NOTTINGHAM CLINICAL TRIALS UNIT

TB-DILI

Reintroduction of anti-tuberculosis therapy following drug-induced liver injury: a randomised clinical trial

Site Initiation Training

10 August 2022

NHS Nottingham University Hospitals NHS Trust

FUNDED BY NIHR | National Institute for Health Research

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Agenda

- Welcome and Introductions
- Trial organisation
- Background
- Trial design
- Protocol
- Study Procedures
- Randomisation system and eCRF

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Welcome and Introductions

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Trial Management

- Shabina Sadiq

(TB-DILI Trial Manager)

- Megan Birchenall

(TB-DILI Trial coordinator)

- Garry Meakin

(TB-DILI Snr. Trial Manager)

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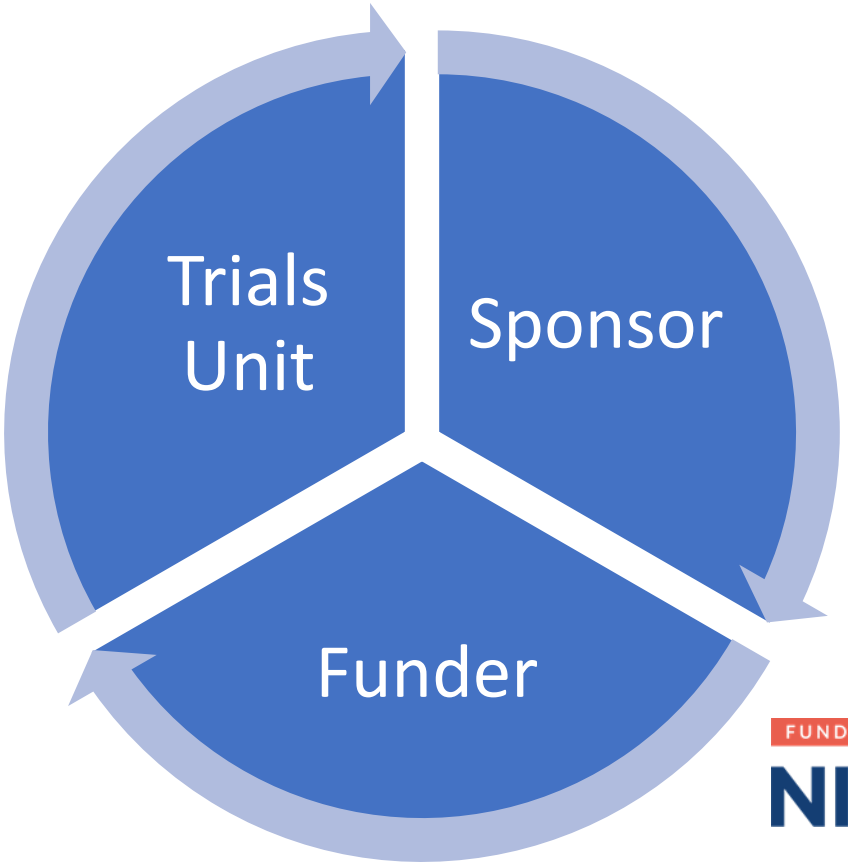
Trial organisation

Trial organisation

NOTTINGHAM CLINICAL TRIALS UNIT
at the University of Nottingham



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NHS Trust

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Key contacts

Role	Name	Organisation
CI	Wei Shen Lim	Nottingham University Hospitals NHS Trust
Trial Manager	Shabina Sadiq	NCTU
Snr Trial Manager	Garry Meakin	NCTU
Trial Coordinator	Megan Birchenall	NCTU
Data Coordinator	Richard Swinden	NCTU

TB-DILI@nottingham.ac.uk

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Oversight Committees

Trial Management Group

- Day-to-day management
- Review recruitment, retention, compliance and data quality to ensure efficient study conduct
- Report to the Trial Steering Committee

Trial Steering Committee

Provide independent oversight of the study.

- Approve trial protocol
- Approve changes to protocol based on considerations of feasibility and practicability
- Review data reports
- Resolve problems
- Ensure publication

Data Monitoring Committee

To safeguard

- Trial participants/families
- Investigators
- Sponsor

- Assess safety and efficacy of the intervention during the trial
- Monitor overall conduct
- Protect validity & credibility
- Monitor evidence of treatment differences
- Monitor safety data
- Review Stop-Go data

Background

Background

- In 2018, 4,655 people were diagnosed with tuberculosis (TB) in the UK. This was the lowest recorded rate of TB in the UK for the last 10 years. People born outside the UK accounted for 72% of notifications in 2018

- The proportion of people with drug-sensitive TB who completed treatment by 12 months was 84.7% in 2017; in addition, 5.3% died and 4.2% were lost to follow up.

