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The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (MDR-TB)

Submission date
04/10/2010

Registration date
14/10/2010

Last Edited
30/05/2025

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[X] Individual participant data

Plain English summary of protocol
https://www.mrcctu.ucl.ac.uk/studies/all-studies/s/stream-stage-1/

Study website
https://www.mrcctu.ucl.ac.uk/studies/all-studies/s/stream-stage-1/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT02409290

Secondary identifying numbers
N/A

Study information

Scientific Title
The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (MDR-TB): a multi-centre international parallel group randomised controlled trial

Acronym
STREAM

Study objectives
To determine whether a standardised regimen utilising existing drugs that has been used in one country setting with excellent treatment outcomes can be used in other settings with comparable success.

Patients with Multi-Drug-Resistant Tuberculosis (MDR-TB) are currently treated for 18-24 months, based on recommendations by the World Health Organisation (WHO). Treatment success rates are poor.

In a prospective cohort study carried out by Dr. Van Deun (2010) in Bangladesh, patients with MDR-TB were treated for only nine months with very promising results.

The STREAM trial assesses whether a treatment closely similar to that used in Bangladesh is as good as the treatment for MDR-TB recommended by WHO. If the results are positive, it will be possible to treat patients with MDR-TB in different countries for only 9 months.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The International Union Against TB and Lung Disease's Ethics Advisory Group, 19/04/2011, ref: EAG Number 07/11. The trial will also be approved in all participating countries prior to the commencement of the study there

Study design
Non-inferiority multi-centre international parallel-group open-label randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Multidrug resistant pulmonary tuberculosis (MDR-TB)

Interventions
Current interventions as of 28/09/2011:
The study regimen (Arm B) is based on the regimen described by Van Deun 2010; it consists of moxifloxacin, clofazimine, ethambutol and pyrazinamide given for nine months (40 weeks), supplemented by kanamycin, isoniazid and prothionamide in the four months (16 weeks) of the intensive phase. All drugs are given daily (seven days a week) except for kanamycin which is given thrice weekly after 12 weeks.

Patients will be randomised to either the study regimen or the locally-used WHO-approved MDR-TB regimen.
Study regimen doses:
Kanamycin: 15 mg per kilogram body weight (maximum 1 g)
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Moxifloxacin: 400 mg (less than 33 kg), 600 mg (33 - 50 kg) or 800 mg (more than 50 kg)
Ethambutol: 800 mg (less than 33 kg), 800 mg (33 - 50 kg) or 1200 mg (more than 50kg)
Isoniazid: 300 mg (less than 33 kg), 400 mg (33 - 50 kg) or 600 mg (more than 50 kg)
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Prothionamide: 250 mg (less than 33 kg), 500 mg (33 - 50 kg) or 750 mg (more than 50 kg)

In the event of delayed smear conversion the intensive phase of the study regimen can be extended 4 or 8 weeks, allowing a maximum total duration of 48 weeks treatment.
Patients on the control regimen will receive the locally-used WHO-approved MDR-TB regimen which should be given for a minimum of 18 months following culture conversion.

All patients in the study will be followed up to 33 months post-randomisation.

Previous interventions:
Patients will be randomised to either the study regimen or the locally-used WHO-approved MDR-TB regimen.

The trial intervention will be a 9-month regimen based on the one described by Van Deun 2010, hereafter referred to as the study regimen: ethambutol, pyrazinamide, moxifloxacin and clofazimine throughout supplemented by kanamycin, prothionamide and isoniazid in the first four months (4KCMEHZP/5MEZC).

Study regimen doses:
Kanamycin: 15 mg per kilogramme body weight (maximum 1 g)
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Moxifloxacin: 400 mg (less than 33 kg), 600 mg (33 - 50 kg) or 800 mg (more than 50 kg)
Ethambutol: 800 mg (less than 33 kg), 800 mg (33 - 50 kg) or 1200 mg (more than 50 kg)

Isoniazid: 300 mg (less than 33 kg), 400 mg (33 - 50 kg) or 600 mg (more than 50 kg)
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Prothionamide: 250 mg (less than 33 kg), 500 mg (33 - 50 kg) or 750 mg (more than 50 kg)

The only change from the regimen described by Van Deun 2010 is that moxifloxacin has been substituted for gatifloxacin because gatifloxacin was withdrawn by the original marketing authorisation holder and generic sources investigated did not meet WHO norms and standards for quality, safety and efficacy.

Patients on the study regimen will receive 9 months of treatment (4 months intensive phase, 5 months continuation phase) and a further 18 months of follow-up, i.e. 27 months post-randomisation. In the event of delayed smear conversion the 4-month intensive phase of the study regimen can be extended by 1 or 2 months, allowing a maximum total duration of 11 months treatment.

