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SURE: Short intensive treatment for children with tuberculous meningitis

Submission date 26/09/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 13/11/2018	**Overall study status** Ongoing	
Last Edited 04/04/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims

Children in close contact with an adult who has tuberculosis (TB) are at a high risk of getting TB themselves and young children are especially prone to getting severe TB which affects the brain. This is called TB meningitis (TBM). About one in five children who get TBM die of the disease, and about two in five have some kind of disability. As well as this tragedy for the child, there is a large personal and financial cost to families who look after these children, often for many years. Health systems and societies are also affected.

The World Health Organization (WHO) currently advises 12 months of anti-TB treatment for children with TBM, whereas children with other sorts of TB are recommended 6 months of treatment. This advice is not based on good quality evidence. Experts have been calling for a study to find out if it is safe and effective to treat children with TBM for only 6 months. Halving the treatment time would potentially have large benefits for families and health systems.

Researchers in South Africa have investigated treating children for 6 months by giving them slightly different anti-TB medicines and at higher doses. This means higher anti-TB medicine concentrations are achieved in the brain. The health outcomes for these children seem at least as good as the health outcomes for children with TBM in other countries where 12 months of treatment are given. However, we cannot be sure if this treatment works well and is safe because it has never been tested in a clinical trial.

Aspirin has been used for many years for fever and pain. It is also known to help reduce blood clots and to reduce inflammation. It is used widely as a treatment for adults who have had heart attacks or strokes to prevent blood clots and is used at high-doses in young children with severe heart disease to prevent damage to blood vessels and heart valves. Much of the damage in children with TBM is caused by strokes, which are thought to be due to increased clotting and inflammation. Aspirin (in addition to TBM treatment) may help to reduce this damage, but studies so far have been small and inconclusive so doctors remain unsure whether to use aspirin for children with TBM.

We plan to carry out a clinical trial to answer two questions:

1. Is it safe and effective to treat children with TBM for 6 months as opposed to 12 months? We plan to see if anti-TB treatment for 6 months is as good as treatment for 12 months.
2. Does aspirin for the first 60 days of anti-TB treatment reduce the risk of disability in children with TBM? We plan to give half the children aspirin and the other half a placebo (sugar pill) so that neither they nor the study team know which child is receiving which treatment.

Who can participate?
Children under 18 years and over 28 days of age with TBM disease, with or without HIV infection

What does the study involve?
Children will be randomised to receive either the shorter or longer TB treatment schedules and then each treatment group will be further randomised to receive either aspirin or placebo resulting in four different treatment groups.
The shorter TB treatment schedule lasts for 6 months and children will be given 4 medicines (rifampicin, isoniazid, pyrazinamide and levofloxacin) every day for 6 months. The longer TB treatment lasts for 12 months. Children will be given rifampicin, isoniazid, pyrazinamide and ethambutol once daily for 2 months, and then rifampicin and isoniazid only every day for 10 months.
In addition, children in both groups will either be given aspirin once daily for 2 months, or a placebo once daily for 2 months. All children will be given ranitidine to protect their stomach and steroid medication for the first 4 weeks.
Children will undergo various tests, most of which are done for any child with TBM and are considered good practice. There will be a spianl tap, where a small sample of cerebrospinal fluid (the fluid that surrounds the brain and spinal cord) is taken, to look for the bacteria that cause TBM and to ensure the medicines received by the child will work. There will be a chest X-ray, to see if TB has affected the lungs. A sputum test will be done, along with blood tests and urine samples. Children will also be asked to complete questionnaires about development (walking, talking, playing and learning) to see if this has been affected by the illness.

