons between the trial researchers and the community, and they help to tailor and deliver proper information to potential participants and other stakeholders. Over time, CABs, because of their role as a 'watchdog' for both the community and the research team, have come to be seen as a key component of ensuring trials is conducted ethically.

REFERENCES FOR FURTHER INFORMATION

VaxLit Core Content, Chs 2, 9 and 10
Research Fundamentals for Activists, TAG
Family Health International Research Ethics Training Curriculum
Nuremburg Code
Belmont Report
International Conference on Harmonisation Guidelines
Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials

Session 8 — Research Ethics Fundamentals — [Chapter III]

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

- Explain how researchers ensure trials are conducted ethically.
- Practice critical thinking about the ethical factors of clinical trials.

METHOD: Group discussion and exercise. Participants will discuss the principles of research ethics and whether certain hypothetical research scenarios are ethical.

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

- Read through the CORE INFORMATION section in Chapter III (pp. 71-76) 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.
- Make copies of the WORKSHEET (p. 79) for all participants.

EXERCISE DELIVERY: Estimated session time: **60 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 INORMATION 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 THREE.

STEP THREE: In plenary, discuss the primary principles of research listed below. Use the CORE INFORMATION section of Chapter III as a guide for your discussion. Engage the participants as much as possible in the discussion.

- Beneficence – the act of goodness of kindness
- Respect for persons
- Justice
- Trial review – IRB, other regulatory bodies, DSMB

- Informed consent
- Research imperialism

TRAINING TIP
It may be helpful to invite a local research ethicist, or member of your clinical trial team who may have specific expertise in research ethics to lead this discussion. Ensure that you have adequately coordinated with this individual ahead of time.

STEP FOUR: Distribute the WORKSHEET and divide participants into small groups to complete the assignment described. Give them about **20-30 minutes**.

STEP SIX: Call groups back together and review their answers for each question.

CLOSING: Close the session by making the point that standard ethical principles and guidelines have now governed clinical research for many years. Additionally, trials go through a lengthy review process to ensure ethical conduct. This is true of clinical trials conducted everywhere in the world.

TEST QUESTIONS: Use or adapt the following question in training pre- and post-test.

1. Which of the following practices is not part of ensuring ethical conduct of clinical trials?
    a. Benefits for trial volunteers greatly outweigh any risk from participating in the trial.
    b. The trial protocol is reviewed and approved by external bodies before starting the trial.
    c. The drug being tested, once developed and licensed for use should be relevant and accessible to the trial population and surrounding community.
    d. A Community Advisory Board is in place to serve as a liaison between the research center and the surrounding community.

TEST ANSWERS 1. A

Trainer's Notes:

WORKSHEET

Research Ethics Fundamentals

Your session facilitator has just reviewed the primary principles of ethics in research. Now, in your small group, consider the research scenarios described below. For each, answer the following questions:

- What is the risk/benefit balance of participating in the study?
- What ethical principles are being violated and/or followed?
- If necessary, how could the scenario be changed to better follow the primary ethical principles?

Scenario #1

A study is being conducted in rural Kenya to determine the safety and efficacy of a new drug to treat TB infection. Adult volunteers with pulmonary TB are divided into two groups: one group receives the standard TB treatment, and the other group receives the experimental treatment. Volunteers who receive the standard TB treatment are followed for 6 months, with sputum testing every week during the first two months, and every month thereafter. Volunteers who receive the experimental treatment are followed for 18 months, with sputum testing every week during the first two months, and every month thereafter. At the end of the study, all participants are evaluated for relapse of infection. Those who received the standard treatment who are still TB sputum positive will be offered the experimental treatment if it has been proven more effective than the standard treatment. Researchers compare the rates of relapse of infection in the two groups.

Scenario #2

A multi-site trial is being conducted in three countries in Africa on Early Bactericidal Activity (EBA) of a novel combination TB regimen for drug sensitive and drug-resistant TB. Previous animal studies showed efficacy of this novel combination against both drug sensitive and drug-resistant TB in mouse models. Trial participants in this EBA study will be receiving this novel combination for the very first time in humans. The length of the trial is 14 days, and after trial participants complete their treatment they will be referred to a local TB clinic for follow up examination. If the EBA study proves effective, this novel combination will move to Phase III clinical studies.

Session 9 The Wrong Foot: Why Community is Important [Chapter III]

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

- Explain why it is important to lay foundations in the community for a clinical trial.