- Early data from 2019 suggests that the rate of TB may be higher in 2019 compared to 2018.

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TB Treatment

- The standard treatment of drug-sensitive TB involves a 4-drug combination of anti-TB therapy (ATT) for 2 months, followed by a 2-drug combination for 4 months making a total treatment duration of 6 months.

- Drug-induced liver injury (DILI) is the commonest serious adverse effect of ATT. DILI may result from direct toxicity of the primary compound or an immunological response to one or more of the drugs.

- DILI is the commonest serious adverse effect of ATT. DILI may result from direct toxicity of the primary compound or an immunological response to one or more of the drugs

Overview

A multicentre randomised, open label, superiority trial

Population	Adults who have experienced a DILI with standard 4-drug ATT for active pulmonary or extra-pulmonary TB
Intervention	Sequential full-dose reintroduction of a non-Z-containing 3-drug ATT regimen comprising ethambutol, isoniazid and rifampicin (EHR), as recommended by the American Thoracic Society (ATS) TB guideline
Comparator	Sequential full-dose reintroduction of a Z-containing 4-drug ATT regimen comprising ethambutol, isoniazid, rifampicin and pyrazinamide (EHRZ), as recommended by the National Institute for Health and Care Excellence (NICE) TB guideline
Primary outcome	DILI recurrence within 12 months following randomisation

Current guidelines

In the National Health Service (NHS), the management of ATT-induced DILI is informed by both the NICE TB Guideline and the American Thoracic Society TB Guideline.

NICE TB Guidelines	sequentially reintroduce each of the anti-TB drugs at full dose over a period of no more than 10 days, starting with ethambutol and either isoniazid (with pyridoxine) or rifampicin.
American TB Guidelines	sequential reintroduction of ATT; beginning with rifampicin (with or without ethambutol), then adding isoniazid after 3 to 7 days. In addition, it recommends “For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampicin and isoniazid, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months

Both regimens are accepted as standard of care in the NHS and globally. Based on weak evidence, one regimen may be associated with a lower DILI recurrence frequency but entails a longer total duration of treatment (9 months vs 6 months).

Equipoise

"A true state of equipoise exists when one has no good basis for a choice between two or more care options."

- Important that clinicians are in equipoise
- We do not know whether 3 drug ATT will be safer than 4 drug ATT
- Difficult for clinicians to advise patients as there is a lack of evidence to prove either way
- That is why we are conducting the trial!

Trial design

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Trial Design

Multicenter, open-label, two-arm, parallel, randomised, superiority trial

- Secondary NHS TB centres
- 3 drug ATT vs 4 drug ATT
- 1:1 ratio
- Is restarting TB treatment with only 3 drugs safer than restarting with 4 drugs?

We aim to recruit 350 participants

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Primary Objective

To determine if reintroduction of a non-pyrazinamide (Z)-containing anti-tuberculosis therapy (ATT) regimen results in a lower drug-induced liver injury (DILI) recurrence rate compared to a Z-containing ATT regimen in adults who have experienced an episode of DILI when being treated for active tuberculosis (TB)

Secondary Objective

- To determine the cost-effectiveness of reintroducing a non-Z containing, versus Z-containing regimen

Cohort study

To determine

- the frequency of DILI recurrence and quality of life impacts of DILI episodes in adults being treated for latent TB infection

Pharmacy

- IMP will not be supplied to sites from the NCTU or Sponsor
- Sites will use local stock of usual 3 drug ATT and 4 drug ATT treatment
- No additional trial specific labelling/accountability needed
- Sites should maintain local accountability and dispensing records as per routine practice
- If treatment is posted this should be in accordance with your local Trust SOP

Blinding

- This is an open label trial, so no emergency unblinding procedures are necessary

- Participants, site-staff and NCTU data coordinators and statisticians will not be blinded

- NCTU trial management and Trial Steering Committee will be blinded to treatment allocations

