Intercountry operational research on all-oral modified shorter treatment regimens for MDR/RR-TB: Informed consent

World Health Organization
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European TB Research Initiative, WHO Regional Office for Europe

7 October 2020

Joint TB, HIV and Viral Hepatitis Programme, Division of Country Health Programmes

History

- The inception of informed consent has its roots in the Nuremberg Code of 1945
- Formulated in response to the shocking discoveries during the Nuremberg trials
- Nazi doctors were found to have committed horrific medical experimentation abuses against the inmates in concentration camps, who were exploited as research subjects

Traditional principles of biomedical research ethics

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Ethics

Autonomy	●	Respect for the person, informed voluntary consent
Avoid harm (non-maleficence)	●	Identifying risks, vulnerable groups, preventing harm fairly to all
Doing good (beneficence)	●	Identifying and providing benefits and advantages to all, benefits outweighing risks
Justice	●	Fair selection, equity to all

The Core Principles of Health Care Ethics

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Autonomy

- to honor the patients right to make their own decision

Beneficence

- to help the patient advance his/her own good

Non-maleficence

- to do no harm

Justice

- to be fair and treat like cases alike

Autonomy
Voluntas aegroti suprema lex

- Autonomy is a general indicator of health.

- autonomy is an indicator for both personal well-being, and for the well-being of the profession

Beneficence
Salus aegroti suprema lex

- beneficence refers to actions that promote the well being of others.
- taking actions that serve the best interests of patients.
- However, uncertainty surrounds the precise definition of which practices do in fact help patients

Non-maleficence
primum non nocere

- many treatments carry some risk of harm
- in desperate situations where the outcome without treatment will be grave, risky treatments that stand a high chance of harming the patient will be justified, as the risk of not treating is also very likely to do harm.
- the principle of *non-maleficence* is not absolute, and balances against the principle of *beneficence* (doing good), as the effects of the two principles together often give rise to a *double effect*

Focus of medical, public health and research ethics

Medical ethics

- individual patients
- doctor-patient relationship
- duties of doctors/ nurses

Public health ethics

- population health
- health programmes and policy issues
- scientific evidence
- public participation
- preventive measures

Research ethics

- protection of study participants
- informed consent
- risk-benefit analysis
- equitable selection & access etc.

Source: Ethics in implementation research. Facilitator's guide. Geneva: World Health Organization; 2019

Definition

Informed consent is the process of obtaining the permission of a subject to participation in studies and have an opportunity to decide about his or her healthcare

Content of the consent

Goal:

to ensure patient understands the role of the new drugs/regimens and has the opportunity to ask questions and have them answered

Main points:

- Necessity in novel treatment regimens, new medications
- Benefits
- Risks
- How drugs would be taken
- Birth control
- How clinicians will monitoring of side effects (including reporting of side effects)
- An invitation to collaborate with his/her care givers

Language

- Local language(s) – make sure that patient understands
- Culturally appropriate
- Avoid medical terms and abbreviations:
    - ECG, Dlm, Bdq, DST
    - Mortality
    - Treatment regimen
    - Lipaze, albumin etc.
    - Arrhythmia

Nocebo effect

«The principle of informed consent obligates physicians to explain possible side effects when prescribing medications. This disclosure may itself induce adverse effects through expectancy mechanisms known **as nocebo effects**, contradicting the principle of nonmaleficence. Rigorous research suggests that providing patients with a detailed enumeration of every possible adverse event can actually increase side effects»

To Tell the Truth, the Whole Truth, May Do Patients Harm: The Problem of the Nocebo Effect for Informed Consent. R.E. Wells; Am J Bioeth. 2012 March ; 12(3): 22–29.

Nocebo effect

The power of nocebo suggests that it may be «healthier» to err on the side of optimism than on the side of pessimism

«The nocebo phenomenon: concept, evidence, and implications for public health» Preventive Medicine. 1997; 26(5 Pt 1)

Personality who gives IC

- good communication - good medical practice
- impact of clinicians conversations on patients' experiences
- not place all responsibility for decision-making on the patient
- informed consent is an ongoing process and dialogue

Basic health communication skills

How *to create good communication* to make patients feel valued and respected and thereby increase possibility for adherence

- Becoming aware of own communication habits
- Pay attention to non-verbal communication
- Provide constructive feedback
- Ask open-ended questions
- Use active listening

From LHL effective health communication course

Informed consent procedure

- Patients who meet the criteria for inclusion in the study will receive information about MDR-TB and mSTR.
- Patients will be provided with the information in their native language.
- Patients should be able to discuss the Patient information sheet with a healthcare professional/treatment assistant.
- Patients should be confident that their decision to participate or not to participate in the study will not affect the quality of care they receive.