METHOD: Modified role play and group discussion. Participants will play the role of a community member responding to news of a TB drug trial in their area.

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

- Read through the CORE INFORMATION section in Chapter III (pp. 71-76) 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.
- Make copies of the WORKSHEET (pp. 82) for all participants.

EXERCISE DELIVERY: Estimated session time: **30 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 INORMATION 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 WORKSHEET and ask one participant to read the introductory paragraph.

> **IMPORTANT!**
> Be sure to explain that the example used here is not typical. In most cases, clinical trial teams and trial sponsors will do some kind of community preparation before a trial begins.

Divide participants into six groups, and assign one role from the list on the worksheet to each group. Ask group members to role-play the answers to the questions on the handout, according to their assigned role. Circulate among the groups, answering any questions. Allow **10 minutes** for group work.

> **TRAINING TIP**
> If there are not enough participants for six groups, you can make three groups and assign each group two roles from the worksheet.

STEP FOUR: Bring the groups together in plenary. Ask for several volunteers to demonstrate their role play. Allow **about 10 minutes** for this step.

STEP FIVE: Lead a brief discussion using the following question:
What might happen if a clinical trial is started without informing and educating people in the community ahead of time?

DISCUSSION PROMPTS
Some of the possible answers here could include:

- Rumors (positive or negative) may start about the trial, the researchers, and the reason for the research.
- You may raise expectations about new TB drugs.
- People may think they are being used as "guinea pigs".

Ask the following question:
In this exercise, how many people said they would volunteer or encourage others to volunteer for participation in a clinical trial?

CLOSING: Close the session by making the point that community engagement is critical to clinical trials for many reasons. This exercise has shown that it would be very difficult to conduct a trial without the understanding and support of various community stakeholders.

TEST QUESTIONS: Use or adapt the following question in training pre- and post-test.

1. TRUE/FALSE: While community stakeholders (e.g. community based organizations, media, community leaders) do not generally have a defined or official role in clinical trials, their support, partnership, and advocacy can be critical to successful research.

TEST ANSWERS 1. TRUE

Trainer's Notes:

WORKSHEET: The Wrong Foot

Imagine the following incident:

Early one morning, a van marked "TB Drug Trial" pulls up to your community center. Three people in white jackets get out of the van, set up a table, and begin distributing brochures explaining that they have come on behalf of an international group to recruit volunteers to test a new experimental drug to treat TB. The brochure explains that this "team" will be available at this location for the next two days to sign volunteers up to participate in the study. Before this there had been no publicity about this TB drug trial, and this is the first time most people in the community have ever heard about the possibility of new TB drugs.

Now pretend that you are one of the following people from the community, and answer the questions at the bottom of the page, as if you were that person:

- A local religious leader
- A nurse in the provincial hospital
- Someone who is infected with TB
- Someone who is not infected with TB
- A journalist who covers this province for a national daily newspaper
- A provincial-level Ministry of Health official

QUESTIONS:

1. Do you think somebody in your position would understand what a "TB drug trial" is?

2. Do you think someone in your position would understand the need for new TB drugs?

3. Would you volunteer for this trial? Would you advise others to volunteer? Why or why not?

Session 10 The Role of CABs in TB Drug Research [Chapter III]

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

- Describe why CABs are essential to clinical trials.
- Discuss the roles CABs play as the link between researchers and community.

METHOD: Group discussion and case studies.

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 III (pp. 71-76) 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.
- Make copies of the WORKSHEET (pp. 85-86) for all participants.
- Gather a flip chart and markers.

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

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

STEP TWO: Lead a group discussion about CABs.
First, ask if anyone can explain the definition of a CAB. If there are any CAB members in the trainee group, ask them to give their own definition and to give some examples of CAB activities.

Discussion prompt: Ask if anyone can explain what it means by saying the CAB is the bridge between researchers and the community.

STEP THREE: Distribute the WORKSHEET to all participants. You may either lead a full group discussion, as described in the worksheet, or if you have a large group, divide participants into groups of 3-4 and ask them to complete the worksheet. Bring the groups back together and have several volunteer their answers.

CLOSING: Close by emphasizing that CABs have an active role to play, both as advocates for the trial site, but also to bring community concerns to researchers and other decision-makers.