What are the possible benefits and risks of participating?
There may not be a direct benefit to a child taking part in the SURE study apart from being seen regularly by a study doctor while they are in the study and being referred for further care, if needed. However, children may benefit from taking treatment for a shorter length of time and also from improved recovery from TB meningitis by taking aspirin. The information we get from this study will also help us to improve future treatments for children with TB meningitis.
The children need to be treated for TB meningitis regardless of whether or not they join the SURE study. Participants might experience some side effects from the medicines that he/she takes in this study. Some of these could happen if they took these medicines if they were not in the SURE study. Children will need to attend the study clinic more often than he or she would do if they were treated for TB Meningitis outside of the SURE study. He/she will also need to have blood tests. There are very few risks from taking blood but side effects may include discomfort, bruising and (very rarely) infection. The study staff will make sure that the amount of blood taken is safe for the child. The risks of lumbar puncture are also few and include discomfort when the needle is inserted into the back, the possibility of infection and headache. Children should lie down for a few hours after the test and get enough fluids.
The medicines being used in the SURE study are all recommended by the WHO and are routinely used for treating adults and children for TB meningitis. Although these medicines are generally safe in children, side effects may rarely occur.
The most common side effects caused by the TB meningitis medicines are red tears and urine. This is not harmful at all. Less commonly, the following side effects may occur: joint pains, yellowing of the skin and eyes, itching skin and rash, vomiting or diarrhoea or problems with vision (very rare).
Both aspirin and steroid medicine may cause the lining of the stomach to become irritated and bleed resulting in blood stained vomits or dark bowel motions. This should be prevented by the ranitidine medicine.
If side effects occur it may be necessary to stop the medicine until the problem goes away or it is safe to re- start the medicine. We will look for side effects carefully and replace any TB

meningitis medicines that cause problems.
For girls who have started to menstruate a pregnancy test will be carried out before entry to the study and at regular intervals during the study. If girls do become pregnant they can continue to be part of the SURE study and receive the TB meningitis medicines.

Where is the study run from?
1. MRC CTU at UCL, London, UK
2. OUCRU Clinical Trials Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam
The trial will recruit patients from sites in Vietnam (managed by OUCRU), India, Uganda, Zambia and Zimbabwe (Indian and African sites to be managed by MRC CTU at UCL)

When is the study starting and how long is it expected to run for?
January 2018 to March 2026

Who is funding the study?
1. Department for International Development (DFID) (UK)
2. National Institute for Health Research (NIHR) (UK)
3. Medical Research Council (MRC) (UK)
4. Wellcome Trust Joint Global Health Trials (UK)

Who is the main contact?
Dr Anna Griffiths, mrcctu.sure@ucl.ac.uk

Study website
https://www.mrcctu.ucl.ac.uk/studies/all-studies/s/sure/

Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
SURE, 106698/Z/14/Z

Study information

Scientific Title
A randomised trial of 6 months enhanced anti-tuberculosis and 2 months anti-inflammatory treatment for HIV-infected and HIV-uninfected African and Asian children with tuberculous meningitis

Acronym
SURE

Study objectives
Short 6-month enhanced anti-TB treatment (ATT) regimen is non-inferior to the current 12-month standard WHO-recommended treatment regimen in terms of all-cause mortality

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/01/2019, UCL Research Ethics Committee (Office of the Vice Provost Research, 2 Taviton Street, University College London, London, UK; Tel: +44 (0)20 7679 8717; Email: ethics@ucl.ac.uk), ref: 14935/001

Study design
Interventional multi-centre partially-blinded factorial randomised phase III 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 contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Tuberculous meningitis

Interventions
Participants in this study will either be given the antibiotic medicines that are usually used to treat children with TB meningitis for 12 months (standard of care treatment) OR the higher dose medicines for 6 months (test treatment). Participants will be randomly allocated to receive the test treatment or the standard of care in a 1:1 ratio, with minimisation by TBM stage (stages 1 and 2 versus stage 3), HIV status, age (<2 years of age versus ≥2 years) and study centre. This stage is open-label.
The standard of care treatment uses 4 medicines at the WHO recommended dosages (rifampicin 15 mg/kg, isoniazid 10 mg/kg, pyrazinamide 35 mg/kg and ethambutol 20 mg/kg) once daily for 2 months followed by 2 medicines (rifampicin 15 mg/kg and isoniazid 10 mg/kg) daily for 10 months.
The test treatment uses 4 medicines (rifampicin 30 mg/kg, isoniazid 20 mg/kg, pyrazinamide 40 mg/kg and levofloxacin 20 mg/kg) once daily for 6 months.
Participants in both groups will then be randomised again (using the same methodology as before) to receive either aspirin to be taken once daily for 8 weeks (20 mg/kg) or a placebo once daily for 8 weeks. Whilst taking the aspirin or the placebo, participants will be given ranitidine to protect the stomach. This stage will be double-blinded. Participants will also receive steroid medication for around the first 4 weeks of their TBM treatment (standard of care for TBM).
Following screening assessments, eligible children will be randomised and enrolled into the trial. The randomisations will occur immediately after screening procedures have been completed and before commencing trial treatment, provided that results of CSF microscopy and results from screening are available, and the participant/carer feels they have adequate time to consider trial participation.
Before treatment allocations, the patient's eligibility will be confirmed, including the results of safety screening laboratory tests, and the minimisation factors entered into the database.
Patients will be randomised in a single process to one of 4 groups (prior to the start of treatments) using a web-based system controlled through an authorised user name and password to. A manual randomisation process will be set up to cover any instances when the main electronic system is not working.
Upon successful randomisation, the clinician should then prescribe the trial drugs.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Isoniazid Rifampicin Pyrazinamide Levofloxacin Aspirin