Informed consent procedure

- After patients agree to participate in the study, they will be asked to sign a consent form.
- In the case of minors, consents must be obtained both from a legal representative and from a child.
- All patients who do not meet the inclusion criteria, refuse to participate in the study or withdraw from it after the inclusion will receive treatment according to national guidelines without any negative consequences for them.

Patient information sheet

Country_____ Study site:☐☐

Participant ID: ☐☐-☐☐☐

Patient information sheet

Version 7 from 10 July 2020

Introduction

You are being invited to take part in a research study, the details of which are described in this information sheet. This study is being conducted at _____. Before you decide to take part in this study, it is important for you to understand why the research is being done and what it will involve. A member of our study team will talk to you about the study and answer any questions that you may have.

Please take time to read the following information carefully and discuss it with relatives, friends, and your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to participate. After you are properly satisfied that you understand this study, and all your queries/questions have been satisfactorily answered, and that you wish to participate, you must sign an informed consent form attached with this information sheet. Your participation in this study is voluntary. This means you will take part in the study if you want to or decide to do so out of your own choice. You do not have to be in this study if you do not want to. Even if you decide to participate in this study, you may withdraw (take back your decision to participate) from this study at any time during the course of study. The records collected prior to your withdrawal from the study will be preserved for analysis purposes and fact of your withdrawal will be recorded, but no additional information will be collected from that time point. Your refusal to participate or withdrawal will not affect any medical or health benefits.

Your personal and health information will be collected, analyzed and reported at the end of the study. All your information will be confidential and not available for medical personnel.

What is the shorter MDR-TB regimen?

MDR-TB is a serious disease that can result in death, and for which there are few treatment choices. Regular treatment for MDR-TB now is at least 18 months and can be extended up to 24.

Internationally, several novel regimens for MDR-TB that are only 9 months (39 weeks) are being evaluated. These regimens use newer drugs such as bedaquiline, delamanid and linezolid and clofazimine which are highly active against MDR-TB. They do not include any injection.

These regimens are currently being evaluated in clinical trials in several different countries. Preliminary results indicate the drugs are effective and well tolerated. While waiting for these trials to finish in 2022 or later, your national TB program, in partnership with WHO is assessing a novel regimen under research conditions in your country.

Which drugs are in the shorter MDR-TB regimen?

The shorter MDR-TB regimen uses a combination of drugs, which have all been recommended for the treatment of MDR-TB. All drugs are taken by mouth. All drugs are taken for the full 9 months every day. In this study, three all-oral shorter RR-TB treatment regimens are being evaluated; two for adult patients and one for children. Regimens have been chosen based on knowledge of drug safety and effectiveness. The study team in your country along with your doctor will decide which regimen is appropriate in your particular case. Each regimen contains five of the six drugs listed below:

- Bedaquiline
  - **Week 1 and Week 2:** Take 400 mg (4 tablets) once a day, 7 days a week.
  - **Week 3 to Week 39:** Take 200 mg (2 tablets) three times a week. For example, you may take bedaquiline on Monday, Wednesday and Friday of every week.
- Delamanid: Take 100 mg (2 tablets) in the morning and again 100 mg (2 tablets) in the evening, every day of the week (including the weekends).
- Linezolid: Take 600 mg (1 tablet) once a day, 7 days a week.

  (In case of problems your doctor may decide to decrease dosage to 300 mg (one-half tablet) once a day, 7 days a week).
- Levofloxacin
  - If you weigh less than 45 kg, take 750 mg (3 tablets) once a day, 7 days a week.
  - If you weigh more than 45 kg, take 1000 mg (4 tablets) once a day, 7 days a week.
- Clofazimine 100 mg (1 capsule) once a day, 7 days a week.
- Cycloserine 750 mg (3 capsules) once a day, 7 days a week.

What are the possible side effects of the short MDR-TB regimen?

All drugs can have side effects, and every patient is different. Preliminary information on new oral drugs indicate they have few adverse events, and they are less toxic than the injectable ones previously used. Following are the side effects (unwanted effects on patient's health) which have been known to occur with various drugs included in this study.