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

1) TRUE/FALSE: While community stakeholders (e.g. community based organizations, media, community leaders) do not generally have a defined or official role in clinical trials, their support, partnership, and advocacy can be critical to successful research.

TEST ANSWERS: 1. TRUE

Trainer's Notes:

WORKSHEET: The Role of CABs in TB Drug Trials

Instructions: Your facilitator has just reviewed to role of CABs in TB clinical drug trials. Now, either in a full group, or in small groups of 3-4 participants, you will review the following case studies and discuss how a CAB or CAB member would respond and take action.

Have one person read each case study, and then answer the questions as a group.

CASE STUDY #1

A TB drug trial is being conducted in a rural area of Malawi. The CAB has been involved in community outreach and is receiving repeated reports that community members are unhappy with certain aspects of the trial. They say that many people are screened out (excluded from participation) without an explanation from the trial staff; further, when people are screened out, they are not referred anywhere else for treatment. CAB members find it difficult to answer questions because they are not familiar with specific inclusion and exclusion criteria, or why trials involve such criteria. They have taken this feedback to the site staff, but the Principal Investigator has not met with them about their concerns.

- What potential ethical violations are occurring in this scenario?
- Why is it important for CAB members to have a solid understanding of given trials as well as basic trial concepts?
- What action should CAB members take in this case?

CASE STUDY #2

A Phase III TB drug trial is taking place in Nairobi, Kenya. The community has been informed of the trial, and the CAB has been involved in outreach. News that the trial has been concluded reaches the community and soon after, an inflammatory article appears in the major Kenyan daily newspaper. The article reports that researchers are keeping results from the community; further, that patients who received the experimental drug are not going to receive standard treatment now that the study is over. CAB members know that this information is false and for some reason the reporter wishes to spread misconceptions about the trial.

- Why is it important for the CAB to take action in this case?
- What information would CAB members need when trying to clear up these misconceptions?
- Describe the specific actions a CAB might take to resolve this situation.

CASE STUDY #3

A Phase III TB drug trial has just been completed throughout Africa. CABs have been very active at all trial sites, and have been a key element in ensuring partnership with civil society groups, policymakers, the media and other stakeholders.

The trial results show that the experimental regimen is just as effective – if not more – as the standard treatment, in a much shorter time period. Word is spreading in the community, however, that the new regimen is not going to be licensed and distributed to people who need it. Many of the civil society groups and policymakers the CAB has been working with are very upset about this news and want to take action.

- As a CAB, how would you take action? How could you mobilize the partners to potentially make the new regimen available?
- What information would the CAB need from the research team in order to move forward?

Chapter IV – General Sessions

This chapter contains training sessions that cover general content about TB drug research and development. These sessions may be very useful as wrap-up sessions in research literacy training workshops.

Session 11 — Ask the Experts: A Clinical Trial in Your Community [Chapter IV]

OBJECTIVES:

By the end of the session, trainees will be able to:

- Anticipate questions they may be asked about TB drug development.
- Demonstrate the ability to answer common questions.

METHOD:

Simulate a call-in radio show. Participants will develop and play various roles — experts, audience members, show host—in a simulated call-in radio show.

RESOURCES:

TB Literacy Toolkit
Research Fundamentals for Activists, Treatment Action Group

PREPARATION:

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

- Read all materials listed above in RESOURCES section, and make sure you are familiar with all content. If necessary, consult with clinical staff member from your trial site to discuss any issues or questions.
- Make copies of the WORKSHEET (pp. 91-92) and INFO SHEET (pp. 93-95) for all participants. You may want to distribute the INFO SHEET in advance of the session to give participants time to review it.
- Give some thought to any questions or issues that might be relevant to the community in which you are conducting this training. Make sure you are prepared to facilitate the discussion around any of these issues.

EXERCISE DELIVERY

Estimated session time: **45 minutes**

STEP ONE: Briefly explain the purpose of the session and how it will be conducted – the group will be simulating a call-in radio show and participants will be assigned to play one of three roles: callers from the listening audience, expert panellists in the studio, or the talk show host.

STEP TWO:
Assign roles to participants as follows:

(1) One or two participants play the role of radio talk show host. Ideally, an outgoing person with a good sense of humour and an ability to facilitate discussion.
(2) Four participants play the role of experts (see WORKSHEET for role definitions):
    - Principal investigator or other clinical site staff
    - Ethicist
    - Community Advisory Board member
    - Epidemiologist

IMPORTANT!
This group should include trainees considered "Intermediate" level, since they will be answering questions from the rest of the trainees.

