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SHINE study: Shorter treatment for minimal TB in children

Submission date
10/09/2014

Recruitment status
No longer recruiting

Registration date
14/10/2014

Overall study status
Completed

Last Edited
10/03/2022

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
Of the estimated 9 million tuberculosis (TB) cases globally annually, more than half a million are in children. This burden is highest in Africa and South East Asia and results in 100,000 deaths each year.
Regimens for prevention and treatment of TB in children have lagged considerably behind those for adults. This is likely because children usually present with 'minimal' (i.e. smear-negative and less severe) disease. Therefore TB in children is very difficult to diagnose and children are rarely infectious, posing little risk of onward transmission. Current TB treatment (for both adults and children) involves six months of treatment: a two month intensive phase of three or four drugs, followed by a maintenance phase lasting four months. Historically, the doses of drugs prescribed to children have been based on a weight-based scaling-down of the adult dose, resulting in uncertainty over the correct paediatric dose.
In 2010, the WHO revised their dose recommendations for anti-TB drugs for children, and now recommends higher doses of many of the commonly used drugs. Based on this dose increase, the SHINE study wants to find out if the standard 6 month regimen can be reduced to 4 months.

Who can participate?
Children under 16 with suspected minimal TB disease (with or without HIV infection) will be screened. A total of 1,200 children will be recruited.

What does the study involve?
A screening visit involving TB tests (skin test and sputum sample), an X-ray and blood tests will be carried out to confirm that the child is eligible. Consenting participants will then be randomly allocated to either the 4-month regimen or the 6-month regimen. Enough anti-TB drugs will be prescribed for the child to take daily until they are seen at their next clinic visit. Visits will be monthly whilst taking the medication, and then every three months. At each visit, details of the child's health, height and weight will be recorded, as well as information about how well children take their medicines and if there are any particular problems taking them. At some visits, blood, urine and hair samples will be collected for storage and future testing.

What are the possible benefits and risks of participating?
There may be no direct benefit to the children participating in the SHINE study. However, the

information we get from this study will help to improve treatment for children with TB in the future.
These children need to be treated for TB regardless of whether or not they participate in the SHINE study, and treatment has risks and side effects. The common side effects of anti-TB drugs are red tears, red urine, joint pains and injury to the liver. Participating children will also need to attend the clinic more frequently than if they were receiving treatment outside of the SHINE study. In addition there will be some extra blood tests.

Where is the study run from?
4 sites:
- South Africa: Stellenbosch University, Cape Town (target recruitment: 250 children)
- India: National Institute for Research in Tuberculosis, Chennai and BJ Medical College, Pune (target recruitment: 450 children)
- Uganda: MU-JHU Care Ltd, Kampala (target recruitment: 250 children)
- Zambia: University Teaching Hospital, Lusaka (target recruitment: 250 children)
Coordinated from MRC Clinical Trials Unit at UCL, London, UK.

When is the study starting and how long is it expected to run for?
The total duration of the study will be 48 months, as follows: 6 months start-up, 18 months enrolment, follow-up until the last patient has reached 18 months, and a further 6 months for close-out and analysis.
- Anticipated start date of recruitment: Q2 2015.
- Anticipated end date of recruitment: Q4 2016.
- Anticipated study end date: Q2 2019.

Who is funding the study?
SHINE is funded by the Joint Global Health Trials Scheme: Department for International Development, the UK Department of Health and Social Care (DHSC), the Wellcome Trust, and the Medical Research Council; and the TB Alliance. Trial drugs were supplied by Macleods Pharmaceuticals Ltd.
(updated 27/05/2021, previously: SHINE is funded by the Joint Global Health Trials Scheme: Department for International Development, the Wellcome Trust, the Medical Research Council and Svizera Ltd.)

Who is the main contact?
SHINE Trial Management Team,
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Contact information

Type(s)
Scientific

Contact name
Prof Diana Gibb

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV-positive and HIV-negative children

Acronym
SHINE

Study objectives
The 4-month regimen will be non-inferior to the 6-month regimen in terms of unfavourable outcomes at 72 weeks.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Lead centre: UCL Research Ethics Committee; 22/05/2014; 5669/001
1. South Africa: Stellenbosch Research Ethics Committee and University of Cape Town Human Research Ethics Committee
2. India: National Institute for Research in Tuberculosis Institutional Ethics Committee and B J Medical College & Sassoon General Hospitals Ethics Committee
3. Uganda: Joint Clinical Research Center Institutional Review Board
4. Zambia: University of Zambia- Biomedical Research Ethics committee

Study design
Parallel-group randomised non-inferiority open label 2-arm phase III clinical endpoint trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Paediatric tuberculosis (minimal TB)

Interventions
Four-month regimen:
The experimental arm will be standard daily first-line anti-TB treatment for 16 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks Isoniazid (H) , Rifampicin (R), Pyrazinamide (Z) with or without Ethambutol (E) according to local practice, HRZ(E), followed by continuation of 8 weeks HR.