Primary outcome measure
The two randomisations have individual primary outcome measures.
Randomisation 1 (standard of care treatment versus test treatment):
1. All-cause mortality at 48 weeks, reported by the site investigators and captured via case report forms (CRFs)
Randomisation 2 (aspirin versus placebo):
1. Neurodevelopment at 48 weeks, assessed using a Modified Rankin score (MRS), captured on a CRF using the standardised MRS measure

Secondary outcome measures
1. Neurodevelopment at 24 and 48 weeks, assessed using a Modified Rankin score (MRS), captured on a case report form (CRF) using the standardised MRS measure (for randomisation 1)
2. All-cause mortality at 72 weeks, reported by the site investigators and captured via CRFs
3. Clinical or microbiological relapse of TBM and/or TB disease at other sites by 72 weeks, reported by the site investigators following up the participants and captured via CRFs
4. Any new grade 3 or grade 4 clinical or laboratory adverse events, and adverse events of any grade, leading to treatment modification, evaluated and reported by the site investigators using the Division of AIDS (DAIDS) toxicity table throughout the study
5. Other specific adverse events, evaluated and reported by the site investigators using the DAIDs toxicity table throughout the study:
5.1. Any gastrointestinal bleeding (any grade)
5.2. Drug-induced liver injury (DILI) of Grade 2 or more
5.3. Development of obstructive hydrocephalus
6. Acquired drug resistance, evaluated and reported by the site investigators using a blood test at screening, randomisation and optionally (if from a local practice) at study days 1 and 2
7. Non-adherence to treatment, evaluated and reported by the site investigators using standardised questionnaires and pill counts at days 1, 7 and 14, and weeks 4, 8, 16, 24, 36, 48 and 72
8. Suppressed HIV viral load and CD4 cell count in HIV-infected children, assessed using a blood test at the baseline and at 24, 48 and 72 weeks

Overall study start date
02/01/2018

Completion date
30/03/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 22/08/2024:

1. Aged between 29 days and <18 years old
2. Weight ≥3 kg
3. Symptoms compatible with tuberculosis meningitis (TBM), including fever, vomiting, anorexia,

listlessness and headache
4. Cerebrospinal fluid (CSF) result with abnormalities compatible with TBM (elevated cell count and/or protein with or without M. tuberculosis detected by microscopy or GeneXpert). Physician believes the child needs immediate initiation of anti-TB drugs.
5. Known (or pending confirmation of) HIV status
6. Parent/carer give informed, written consent
7. CSF sample processed for chemistry, microscopy, Ziehl–Nielsen or auramine stain and, mycobacterial culture (in process) and, where available, Xpert (Gene Xpert/Rif or Xpert Ultra) prior to commencing treatment. Where patients have already been started on ATT, pre-screening CSF results should be available.
8. Carer/parent can comply with the protocol requirements in the opinion of the site investigator
9. Home address accessible for visiting and intending to remain within the recruitment area for follow up period of at least 18 months

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Previous inclusion criteria:

