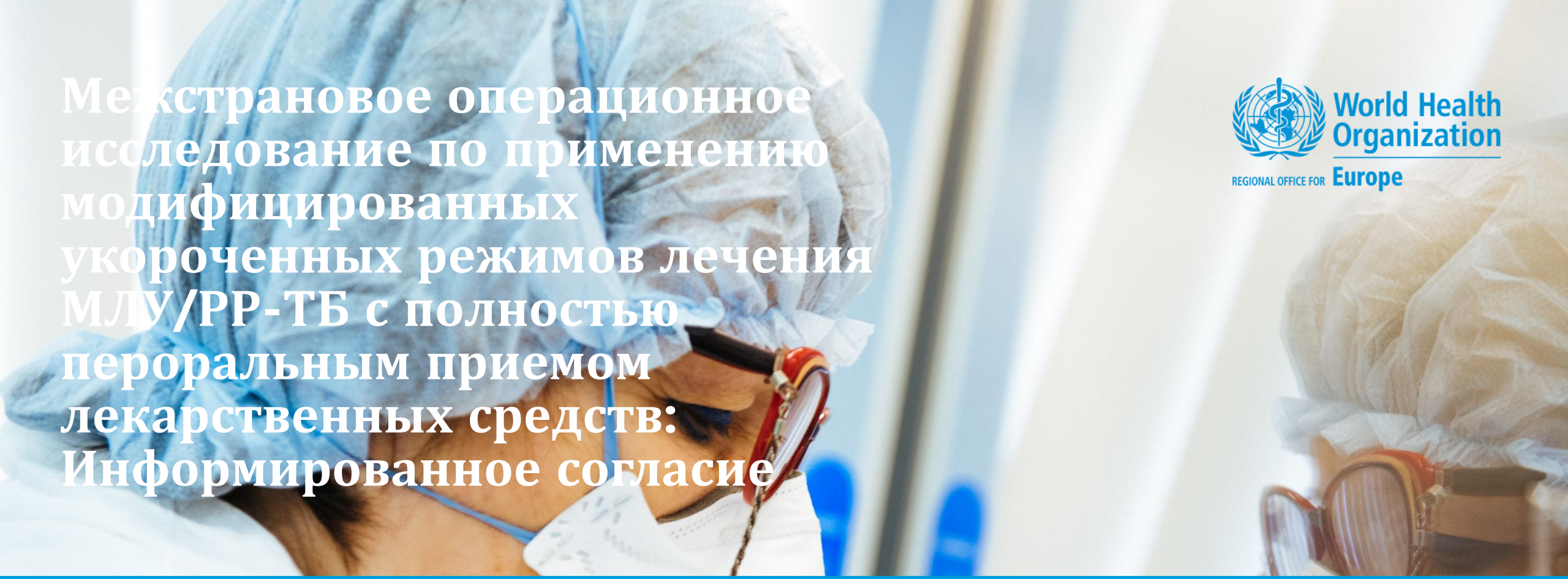


Межстрановое операционное исследование по применению модифицированных укороченных режимов лечения МЛУ/РР-ТБ с полностью пероральным приемом лекарственных средств: Информированное согласие

World Health Organization
REGIONAL OFFICE FOR Europe

Европейская инициатива по исследованиям туберкулеза, Европейское региональное бюро ВОЗ