(3) All remaining participants play the role of community members who will call into the radio show with questions for the experts.

STEP THREE: Distribute the WORKSHEET and INFO SHEET to all participants (if not previously distributed). Give participants **10 minutes** to review the sheets and consider their roles. They can discuss potential questions and answers with other participants if they like.

STEP FOUR: Seat panellists and talk show host at the front of the room. Have the host begin the radio show by introducing the panel members and then asking community members to call in with their questions. Allow the talk show to last for **30 to 40 minutes** and facilitate as necessary.

TRAINING TIPS
- Make sure the host keeps this "show" moving.
- Allow two minutes maximum for each question and answer.
- Try to ensure that most community members get to ask their questions.
- Stay near the host and prompt him/her whenever the panellists/audience members need to be interrupted to keep things moving along.

CLOSING: Conclude the radio show by recapping any important comments or questions. Close by asking participants what they think are the two or three most important things for the community to know about TB drug development and clinical trials.

TEST QUESTIONS: Use the following questions in training pre- and post-test.

1. TRUE/FALSE: Clinical trials are the only way to determine if a new product (drug, vaccine, etc.) will work in humans.
2. Which of the following is not true for Phase III TB drug trials?
   a. Trial volunteers will know if they receive the new drug or not during the trial.
   b. An individual's participation lasts about a year longer than the standard course of TB treatment.
   c. The trial is always guided by international ethical standards.
   d. All participants must give written, voluntary, informed consent before enrolling in the trial.

TEST ANSWERS: 1. TRUE; 2. a

Trainer's Notes:

WORKSHEET: Ask the Experts – Common Questions about TB Drugs
For distribution to participants

Scenario: A Phase III TB drug trial is currently being conducted in the country, and today four panellists appear on the radio show to take questions from interested community members.
You have been assigned to play one of the roles described below.

ROLE 1 – *Radio talk show host*
You are the host of a popular radio talk show in your country. Today you have invited a panel of four experts on TB drug development to take questions from community members. Your task is to facilitate the interaction between callers and experts (see roles below). As you take each call, make sure the experts understand the question, give them time to answer, ask the caller if he/she understands the answer or has a follow-up question, ask your own questions of the panel, etc. Try to have fun with the audience and with the experts.

You will start the show by welcoming your audience, introducing the topic, and briefly introducing the panel. Then open for questions from community members.

ROLE 2 – *Expert panellists*
You will play one of the following four roles:

(1) *Principal investigator or other site staff*. The principal investigator is the physician in charge of running the clinical vaccine trial and providing clinical attention to volunteers. You could also play a study coordinator or nurse counsellor.
(2) *Ethicist*. This is an expert in ethical issues. This person will speak on any issues with ethical implications, such as how volunteers are protected and cared for during trials.
(3) *Community Advisory Board member*. This is a person who acts as a liaison between the community and the researcher team.
(4) *Epidemiologist*. This is a person who studies issues related to trends in diseases, such as how often people become infected with certain diseases, and the sources of diseases in large populations. This expert might comment on why the trial is being conducted in the particular community or country.

You may use the INFO SHEET to help answer questions from community members.

NOTE: If you do not know the answer to a question, it is always fine to say that need to refer back to a different expert before giving an answer. In this case, you may ask the trainer to help answer the question.

ROLE 3 – *Community members*

You are listeners of the radio show, a very popular talk show in your country. You've heard that TB drug trials are being conducted in your community/country, and you have questions or concerns that you'd like to air with the expert panellist on today's radio show.

You will call into the radio show, introduce yourself and your background/role and why you are interested in the research (e.g. 'I am a community member and am interested in participating in the trial', 'I am a journalist for one of the leading newspapers and would like to write an article about TB drug trials). Then pose your question to the appropriate expert panellist (see descriptions above). You may use the INFO SHEET as a guide for questions, but are not restricted to these questions.

INFO SHEET: Ask the Experts – Common Questions about TB Drugs
For distribution to trainees

_____

The following information can serve as a reference for coming up with your questions or answers. Remember that both questions and answers about TB drug development will vary greatly depending on the audience. This sheet lists some of the most common questions from a general audience, but you and your group should consider additional questions based on your community and clinical trial context.

Why do we need new TB drugs?

