

HARVEST trial - improving outcomes from TB meningitis with high-dose oral rifampicin

Submission date 23/05/2019	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 17/06/2019	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 09/05/2025	Condition category Infections and Infestations	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English Summary

Background and study aims

Tuberculous meningitis accounts for 1-5 % of all TB infections and carries a high case-fatality (up to 50%) and many survivors are left with long-term disabilities. Rifampicin is the most important anti-TB drug but at the currently recommended dose (10 mg/kg) it fails to penetrate into the brain and spinal fluid adequately. This trial is testing whether giving a much higher dose of rifampicin by mouth, in addition to the normal anti-TB drugs, can reduce death and disability caused by TB meningitis.

Who can participate?

Patients aged 18 and over with first episode tuberculous meningitis suspected by attending physician and anti-TB treatment planned

What does the study involve?

Participants are allocated by chance to receive either four rifampicin 300 mg capsules in addition to standard fixed dose combination TB treatment, or standard fixed dose combination TB treatment. Participants are followed up in hospital until discharge and then as an outpatient for 12 months.

What are the possible benefits and risks of participating?

The high dose rifampicin may be more effective at treating the infection so the participants' chance of dying or being left with a disability may be reduced (though this won't be known until the end of the trial). More intensive monitoring of blood tests and clinical status may allow complications to be picked up and treated earlier than in they would in the normal care environment. Transport and costs of follow-up are covered by the study which may reduce financial burden on the participant. Possible risks of participation include: side effects or toxicity from the high-dose rifampicin; more frequent blood tests and an additional lumbar puncture; and the high dose rifampicin may not have an impact on clinical outcomes.

Where is the study run from?

1. Infectious Diseases Institute (Uganda)

2. University of KwaZulu Natal (South Africa)
3. Eijkman-Oxford Clinical Research Unit (Indonesia)
4. Universitas Padjadjaran (Indonesia)

When is the study starting and how long is it expected to run for?
November 2019 to June 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Fiona Cresswell
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
MHREC 1554

Study information

Scientific Title

High-dose oral rifampicin to improve survival from adult tuberculous meningitis: a double-blinded randomised placebo-controlled Phase III trial

Acronym

HARVEST

Study hypothesis

High dose oral rifampicin (35 mg/kg) alongside other regular first-line antituberculous drugs will improve survival and neurological outcomes from Tuberculous meningitis compared to standard of care TB treatment.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approvals have been received from 8 regulatory authorities across the 3 participating countries: UGANDA

Approved 17/06/2020, Mulago National Referral Hospital IRB (Mulago National Referral Hospital, P.O. Box 7051, Kampala, Uganda; +256 414 53 25591; admin@mulago.or.ug), ref: MHREC 1554.

National Drug Authority; ref: CTA0118

Uganda National Council of Science and Technology; ref: HS428ES

SOUTH AFRICA

Approved 20/04/2021, University of KwaZulu-Natal Biomedical Research Ethics Committee (Research Ethics Office, Westville Campus, Govan Mbeki Building; Private Bag X54001, Durban 4000; BREC@ukzn.ac.za); ref: BFC003/19

South Africa Health Product Regulatory Authority; ref: 20200331

INDONESIA

Approved 22/07/2020, Universitas Indonesta Fakultas Kedokteran (Gedung Fakultas Kedokteran UI, Jl. Salemba Raya No.6, Jakarta 10430, PO.Box 1358); +62.21.3912477, 3193037 1, 31 930373, 3922977, 3927360, 31 53236; E. humas @fk.ui.ac.id, office @fk.ui.ac.id); ref: 19-03-0238

Universitas Padjadjaran Research Ethics Committee (Jl. Prof Eyckman No. 38 Bandung 40161; 022-2038697; etik.unpad@gmail.com); ref: 0719070991

National Agency of Drug and Food Control (Badan Pengawas Obat dan Makanan); ref: BPOM-B-RG.01.06.32.321.08.20.513

Study design

Double-blinded parallel group randomised placebo-controlled Phase III trial

Primary study design

Interventional

Secondary study design

Non randomised study

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.

Condition

Tuberculous meningitis

Interventions

Participants are allocated by chance to receive either:

1. Four oral rifampicin 300-mg capsules in addition to standard fixed-dose combination TB treatment
2. Standard fixed-dose combination TB treatment

Participants are followed up in hospital until the time of discharge and then as an outpatient for 12 months.

