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

**Submission date**
23/05/2019

**Recruitment status**
No longer recruiting

**Registration date**
17/06/2019

**Overall study status**
Completed

**Last Edited**
02/01/2026

**Condition category**
Infections and Infestations

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

## Plain English summary of protocol

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
fiona.cresswell@lshtm.ac.uk

# Contact information

### Type(s)
Scientific

### Contact name
Dr Fiona Cresswell

### ORCID ID
https://orcid.org/0000-0002-5070-532X

### Contact details
Infectious Diseases Institute
Kampala
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# Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
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 objectives
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 Kidokteran (Gedung Fakultas Kedokteran Ul, 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

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
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(s)
6-month survival

### Key secondary outcome(s))
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

### Completion date
01/06/2025

## Eligibility

### Key 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

### Healthy volunteers allowed
No

### Age group
Mixed

### Lower age limit
18 years

### Upper age limit
100 years

### Sex
All

### Total final enrolment
0

### Key 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

### Date of first enrolment
01/01/2020

### Date of final enrolment
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**
Makerere College of Health Sciences

**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, Medical Research Committee and Advisory Council, MRC

### Funding Body Type
Government organisation

### Funding Body Subtype
National government

### Location
United Kingdom

# Results and Publications

### 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? |
|---|---|---|---|---|---|
| Results article | | 18/12/2025 | 02/01/2026 | Yes | No |
| Protocol article | | 25/08/2020 | 23/10/2020 | Yes | No |