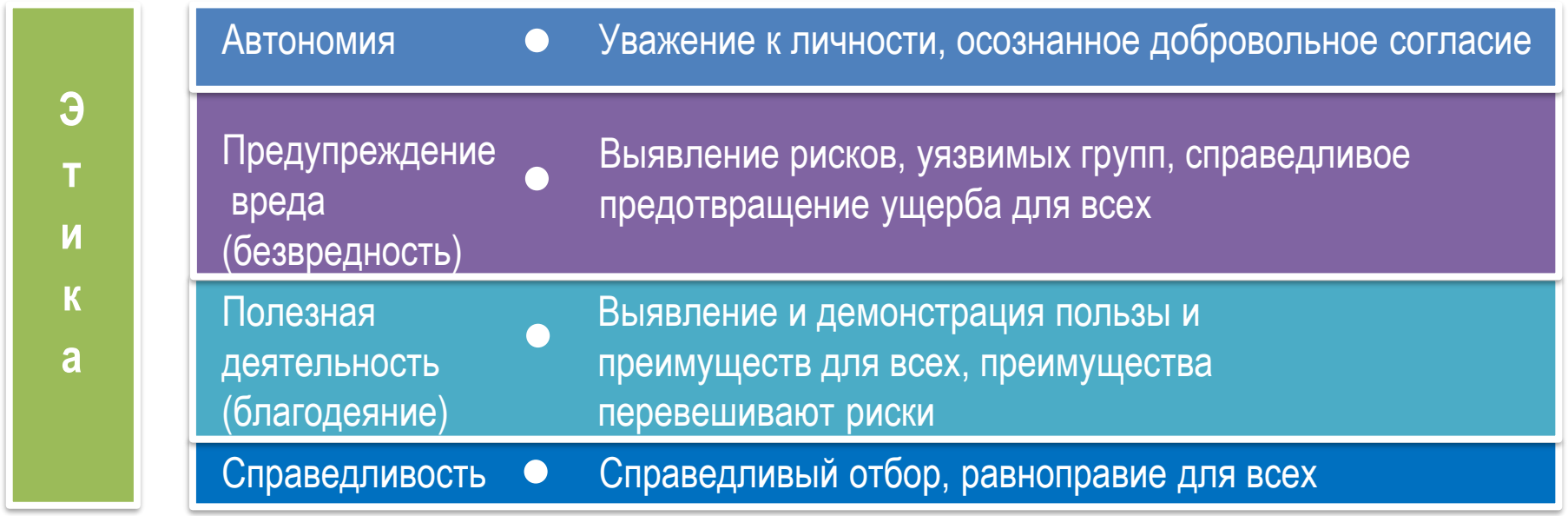
7 октября 2020 г.

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

Историческая справка

- Понятие информированного согласия уходит своими корнями в Нюрнбергский кодекс 1945 года
- Понятие сформулировано в ответ на шокирующие открытия, сделанные во время Нюрнбергского процесса
- Тогда было установлено, что нацистские врачи проводили ужасные медицинские эксперименты над заключенными в концентрационных лагерях, где они использовались в качестве объектов исследования

Традиционные принципы этики биомедицинских исследований



Основные принципы этики здравоохранения

World Health Organization
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Автономия

- Уважать право пациента принимать собственное решение

Принцип «делай благо»

- Оказывать помощь пациенту в приумножении пользы для него самого

Безвредность

- Непричинение вреда

Справедливость

- Быть справедливым и относиться к подобным случаям одинаково

Автономия
Voluntas aegroti suprema lex
(Пациенты будут высшим законом)

- Автономия - это общий показатель здоровья
- Автономия - это показатель как для личного благополучия, так и для благополучия профессии

Принцип «делай благо»
Salus aegroti suprema lex
(Безопасность пациентов - высший закон)

- Благодеяние относится к действиям, способствующим благополучию других людей
- Принятие мер, которые наилучшим образом отвечают интересам пациентов.
- Однако точное определение того, какие практики действительно помогают пациентам, пока не установлено

Предупреждение вреда primum non nocere (Главное, не навреди)

World Health Organization
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- Многие методы лечения несут в себе некоторый риск причинения вреда
- В отчаянных ситуациях с ожидаемым неблагоприятным исходом без лечения рискованные методы лечения с высокой вероятностью отрицательного эффекта будут оправданы, поскольку риск отсутствия лечения также с большой вероятность навредит пациенту.
- Принцип *«не навреди»* не является абсолютным и уравновешивает принцип благодеяния, поскольку единое действие этих двух принципов часто приводит к *двойному эффекту*

Направленность медицинской, общественной и исследовательской этики

Медицинская этика

- Отдельно взятые пациенты
- Отношения между врачом и пациентом
- Обязанности врачей/ медсестер

Этика общественного здоровья

- Здоровье населения
- Программы и вопросы политики в сфере здравоохранения
- Научные факты
- Участие общественности
- Меры профилактики

Этика научных исследований

- Защита участников исследования
- Информированное согласие
- Анализ рисков и выгод
- Справедливый отбор и доступ и т.д.