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Rifampicin

Primary outcome measure

6-month survival

Secondary outcome measures

1. 12-month survival
2. Functional and neurocognitive outcomes measured using the following instruments:
 - 2.1. Normalization of mental status with Glasgow coma scale score (GCS) of 15 and maintained for >2 days (among those with GCS <15 at study entry). A substantial proportion of TBM patients (~50%) present with altered mental status and depressed consciousness. In these participants, early response to treatment is assessed by determining the days from randomization until observation of a GCS of 15 which is achieved for >2 consecutive days
 - 2.2. Functional outcomes assessed by Liverpool Outcome Score at month 6 (Appendix C)
 - 2.3. Quantitative neurocognitive performance Z-scores (QNPZ-8) at 2 and 12 months (Uganda only). QNPZ-8 is derived from a test battery, which includes:
 - 2.3.1. Grooved Pegboard test
 - 2.3.2. Colour Trails 1 and 2 tests
 - 2.3.3. WAIS-III Digit Symbol test
 - 2.3.4. Finger Tapping test
 - 2.3.5. WHO-UCLA Auditory Verbal Learning Test
 - 2.3.6. Semantic Verbal Fluency test (category fluency)
3. Safety and tolerability endpoints:
 - 3.1. Clinical AEs, grade 3-5 as classified by Division of AIDS (DAIDS) Toxicity Scale
 - 3.2. Laboratory AEs, grade 3-5 as classified by DAIDS Toxicity Scale
 - 3.3. All Serious AEs (SAEs)

3.4. Drug-induced liver injury (grade 3-5)

§ Alanine transaminase (ALT) or aspartate transaminase (AST) >5x upper limit of normal (ULN)

3.5. Discontinuation of TB treatment for >5 days in the first 8 weeks for any cause

4. Cumulative days of hospitalization (and re-hospitalization)

5. Incidence of re-hospitalization for neurologic deterioration

6. Incidence and management of drug-induced liver injury

Overall study start date

01/11/2019

Overall study end date

01/06/2025

Eligibility

Participant inclusion criteria

1. First episode TBM suspected by attending physician (>3 days of meningitis symptoms and CSF abnormalities) and anti-TB treatment planned

2. Age ≥18 years

3. Provision of written informed consent by participant or surrogate

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

500

Participant exclusion criteria

1. Presence of jaundice, known liver cirrhosis, or known elevated ALT >5x ULN

2. More than 5 doses of any TB treatment received within the previous 7 days

3. Known allergy to: isoniazid, rifampicin, ethambutol, or pyrazinamide

4. Known current/previous rifampicin-resistant M.tb infection

5. Additional active and confirmed CNS infection

6. Corticosteroids contraindicated

7. Cannot or unlikely to attend regular clinic visits

8. Pregnancy or breastfeeding

9. Known renal failure with eGFR <30 ml/min by Modification of Diet in Renal Disease (MDRD)

Study equation

10. HIV Protease Inhibitor ongoing use

Recruitment start date

01/01/2020

Recruitment end date

01/06/2024

Locations

Countries of recruitment

Indonesia

South Africa

Uganda

Study participating centre

Infectious Diseases Institute

Kampala

Uganda

PO Box 22418

Study participating centre

University of KwaZulu Natal

719 Umbilo Road

Durban

South Africa

4001

Study participating centre

Eijkman-Oxford Clinical Research Unit

University of Oxford; Faculty of Medicine Universitas Indonesia

Jl Diponegoro 69

Jakarta

Indonesia

10430

Study participating centre

Universitas Padjadjaran

Bandung

Indonesia

40161

Sponsor information

Organisation

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Sponsor type

University/education

Website

<https://www.idi-makerere.com>

ROR

<https://ror.org/03dmz0111>

Funder(s)

Funder type

Government

Funder Name

Medical Research Council

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Publication and dissemination plan

The researchers plan to publish the protocol in Wellcome Open Research once they have ethical approval.
The main trial paper will be published open access within 6 months of the last participant completing follow up.
Additional sub-studies will be published open access at the appropriate intervals.
The Meningitis Research Foundation is the researchers' communications partner to maximise the impact of the results. The researchers will engage other stakeholders in trial countries.

Intention to publish date

01/08/2025

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Fiona Cresswell, IDI/LSHTM (fiona.cresswell@lshtm.ac.uk).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	25/08/2020	23/10/2020	Yes	No