The current first-line treatment for TB was discovered over 40 years ago and can cure active, drug-sensitive TB, as long as treatment for six to nine months is completed properly with no interruptions. This treatment is long and burdensome, often with difficult side effects, and many TB patients do not, or cannot complete the treatment properly. When treatment is not taken properly; when doses are missed, or when treatment is stopped, TB bacteria can quickly become drug-resistant and much more difficult to treat and cure. Second-line treatment of multi-drug resistant TB is much longer and more expensive than first-line treatment. It is more difficult for both the patient and the health care provider to treat drug-resistant TB. A new shorter TB drug treatment, with fewer side effects would help to improve compliance to treatment, improve cure rates, and prevent development of drug-resistant TB. Some of the current first-line TB drugs are also not compatible with commonly used antiretroviral (ARV) therapies, used to treat HIV. This means that sometimes TB and HIV/AIDS cannot be treated at the same time; which is very dangerous for people who are HIV and TB co-infected. A new drug treatment for TB must also be compatible with ARV therapy.

What is a clinical trial?

Clinical trials are studies conducted in humans to determine if a new product (vaccine, drug, or other intervention) is safe and effective. Any new product must go through a rigorous series of trials before it can be licensed and distributed to the public.

What are TB clinical drug trials designed to tell us?

Each TB drug trial is designed to answer specific questions about a new drug treatment, or about a new way of using a known treatment. These research questions will vary from trial to trial, but in general, a series of trials will determine if a new drug or regimen is safe and effective against the illness it is being tested to treat.

What does testing for safety mean? Is it not safe to participate in a trial?

All experimental TB drugs are tested extensively before they enter human clinical trials. Human trials are carefully designed in phases going from a small number of healthy volunteers (Phase I), eventually to a much larger number of participants who are TB-infected (Phase III). This progression helps ensure the safety of volunteers with an acceptable degree of certainty. If an experimental drug is considered unsafe for humans, it will not continue to be tested in clinical trials. All trials must be reviewed and approved by several regulatory, scientific and ethics committees, with a primary consideration being safety of volunteers.

Before a volunteer agrees to participate in a trial, he or she should have a full understanding of any potential risks (as well as benefits) of participation.

How do we know that new TB drug combinations/regimens are more effective?
We don't. The purpose of clinical research is to answer this question. Clinical trial volunteers will not know if they are receiving the new experimental drug, or the standard treatment until after the trial has been completed and the data has been analyzed. The current Phase III TB drug trial is a non-inferiority trial; and compares a 4-month TB drug regimen to the standard 6-month TB drug regimen.

Why do we think new TB drugs will be better than the old ones?
Considering that the current treatment for drug-sensitive TB is 6 months, and up to 2 years for drug-resistant TB, a shorter treatment that is as effective, of more effective than the standard treatment could be considered more optimal, or "better". Researchers think that a new TB drug regimen could eventually be more effective than the standard TB treatment, and the aim of current clinical trials is to find a shortened treatment for TB, with fewer side effects.

Will the new TB drugs cause more side effects than the standard treatment?
All medications can have side effects, and the current TB drug treatment has many difficult side effects. The aim of TB drug research is to find new treatments with fewer side effects. Based on Phase I and II studies, drugs that are currently being tested in Phase III TB drug trials do not have more side effects than standard TB drugs, however there are still some side effects. Since Phase III trials involve such a large group of participants, it is possible that some participants may experience side effects from the medications provided in the trial, however participants are very carefully observed throughout the trial and any side effects that do occur are treated and documented.

Why is blood taken from volunteers in the TB drug trial?
Blood is taken from trial participants to evaluate how the body is responding to the medication, specifically looking for any toxic effects of medication in the body.

Why is sputum collection needed so often in the trial?
Sputum is collected at each clinic visit to test for the presence of TB bacteria. When testing an experimental TB drug, researchers want to know how quickly participants' sputum converts to negative; indicating how well the treatment is working. Sputum is collected during the 6 months of treatment, and during the 12 months of follow-up, to determine if the infection is cured, of if there is a recurrence.

Why is there a consent process? Why is the informed consent document so long?
It is the ethical responsibility of researchers to ensure that trial volunteers understand the potential risks and benefits of the trial, why the trial is being conducted, and what will occur throughout the course of the clinical trial; such as the type of medication volunteers will be taking, the number of clinic visits they will have, and what tests will be performed during those visits, etc.

