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 CD4 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

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 INFORMATION section as a guide.

Make this overview as interactive as possible. Ask trainees to volunteer answers, write important points on a flip chart, use diagrams or any relevant handouts, etc. If possible, work with a co-facilitator, ideally a clinical site staff member. For an intermediate/advanced audience, the overview can be skipped.
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 INFORMATION section as a guide.

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

**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.