- **Bedaquiline –** headache, common cold, sore throat, fainting, lightheadedness, joint pain, nausea, vomiting, diarrhea, palpitation (feeling an irregular, fast or slow heartbeat), jaundice, abdominal pain and heart rhythm may change (QTc in ECG)
- **Levofloxacin –** Diarrhea, abdominal or stomach cramps or pain, skin rash, itching, or redness, joint pain
- **Linezolid** - peripheral neuropathy (which can be permanent if not caught early), blindness secondary to optic neuritis (which also can be permanent if not caught early) and low blood count
- **Delamanid** - few side-effects, but may include dizziness, nausea and anxiety.
- **Clofazimine –** dark discoloration or hyperpigmentation of skin, rashes, which is reversible on stopping the drug
- **Cycloserine** - sleep disorders, seizures, neuropathy, and depression

Other less common side effects have also been reported. The study doctor or study staff can discuss with you. In addition, you may suffer harms that have not been reported. You will be checked for the possibility of any harm throughout the study. You should immediately contact your treating doctor at this hospital, in case you experience any undesirable or negative effect.

Always tell your health-care provider of any side effects or problems you are having.

What monitoring tests do I need while taking the short MDR-TB regimen?

You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need testing of the nerves in your feet, testing of the level of red blood cells, and vision testing. You should see your doctor at least monthly while you are taking treatment and 6 and 12 months after completion of the treatment.

Tell your doctor right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your doctor will check your heart rhythm with a machine (ECG) to make sure that it is normal.

Risks and benefits of taking the short MDR-TB regimen

RISK: It is possible that you will have a greater risk of relapse after treatment with the short regimen. If relapse occurs, you will receive treatment from the national program in accordance with National TB treatment guidelines. The treatment would be chosen by the national expert panel, but is likely to be between 18-24 months in duration and may require the use of older TB drugs.

You will also have a greater risk for certain side effects due to drugs in this regimen.

BENEFIT: You may become cured of MDR-TB sooner than if you took the regular MDR-TB regimen. You will also avoid many side effects of drugs in the regular regimen. There are **no daily injections in this regimen** and the total duration of treatment is for 9 months only. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with TB better. You will get close medical attention by participating in this study which may provide you useful information about your health. All the study medicines, tests, and procedures will be provided free of cost to you.

Confidentiality

Your medical records will be kept confidential. The sputum samples collected during the study will be analyzed. The initial culture isolates from the sputum collected as part of the TB diagnosis and treatment monitoring process outlined in the national policy will be stored in the National TB Reference Laboratory for 36 months from your enrolment into the study, unless you object. If you are successfully treated then develop TB within the 12 months after completing treatment, additional testing will be carried out on the initial and repeated isolates from sputum specimens to detect whether you have developed recurrent disease due to unsuccessful treatment or whether you have been re-infected. Confidentiality will be maintained. If you object against additional testing of isolates from your sputum, inform study team at any time of the study. By signing this document, you will be allowing the study team to view your data and store. The results of the study will be made public in generalized manner, so that it is used for the benefit of patients' and healthcare provider community. Your name will not be disclosed outside the hospital, or in publication and presentation materials.

Right to refuse or withdraw

You do not have to agree to take the short MDR-TB regimen if you do not wish to do so. Instead, you can take the regular 18 month MDR-TB regimen. Your participation in this study is voluntary. This means you will take part in the study if you want to or decide to do so out of your own choice. Even if you decide to participate in this study, you may withdraw (take back your decision to participate) from this study at any time during the course of study. Your refusal to participate or withdrawal will not affect any medical or health benefits. If you refuse to participate in this study, you will be evaluated and managed by your national TB authorities according to national guidelines.

Contact person

If you have any questions, you may contact any of the following persons:

Name_____. Title_____. Phone_____.