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

Определение

Информированное согласие - это **процесс** получения разрешения субъекта на участие в исследованиях и возможности принять решение, касающееся своего здоровья

Цель:

Обеспечить понимание пациентом роли новых лекарственных препаратов/режимов лечения и возможность задавать вопросы и получать на них ответы

Содержание согласия

Основные пункты:

- Необходимость в новых режимах лечения, новых лекарственных средствах
- Выгоды
- Риски
- Как будет осуществляться прием лекарственных препаратов
- Контрацепция
- Контроль побочных эффектов клиницистом (включая отчетность о побочных эффектах)
- Приглашение к сотрудничеству с людьми, осуществляющими уход за пациентом

Язык

- Местный язык (и) – убедитесь, что язык понятен для пациента
- Учет культурных особенностей
- Исключение медицинских терминов и сокращений:
  - ЭКГ, Dlm, Bdq, ТЛЧ
  - Смертность
  - Схема лечения
  - Липаза, альбумин и др.
  - Аритмия

Эффект Ноцебо

«Принцип информированного согласия обязывает врачей объяснять возможные побочные эффекты при назначении лекарственных средств. Раскрытие этой информации само по себе может вызвать неблагоприятные эффекты через механизмы ожидания этих последствий. Они известны как **эффекты ноцебо**, что противоречит принципу «не навреди». Тщательные исследования показывают, что предоставление пациентам подробного перечня всех возможных нежелательных явлений может фактически привести к усилению побочных эффектов»

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.

Эффект Ноцебо

Влияние эффекта ноцебо дает основания предполагать, что для здоровья лучше ошибаться на стороне оптимизма, чем на стороне пессимизма

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

Особенности процесса информированного согласия

- Хорошее общение - надлежащая медицинская практика
- Влияние бесед с клиницистом на впечатления пациентов
- Не возлагайте всю ответственность за принятие решений на пациента
- Информированное согласие - это непрерывный процесс и диалог

Основные навыки эффективной коммуникации

Как *нужно общаться с пациентом*, чтобы он чувствовал, что его участие в исследовании ценят и уважают, тем самым повышая вероятность соблюдения установленных требований лечения

- Оцените собственное общение
- Обратите внимание на невербальную коммуникацию
- Обеспечьте конструктивную обратную связь
- Задавайте открытые вопросы
- Умейте слушать

Из курса LHL effective health communication

Процедура информированного согласия

- Пациенты, соответствующие требованиям включения в исследование, получат информацию о МЛУ-ТБ и мКРЛ
- Пациентам предоставят информацию на родном языке
- Пациенты должны иметь возможность обсудить Информационный листок пациента с медицинским работником/ помощником в лечении
- Пациенты должны быть уверены, что их решение об участии или неучастии в исследовании не повлияет на качество получаемой ими медицинской помощи

Процедура информированного согласия

- После согласия на участие в исследовании пациенту будет предложено подписать форму согласия

▪ В случае лечения детей согласие должно быть получено от законного представителя, а также от самого ребенка

▪ Все пациенты, не соответствующие критериям включения в исследование, отказывающиеся от участия в исследовании или выходящие из него после включения, будут получать лечение согласно национальным руководствам без каких-либо отрицательных последствий для самих пациентов.

Информационный листок пациента

World Health Organization
REGIONAL OFFICE FOR Europe

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: _____

Учебные материалы

World Health Organization
REGIONAL OFFICE FOR Europe

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.

Спасибо!

Европейское региональное бюро ВОЗ

UN City
Marmorvej 51
Copenhagen Ø
Denmark

WHO_Europe

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youtube.com/user/whoeuro

World Health Organization
REGIONAL OFFICE FOR Europe

Weltgesundheitsorganisation
REGIONALBÜRO FÜR Europa

Organisation mondiale de la Santé
BUREAU RÉGIONAL DE L' Europe

Всемирная организация здравоохранения
Европейское региональное бюро