The informed consent document is long because there is a lot of information to give potential volunteers about the trial. It is the researcher's responsibility to make this information available, in a form that is easy to understand, and in the local native language.
To give informed consent means that the volunteer fully understands the risks and benefits of the trial, and that they want to participate. The volunteer's signature is required on the informed consent document in order to be enrolled in a clinical trial. The volunteer must never be unfairly influenced to participate by anyone—friends, family, or trial site staff.
If the volunteer does not understand the informed consent document, or if they have any questions or concerns about participating in the clinical trial, the volunteer must ask for clarification. It is the volunteer's choice to participate in the clinical trial or not, and it is the volunteer's right to have all information about the clinical trial available and explained to them.

Why are clinical trials so long?
TB treatment is 6 months long. The reason a participant's involvement in Phase III TB drug trials may last up to 18 months or more is because enrolled patients must be followed for a full year after the completion of treatment, to assess for relapse of infection.

Why are some patients eligible to participate in the trial, and some are not?
Inclusion/exclusion criteria are developed to help ensure the safety of trial participants, and to define the population needed for the clinical trial. The specific type of TB patient needed for a given trial is defined by the types of drugs being tested in the new regimen.

Are TB drug trials conducted in an ethical way?
All clinical trials are carefully reviewed by independent ethics committees and regulatory authorities before they are allowed to begin to make sure that they are both scientifically and ethically sound, and safe for participants. TB drug trials follow strict international ethical guidelines to ensure the protection each participant's health, dignity, and well-being. Obtaining participants' informed consent to participate in a trial is also essential to conducting ethical research and protecting participants.

Why are new TB drugs being tested in developing countries?
TB drug trials are being conducted in areas with a high prevalence of TB infection. This is done to ensure that enough TB patients will be available for trials that require a large number of participants, and also because new TB drugs should be tested in populations that would most likely use the new product. To determine if a new drug would be safe, effective, and accessible to a particular population it is best to include members of that population in trials.

Do experimental TB drug regimens carry new strains of TB?
No. TB is treated with a combination of antibiotics, none of which carry any bacterial strain.

Session 12 Agree or Disagree [Chapter IV]

OBJECTIVES: By the end of the session, participants will have:

- Enhanced knowledge of issues involved in TB drug research and development;
- Increased skills to debate these issues.

METHOD: Group debate. Participants read statements on TB drug research, decide whether they agree or disagree, and debate other participants with opposing positions.

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

- Make a banner that says AGREE and a banner that says DISAGREE and tape them on opposite sides of the room.
- Review the AGREE/DISAGREE STATEMENT LIST (p. 98), and choose 3 to 5 statements to be debated by the participants (allow about **15 minutes** for each statement). You may also develop new statements based on the most relevant issues around TB drug research in your community.
- Write each statement on a separate sheet of flip chart paper for display during the exercise. Make sure the statements are written where participants *cannot* see them ahead of time.

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

STEP ONE: Explain that the purpose of the session is to explore issues in TB drug research and development.

STEP TWO: Ask all participants to stand in the middle of the room between the AGREE and DISAGREE signs. Reveal the flip chart paper with the first statement for debate. Read the statement aloud. Ask participants to decide if they agree or disagree with the statement, without saying aloud or discussing with other participants. After everyone has decided, tell them to move to the appropriate sign.

> **NOTE**
> Participants cannot be undecided, or 'in the middle'; they must either agree or disagree with the statement.

STEP THREE: Give each group **3 to 5 minutes** to discuss amongst themselves why they chose to agree or disagree. They will come up with an argument to convince members of the other side to change their minds.

STEP FOUR: Bring the groups together. Facilitate a debate between the two groups by asking representatives to present each group's argument. Let each group try and convince members of the other group to reconsider their opinion. Moderate the debate as necessary.

> **TRAINING TIP**
> Let the debate happen in a free-form manner, but ensure that each group gets the chance to present its side. Make sure to facilitate effectively so that as many trainees as possible get a chance to join the debate.

Once the discussion has ended, repeat with the next statement. Proceed until all statements have been debated.

STEP FIVE: Once several statements have been debated, bring the group together and facilitate a discussion about some of the key issues discussed. Try to keep focus on TB drug research and clinical trials.

> **IMPORTANT!**
> Be sure to acknowledge the differences in people's values, and emphasize the importance of separating personal values from professional practice, particularly when working in clinical research.