The control regimen will be the locally used regimen in each country that follows the WHO MDR-TB treatment guidelines. This may differ in each country but will be the best standardised regimen in that country as recognised by the National Treatment Programme. Patients on the control regimen will also be followed up to 27 months post-randomisation.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Moxifloxacin, clofazimine, ethambutol, pyrazinamide, kanamycin, isoniazid, prothionamide

Primary outcome measure
Current primary outcome measures as of 25/01/2016:
The primary efficacy outcome is the proportion of patients with a favourable outcome 132 weeks after randomisation, having not previously had an unfavourable outcome or been retreated.
The primary safety outcome is the proportion of patients experiencing a grade 3 or greater adverse event during treatment and follow-up.

Previous primary outcome measures from 28/09/2011 to 25/01/2016:
The primary efficacy outcome is the proportion of patients with a favourable outcome 27 months after randomisation, having not previously had an unfavourable outcome or been retreated.
The primary safety outcome is the proportion of patients experiencing a grade 3 or greater adverse event during treatment and follow-up.

Original primary outcome measures:
Measured at the end of follow-up:
1. Efficacy: proportion of patients with a favourable outcome. A patient will be classified as favourable if they have a negative culture result at the end of follow-up having not been previously classified as unfavourable. A patient will be classified as unfavourable if:
1.1. They are discontinued from treatment and restarted on MDR-TB treatment, or
1.2. They are restarted on MDR-TB treatment after the end of the treatment phase.

Change of regimen for any reason other than the replacement of a single drug will result in the patient being classified as having an unfavourable outcome. In addition, the following will also be classified as unfavourable:
1.3. All deaths at any point during treatment or follow-up
1.4. A patient who has a positive culture result at the end of follow-up or if withdrawn from the study or lost to follow-up, was culture positive when last seen
2. Safety: proportion of patients experiencing a grade 3 or greater adverse event during the study

Secondary outcome measures
Current secondary outcome measures as of 28/09/2011:
1. Time to sputum (smear and culture) conversion
2. Time to unfavourable efficacy outcome
3. Efficacy status at the end of follow-up (33 months for those with extended follow-up)
4. All-cause mortality during treatment and follow-up
5. Change of regimen for adverse drug reactions
6. Number of adverse reactions occurring on treatment
7. Adherence to treatment
8. Acceptability of regimen to all stakeholders in terms of:
8.1. Costs to the health system related to delivering the regimen and conducting follow-up tests
8.2. Household costs
8.3. Patient treatment and support experiences (frequency of health facility visits, side effects)
8.4. Health worker experiences of delivering treatment and support

Previous secondary outcome measures:
Measured at the end of follow-up:
1. Time to sputum culture conversion
2. Time to sputum smear conversion
3. All-cause mortality during treatment and follow-up
4. Adherence to treatment
5. Time to unfavourable efficacy outcome
6. Time to cessation of clinical symptoms
7. Cost per patient (from both health system and patient perspectives)

Overall study start date
27/07/2012

Completion date
31/07/2018

Eligibility

Key inclusion criteria
Current inclusion criteria as of 25/01/2016:
1. Is willing and able to give informed consent to participate in the trial treatment and follow-up (signed or witnessed consent if the patient is illiterate)
2. Is aged 18 years or older
3. Has a positive Acid Fast Bacilli (AFB) sputum smear result at screening (at least scanty), unless they are HIV positive in which case a positive GeneXpert result within 4 weeks prior to screening is sufficient
4. Has evidence of resistance to rifampicin either by line probe assay (Hain Genotype21),

GeneXpert or culture-based drug susceptibility testing (DST), from a test performed at screening or from a test performed within the 4 weeks prior to screening
5. Is willing to have an HIV test and, if positive, is willing to be treated with ART in accordance with national policies but excluding ART contraindicated for use with bedaquiline
6. Is willing to use effective contraception: pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilised must use 2 methods of contraception; men who have not had a vasectomy must agree to use condoms

Previous inclusion criteria:
1. Willing and able to give informed consent for treatment and follow-up (signed or witnessed consent if the patient is illiterate)
2. Aged 15 years or older, either sex
3. Has smear-positive pulmonary tuberculosis with initial laboratory result of resistance to rifampicin by line probe assay or other DST
4. Is willing to have an HIV test and if positive is willing to be treated with ART in accordance with national policies
5. Agrees to use effective barrier contraception or an intrauterine contraceptive device during treatment phase if a pre-menopausal woman
6. Has an identifiable address and expects to remain in the area for the duration of the study
7. Is willing to adhere to the follow-up schedule and to study procedures