Six-month regimen;
The control arm will be standard daily first-line anti-TB treatment for 24 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks HRZ(E), followed by continuation of 16 weeks HR.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Isoniazid (H) , Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E)

Primary outcome measure
1. Efficacy: Unfavourable outcome, defined by the composite endpoint of TB treatment failure, relapse (or re-infection) or death
2. Safety: Grade 3/4 adverse events

Secondary outcome measures
Current secondary outcome measures as of 27/05/2021:

1. Mortality
2. Adverse drug reactions up to 30 days of completing treatment
3. Unfavourable outcome in those with definite TB as adjudicated by the ERC
4. Suppressed HIV viral load at 24 and 48 weeks in HIV infected children
5. Adherence and acceptability
6. Bacterial infections (requiring hospitalisation)

Previous secondary outcome measures:

1. Mortality
2. Adverse drug reactions up to 30 days of completing treatment
3. Unfavourable outcome in those with definite TB
4. Suppressed HIV viral load at 24 and 48 weeks in HIV infected children starting ART, measured centrally on stored samples
5. Adherence and acceptability
6. Bacterial infections

Overall study start date
01/04/2015

Completion date
01/06/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 27/05/2021:

1. Aged 0-16 years
2. Weight ≥3kg. This has been expanded to include children weighing between 3 and 4kg; a detailed PK study of individual drugs in infants is ongoing and data using the new FDC from this study will ensure that use of this new formulation is also studied in these smallest infants.
3. Clinician has decided to treat with standard first-line regimen (intensive phase of 4 drugs or 3 drugs as per local practice)
4. symptomatic but non-severe TB including:
4.1. extrathoracic lymph node TB; intra-thoracic uncomplicated (hilar) lymph node TB
4.2. minimal or no parenchymal abnormality on CXR
4.3. smear negative on gastric aspirate/other respiratory sample
Note: GeneXpert may be positive or negative and a negative GeneXpert can be used as a substitute for a negative smear; culture of respiratory sample may be positive or negative; lymph node aspirate may be smear/culture/GeneXpert positive or negative)
5. Not treated for previous TB unless successfully treated over 2 years since last completed treatment
6. Known (or pending confirmation of) HIV status; HIV-infected or HIV-uninfected
7. Willing and likely to adhere to 72 weeks follow up
8. Informed written consent from the parent/legal caregiver(s) and assent in children, as per local Ethics Committee guidance
9. Home address accessible for visiting and intending to remain within the recruitment area for follow up

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Previous inclusion criteria:

1. Aged 0-16 years
2. Weight over 4 kg
3. Clinician has decided to treat with standard first-line regimen
4. Asymptomatic or symptomatic but non-severe TB including:
4.1. extrathoracic lymph node TB; intra-thoracic uncomplicated lymph node TB
4.2. minimal or no parenchymal abnormality on CXR

4.3. smear gastric aspirate/other respiratory sample (minimum 2 samples) negative
5. Not previously treated for TB or successfully treated for TB over 2 years since last completed treatment
6. Known HIV status; HIV-infected or HIV-uninfected
7. Willing and likely to adhere to 72 weeks follow up
8. Informed written consent from the parent/legal caregiver(s)
9. Home address accessible for visiting and intending to remain within the recruitment area for follow up

Participant type(s)
Patient

Age group
Child

Lower age limit
0 Years

Upper age limit
16 Years

Sex
Both

Target number of participants
1,200

Total final enrolment
1204

Key exclusion criteria
Current exclusion criteria as of 27/05/2021:

1. Smear-positive respiratory sample TB (note: smear-positive peripheral lymph node sample is allowed)
2. Premature (<37 weeks) and aged under 3 months
3. Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
4. Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
5. Any known contraindication to taking anti-TB drugs
6. Known contact with drug resistant adult source case (including mono-resistant TB)
7. Known drug resistance in the child
8. Severely sick
9. Pregnancy

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Previous exclusion criteria:

1. Smear-positive respiratory sample TB (note: smear-positive peripheral lymph node sample is allowed)

2. Premature (<37 weeks) and aged under 3 months
3. Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
4. Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
5. Any known contraindication to taking anti-TB drugs
6. Known contact with MDR, pre-XDR or XDR adult source case
7. Proven anti-TB drug resistance in the child
8. Severely sick
9. Pregnancy

Date of first enrolment
01/07/2016

Date of final enrolment
23/07/2018

Locations

Countries of recruitment
England

India

South Africa

Uganda

United Kingdom

Zambia

Study participating centre
MRC Clinical Trials Unit at UCL
London
United Kingdom
WC1V 6LJ

Sponsor information

Organisation
University College London (UK)

Sponsor details
90 High Holborn 2nd Floor
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England

United Kingdom
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Sponsor type
University/education

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Department for International Development (DFID) (UK)

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 (MRC) (UK) grant number MR/L004445/1

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
Macleods Pharmaceuticals Ltd. (India) - Anti-tuberculosis trial drugs

Funder Name
Department of Health and Social Care

Alternative Name(s)
Department of Health & Social Care, DH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
TB Alliance

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
31/12/2021

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol acceptability results	19/04/2018	16/06/2020	Yes	No

Results article		01/12/2019	16/06/2020	Yes	No
Other publications	Pharmacokinetics results	22/08/2021	10/03/2022	Yes	No
Other publications	Substudy results	24/08/2020	10/03/2022	Yes	No
Results article		10/03/2022	10/03/2022	Yes	No