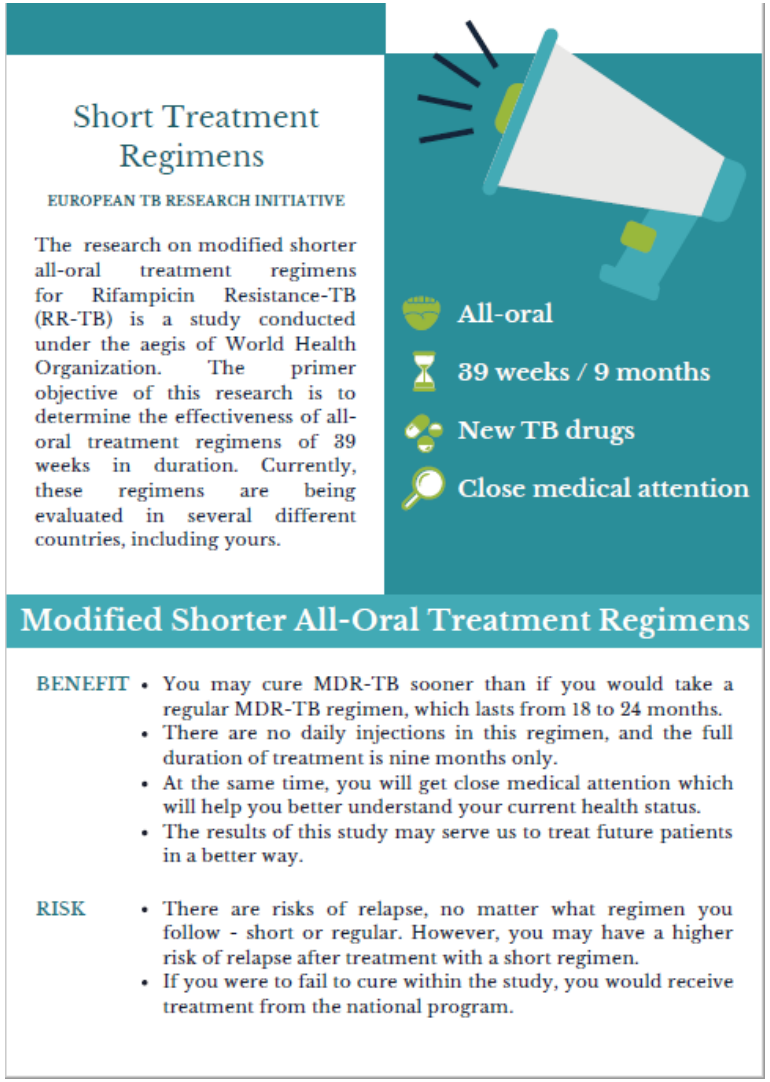
Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name of responsible physician: _____

Name of clinic/hospital/institution: _____

Educational materials



Short Treatment Regimens

EUROPEAN TB RESEARCH INITIATIVE

The research on modified shorter all-oral treatment regimens for Rifampicin Resistance-TB (RR-TB) is a study conducted under the aegis of World Health Organization. The primer objective of this research is to determine the effectiveness of all-oral treatment regimens of 39 weeks in duration. Currently, these regimens are being evaluated in several different countries, including yours.

All-oral

39 weeks / 9 months

New TB drugs

Close medical attention

Modified Shorter All-Oral Treatment Regimens

BENEFIT
- You may cure MDR-TB sooner than if you would take a regular MDR-TB regimen, which lasts from 18 to 24 months.
- There are no daily injections in this regimen, and the full duration of treatment is nine months only.
- At the same time, you will get close medical attention which will help you better understand your current health status.
- The results of this study may serve us to treat future patients in a better way.

RISK
- There are risks of relapse, no matter what regimen you follow - short or regular. However, you may have a higher risk of relapse after treatment with a short regimen.
- If you were to fail to cure within the study, you would receive treatment from the national program.

WHO CAN APPLY FOR THE SHORT MDR-TB REGIMEN?

The study on modified shorter all-oral treatment regimens focuses on individuals with evidence of resistance to first-line drugs, at least resistance to Rifampicin. The test to resistance is made by rapid molecular Drug Susceptibility Testing (DST).

STEPS TO FOLLOW FOR THOSE WHO WISH TO PARTICIPATE:

- **Approach your doctor**
- **Inform your willingness to apply for the short MDR-TB regimen**
- **Follow all the required tests to check your eligibility**
- **If you are found eligible, you will be offered participation in the study**
- **Read, fill and sign the informed consent**
- **When written informed consent form is approved, you will start your 39-week treatment**

Your participation in this study is voluntary. Nobody can be enrolled in the study unless the written informed consent is signed.

Even if you decide to participate in this study, you may withdraw (take back your decision to participate) at any time.

Although, if you are not eligible or decline participation in the study, you will be referred for regular treatment and care provided by the National TB Program with no negative consequences.

Thank you!

WHO Regional Office for Europe

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BUREAU RÉGIONAL DE L' Europe

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Европейское региональное бюро