Protocol

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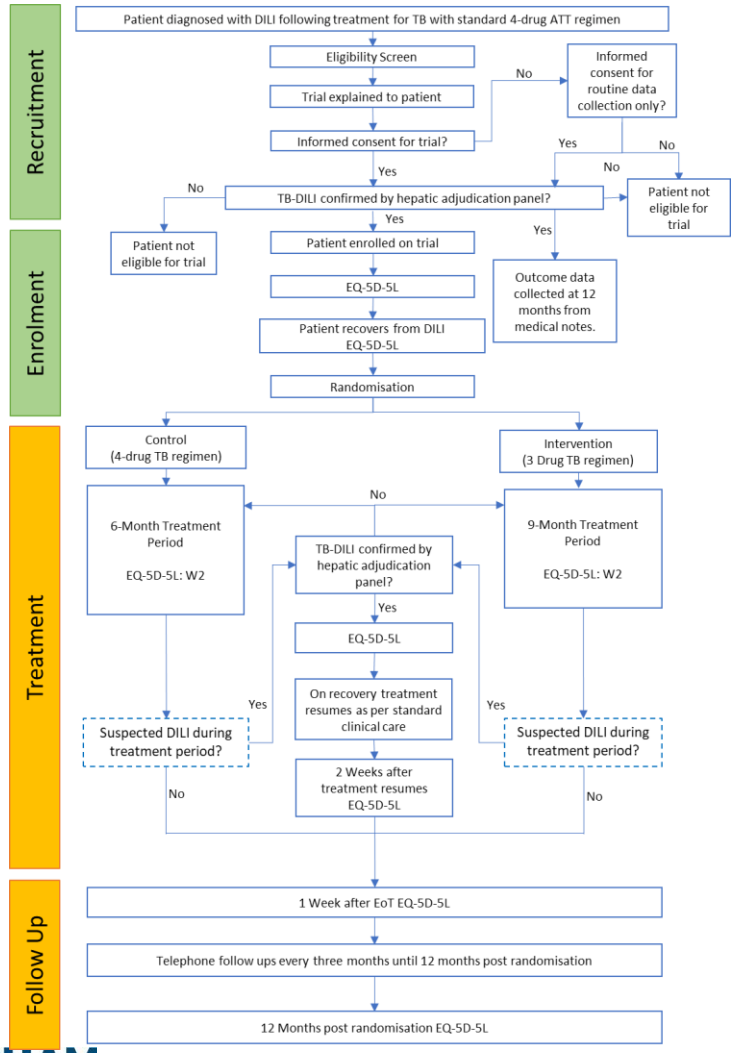
Patient pathway



Potentially eligible patients will generally be identified in the following ways:

- During routine outpatient clinics/consultations
- Community clinics and mobile clinics
- Hospital in-patients

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Trial entry criteria

Inclusion Criteria

- Aged ≥18 years
- Experienced DILI with standard 4-drug ATT for active pulmonary or extra-pulmonary TB
- Medically suitable for re-introduction of standard 4-drug ATT