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
At least 400

Total final enrolment
424

Key exclusion criteria
Current exclusion criteria as of 25/01/2016:
1. Is infected with a strain of M. tuberculosis resistant to a second-line injectables by line probe assay
2. Is infected with a strain of M. tuberculosis resistant to a fluoroquinolone by line probe assay
3. Has tuberculous meningitis or bone and joint tuberculosis
4. Is critically ill, and in the judgment of the investigator, unlikely to survive more than 4 months
5. Is known to be pregnant or breast-feeding
6. Is unable or unwilling to comply with the treatment, assessment, or follow-up schedule
7. Is unable to take oral medication
8. Has aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 5 times the upper limit of normal for stage 1 and AST or ALT more than 3 times the upper limit of normal

for stage 2
9. Has any condition (social or medical) which in the opinion of the Investigator would make study participation unsafe
10. Is taking any medications contraindicated with the medicines in any trial regimen
11. Has a known allergy to any fluoroquinolone antibiotic
12. Is currently taking part in another trial of a medicinal product
13. Has a QT or QTcF interval at screening or immediately prior to randomisation of ≥ 450 ms for stage 1, and ≥ 500 ms for stage 2

Previous exclusion criteria from 28/09/2011 to 25/01/2016:
1. Is infected with a strain of M. tuberculosis resistant to a second-line injectable drug by line probe assay
2. Is infected with a strain of M. tuberculosis resistant to a fluoroquinolone by line probe assay
3. Has tuberculous meningitis or bone and joint tuberculosis
4. Is critically ill, and in the judgment of the investigator, unlikely to survive more than 4 months
5. Is known to be pregnant or breastfeeding
6. Is unable to attend or comply with treatment or follow-up schedule
7. Is unable to take oral medication
8. Has AST or ALT >5 times the upper limit of normal
9. Has any condition (social or medical) which in the opinion of the investigator would make study participation unsafe
10. Is taking any medications contraindicated with the medicines in either the trial or control regimen
11. Has a known allergy to any fluoroquinolone antibiotic
12. Is currently taking part in another trial of a medicinal product
13. Has a QTc interval ≥500 msec at screening

Original exclusion criteria:
1. Resistant to a second-line injectable drug by line probe assay
2. Resistant to a fluoroquinolone by line probe assay
3. Critically ill, and in the judgment of the investigator, unlikely to survive more than 4 months
4. Known to be pregnant or breastfeeding
5. Unable to attend or comply with treatment or follow-up schedule
6. Unable to take oral medication
7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times the upper limit of normal
8. Any condition (social or medical) which in the opinion of the investigator would make study participation unsafe or complicate data interpretation
9. Taking any medications contraindicated with the medicines in the study regimen
10. Known allergy to any fluoroquinolone antibiotic
11. Currently taking part in another trial of a medicinal product

Date of first enrolment
15/11/2011

Date of final enrolment
30/06/2015

Locations

Countries of recruitment

England

Ethiopia

Mongolia

South Africa

United Kingdom

Viet Nam

Study participating centre
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials & Methodology
90 High Holborn 2nd Floor
London
United Kingdom
WC1V 6LJ

Sponsor information

Organisation
International Union Against Tuberculosis and Lung Disease (IUATLD, Inc.) (USA)

Sponsor details
61 Broadway
Suite 1720
New York
United States of America
10006

Sponsor type
Research organisation

Website
http://www.theunion.org/what-we-do/research/clinical-trials

Funder(s)

Funder type
Research organisation

Funder Name
United States Agency for International Development

Alternative Name(s)
U.S. Agency for International Development, Agency for International Development, USAID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
The entire anonymized trial dataset and the health system level health economics data are stored in the CPATH-TB PACTS repository (https://c-path.org/programs/tb-pacts/) meeting Clinical Data Interchange Standards Consortium (CDISC) standards. Please register for access to the TB-PACTS data platform via https://c-path.org/programs/tb-pacts/ and review the terms and conditions in the ”Training videos and supporting documents” section. The TB-PACTS steering committee will review all user access applications in a timely manner and this may take up to 4 weeks to process. Stage 1 is available now; Stage 2 will be available some time in 2023. Individual patient consent wasn’t obtained. However, approval was obtained from all ethic committees involved in the study to anonymise and post the data. Data is fully anonymised and is only available to qualified researchers engaged in non-profit, non-commercial TB research.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		09/09/2014		Yes	No
Protocol article		17/10/2016		Yes	No
Results article		28/03/2019		Yes	No
Dataset			01/09/2022	No	No
Statistical Analysis Plan	version 1.1	01/06/2017	01/09/2022	No	No
Other publications		31/01/2024	31/01/2024	Yes	No
			11/03		

Results article		10/03/2024	/2024	Yes	No
Other publications	The role of stakeholder mapping and engagement	29/05/2025	30/05 /2025	Yes	No