1. Aged between 29 days and 15 years
2. Weight ≥3 kg
3. Symptoms compatible with tuberculosis meningitis (TBM), including fever, vomiting, anorexia, listlessness and headache
4. Cerebrospinal fluid (CSF) result with abnormalities compatible with TBM (elevated cell count and/or protein with or without M. tuberculosis detected by microscopy or GeneXpert). Physician believes the child needs immediate initiation of anti-TB drugs.
5. Known (or pending confirmation of) HIV status
6. Parent/carer give informed, written consent
7. CSF sample processed for chemistry, microscopy, Ziehl–Nielsen or auramine stain and, mycobacterial culture (in process) and, where available, Xpert (Gene Xpert/Rif or Xpert Ultra) prior to commencing treatment. Where patients have already been started on ATT, pre-screening CSF results should be available.
8. Carer/parent can comply with the protocol requirements in the opinion of the site investigator
9. Home address accessible for visiting and intending to remain within the recruitment area for follow up period of at least 18 months

Participant type(s)
Patient

Age group
Child

Lower age limit
29 Days

Upper age limit
18 Years

Sex
Both

Target number of participants

400

Total final enrolment
369

Key exclusion criteria
1. Recent contact (last 12 months) with known or suspected rifampicin-resistant TB
2. Proven drug resistance to rifampicin in the child
3. On ATT for >7 days
4. Severely moribund - high risk of death within 24 hours
5. History or presence of known allergy or other contraindication to any of the following:
5.1. First-line anti-tuberculosis drugs
5.2. Corticosteroids
5.3. Aspirin
6. Pregnancy
7. History of gastrointestinal (GI) bleeding or bleeding diathesis
8. Active clinical infection with influenza or varicella
9. Grade 4 liver toxicity or other contraindications for taking part in the trial

Date of first enrolment
01/01/2020

Date of final enrolment
06/07/2024

Locations

Countries of recruitment
India

Uganda

Viet Nam

Zambia

Zimbabwe

Study participating centre
TBC
India
-

Sponsor information

Organisation

University College London

Sponsor details
MRC CTU at UCL
90 High Holborn 2nd floor
London
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United Kingdom
WC1V 6LJ

Sponsor type
University/education

Website
http://www.ctu.mrc.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Department for International Development

Alternative Name(s)
Department for International Development, UK, DFID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

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

Funder Name
National Institute for Health Research (NIHR). Grant reference number: MR/R006113/1.

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The SURE TSC is the custodian of the data and specimens generated from the SURE trial; SURE trial data are not the property of individual participating investigators or health care facilities

where the data were generated.
It is anticipated that a number of opportunities will arise for publication during the course of and following completion of the SURE trial. Publications include papers (including abstracts) for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the Lancet and from the publication policies used in other clinical trials coordinated by the MRC CTU:
All publications are to be approved by the TMG and TSC before submission for publication. Any publication arising before the end of the trial (not by randomised groups) will also be approved by the IDMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. In particular, no analyses by randomised group of any outcome (primary, secondary or other) in either the main trial or associated sub studies will be conducted or presented before the end of the trial, other than those for interim review by the IDMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.
In line with UCL policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All conference presentations will be made available as soon as possible after the event via the MRC CTU website. All publications will acknowledge the trial's funding sources.
For all publications, the TMG will nominate a chairperson or approve an individual’s request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.
The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, sub study reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub studies must have a made a substantive academic or project management contribution to the work that is being presented. “Substantive” must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript and/or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.
The SURE TSC is the custodian of the data derived from this clinical trial. The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of the TMG and TSC (and the IDMC before the end of the trial). This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the IDMC before the end of the trial), they will be encouraged to develop sub studies or propose analyses subject to the approval by the TMG and TSC (and the IDMC before the end of the trial). Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team.
Outcome data by randomised group will not be revealed to the participating investigators until

the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The IDMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

Intention to publish date
30/06/2026

Individual participant data (IPD) sharing plan
Data will be shared according to the MRC CTU's controlled access approach, based on the following principles:
1. No data should be released that would compromise an ongoing trial or study.
2. There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
3. Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
4. The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
5. Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
Data will be available for sharing after the primary trial publication. Researchers wishing to access SURE data should contact the TMG in the first instance.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		02/04/2025	04/04/2025	Yes	No