CLOSING: Wrap up any final points that emerged during the discussion.

TEST QUESTION: Develop one question to be used in your training pre- and post-test that reflects issues debated.

AGREE/DISAGREE STATEMENT LIST

The list below contains statements to be used in this exercise. Choose as many statements as you think you will have time for. Feel free to develop statements that are not included below. Allow about **15 minutes** for each statement.

Trial Participation Issues

- A trial volunteer's participation should be kept confidential from his/her healthcare provider.
- Trial volunteers should know whether they are receiving the experimental drug or placebo during the trial.
- Trial volunteers should receive reimbursement in return for their participation.
- Potential volunteers should discuss participation with family members before deciding to enroll in a trial.
- The trial team should discourage people from participating if they might not be able to stay enrolled throughout the duration of the trial.
- Potential volunteers do not need to fully understand every aspect of trial participation before giving informed consent to participate.

TB Drug Issues

- There is not a need for new TB drug regimens.
- A shorter TB drug regimen is better for patients.
- TB drug research and development is taking resources away from efforts to deliver existing drugs and related care for TB patients.

Trial Design Issues

- It is not necessary for TB drugs to be tested in the developing world.
- TB drugs should always be tested in industrialized countries before they are tested in developing countries.
- Ethical standards of running a trial should depend on the standard of living in a given country.
- Developing countries do not operate according to the same ethical and regulatory standards as developed countries.

Community Engagement Issues

- CABs are not needed to ensure TB drug trials are conducted ethically and appropriately.
- CABs should exist after a TB drug trial has been completed.

Session 13	**Popcorn**	**[Chapter IV]**

OBJECTIVES: By the end of this session participants will:

- Have answers to any outstanding questions they may have about TB drug research and development.

METHOD: Interactive Question & Answer

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

- Read through relevant CORE INFORMATION sections of each Chapter if you need to familiarize yourself with any information, and make sure you are familiar with all concepts. If necessary, discuss any questions with a clinical staff member of your trial site team.
- You may want to ensure that a clinical site staff member is present for this session.
- Gather enough pieces of paper for all participants.

EXERCISE DELIVERY: Estimated exercise time: **as determined**

STEP ONE: Explain that the purpose of the session is to reinforce concepts in TB drug research and development.

STEP TWO: Pass out pieces of blank paper to all participants. Ask participants to write any question they may have about TB drug research and development on the paper. The question may be something you have discussed in a different session, or a new issue that was not addressed in the workshop.

STEP THREE: When all participants have written a question, instruct them to crumble their pieces of paper into balls. Then they throw their papers together on the floor, like a bowl of popcorn.

STEP FOUR: Pick pieces of paper randomly and answer the questions written. Use as much time as needed to answer as many questions as possible. Engage the participants as much as possible. Call upon any clinical staff member present to help answer questions.

CLOSING: Close by reiterating any important points discussed during the session.

Glossary of Clinical Trials Terms

Adherence:
Adverse Reaction (Adverse Event): Any unwanted effect that may or may not be caused by the study drug. Onset may be sudden or develop over time. Adverse reactions are evaluated by the study doctor for causality and severity.
Advocacy and Support Groups: Organizations and groups that actively support participants and their families with valuable resources, including self-empowerment and survival tools.
Arm: Any of the treatment groups in a randomized trial. Most randomized trials have two "arms," but some have three "arms," or even more.

Bias: When a point of view prevents impartial judgment on issues relating to the subject of that point of view. In clinical studies, bias is controlled by blinding and randomization.
Blind: Patients are not told which treatment they are taking; experimental or control. Patients are randomized and the assigned treatment is revealed after completion of the study.

Clinical: Pertaining to or founded on observation and treatment of human participants, as distinguished from theoretical or basic science.
Clinical Investigator: A medical researcher in charge of carrying out a clinical trial's protocol.
Clinical Trial: A research study involving human volunteers, typically designed to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work and are safe in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group, usually of healthy volunteers; Phase II expands the study to a larger group of people and typically is conducted with patients; Phase III expands the study to an even larger group of patients; and Phase IV takes place after the drug or treatment has been licensed and marketed.
Confidentiality Regarding Trial Participants: Refers to maintaining the confidentiality of trial participants including their personal identity and all personal medical information. The trial participants' consent to the use of records for data verification purposes should be obtained prior to the trial and assurance must be given that confidentiality will be maintained.
Controlled Trials: Control is a standard against which experimental observations may be evaluated. In clinical trials, one group of participants is given an experimental drug, while another group (i.e., the control group) is given either a standard treatment for the disease or a placebo.

Data Safety and Monitoring Board (DSMB): An independent committee composed of community representatives and clinical research experts; that review data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.
Double-Blind Study: A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study.

Dose-Ranging Study: A clinical trial in which two or more doses of an agent (such as a drug) are tested against each other to determine which dose works best and is least harmful.
Drug-Drug Interaction: A modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug.

Enrolling: The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the **informed consent** process.
Epidemiology: The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population.
Experimental Drug: A drug that is not licensed for use in humans, or as a treatment for a particular condition.
Efficacy (of a drug or treatment): The ability of a drug or treatment to produce the intended result in a research study or trial. A drug passes efficacy trials if it works at the dose tested and against the illness for which it is prescribed. In the procedure mandated by the FDA, Phase II clinical trials of TB drugs are meant to give some indication of efficacy, and Phase III trials confirm it.
Endpoint: Overall outcome that the protocol is designed to evaluate. Common endpoints, for example, are severe toxicity, disease progression, disease cure, or death.

Hypothesis: A supposition or assumption advanced as a basis for reasoning or argument, or as a guide to experimental investigation.

Immune System: The set of organs, tissues and cells that help defend the body against infection.
Inclusion/Exclusion Criteria: The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but rather to identify appropriate participants and keep them safe.
Informed Consent: The process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study.
Informed Consent Document: A document that describes the rights of the study participants, and includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time.
Institutional Review Board (IRB): 1. A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. 2. Every institution that conducts or supports biomedical or behavioral research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants.

Pharmacokinetics: The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.
Phase I Drug Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of efficacy; may include healthy participants and/or patients.
Phase II Drug Trials: Controlled clinical studies conducted to evaluate the efficacy of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Drug Trials: Expanded controlled and uncontrolled trials after preliminary evidence of drug safety and efficacy has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for drug-labeling.
Phase IV Drug Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.
Placebo: An inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness.
Placebo Controlled Study: A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition than the inactive placebo.
Preclinical: Refers to the testing of experimental drugs in the test tube or in animals - the testing that occurs before trials in humans may be carried out.
Protocol: A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

Randomization: A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant.
Randomized Trial: A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. In some cases, placebos are utilized.
Recruiting: The period during which a trial is attempting to identify and enroll participants. Recruitment activities can include advertising and other ways of soliciting interest from possible participants.
Recruitment Status: Indicates the current stage of a trial, whether it is planned, ongoing, or completed. Possible values include:

- Not yet recruiting: participants are not yet being recruited or enrolled
- Recruiting: participants are currently being recruited and enrolled
- Enrolling by invitation: participants are being (or will be) selected from a predetermined population
- Active, not recruiting: study is ongoing (i.e., patients are being treated or examined), but enrollment has completed
- Completed: the study has concluded normally; participants are no longer being examined or treated (i.e., last patient's last visit has occurred)

- Suspended: recruiting or enrolling participants has halted prematurely but potentially will resume
- Terminated: recruiting or enrolling participants has halted prematurely and will not resume; participants are no longer being examined or treated
- Withdrawn: study halted prematurely, prior to enrollment of first participant

Risk-Benefit Ratio: The risk to individual participants versus the potential benefits. The risk/benefit ratio may differ depending on the condition being treated.

Side Effects: Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects.
Standards of Care: Treatment regimen or medical management based on state of the art participant care.
Standard Treatment: A treatment currently in wide use and approved by the FDA or relevant regulatory authority, considered to be effective in the treatment of a specific disease or condition.
Statistical Significance: The probability that an event or difference occurred by chance alone. In clinical trials, the level of statistical significance depends on the number of participants studied and the observations made, as well as the magnitude of differences observed.
Study Endpoint: A primary or secondary outcome used to judge the effect of a treatment.
Symptom: A sign or an indication of disorder or disease, especially when experienced by an individual as a change from normal function, sensation, or appearance.

Toxicity: An adverse effect produced by a drug that is detrimental to the participant's health. The acceptable level of toxicity associated with a drug will vary depending on the condition which the drug is used to treat.
Treatment Trials: Trials that test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

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