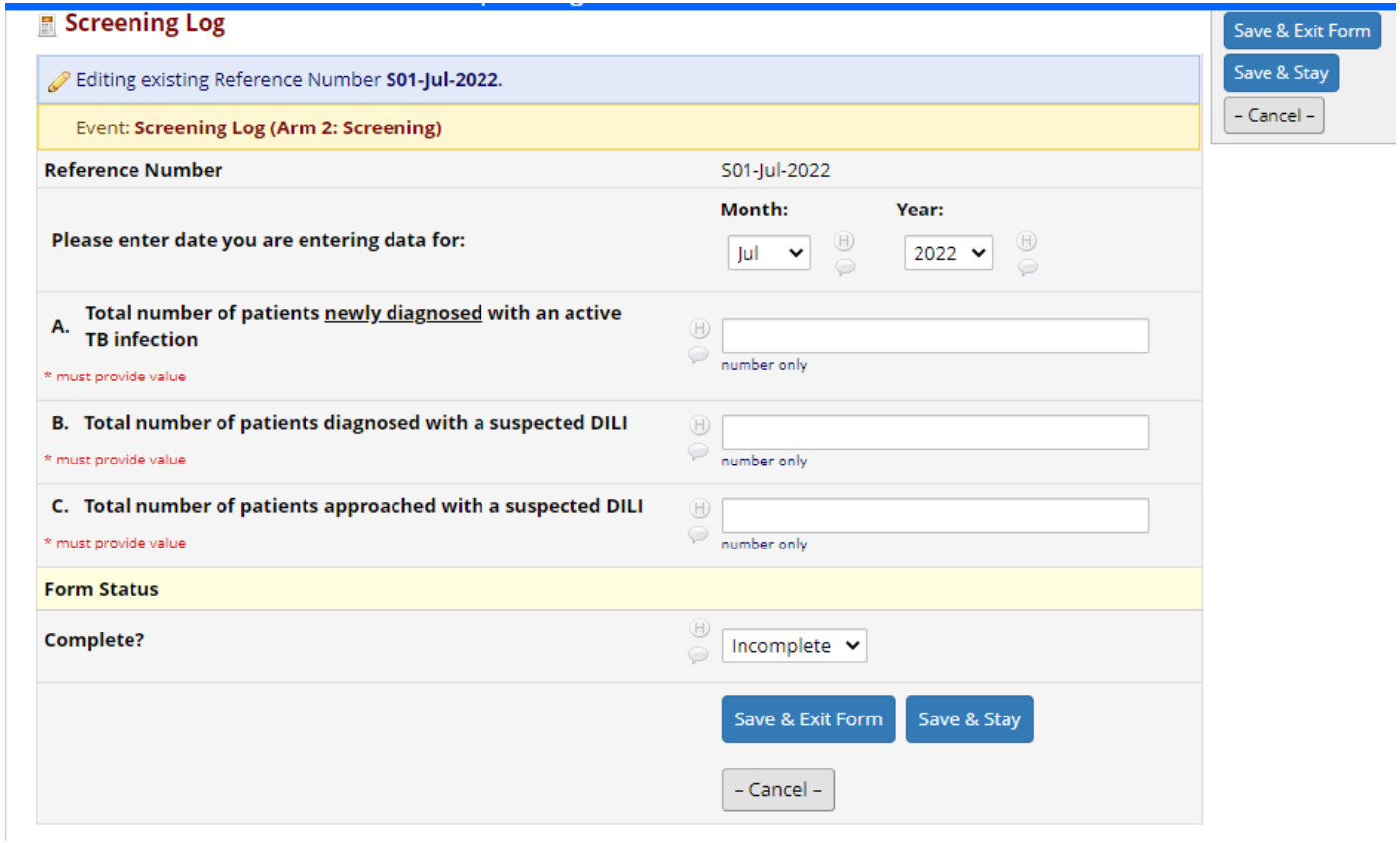
Exclusion Criteria

- Requirement for alternative ATT
- Unable to provide written informed consent

Screening

- Screening data is only being collected for the main trial.
- All screening information will be collected and entered directly into REDCap.
- Email reminders will be circulated on a monthly basis for sites to enter this.
- We will not be collecting individual participant reasons for non consent.
- Reasons for non-enrolment will be discussed with sites on an individual basis or as part of site teleconferences.

Screening on REDCap



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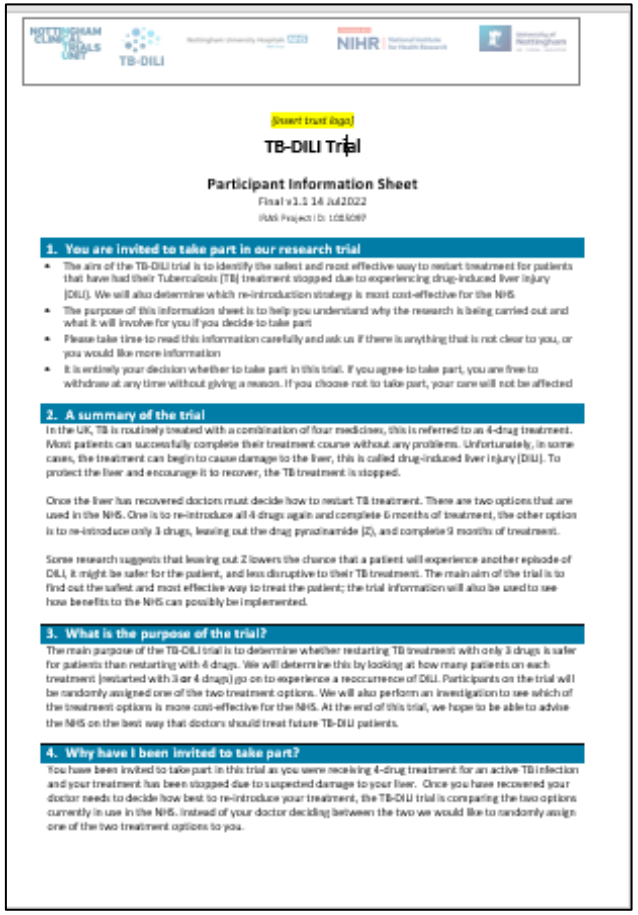
Patient information and consent

Main trial & Routine data



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TB-DILI Trial

Participant Information Sheet

Final v1.1 14 Jul2022

RAS Project ID: 1018097

1. You are invited to take part in our research trial

- The aim of the TB-DILI trial is to identify the safest and most effective way to restart treatment for patients that have had their Tuberculosis (TB) treatment stopped due to experiencing drug-induced liver injury (DILI). We will also determine which re-introduction strategy is most cost-effective for the NHS
- The purpose of this information sheet is to help you understand why the research is being carried out and what it will involve for you if you decide to take part
- Please take time to read this information carefully and ask us if there is anything that is not clear to you, or you would like more information
- It is entirely your decision whether to take part in this trial. If you agree to take part, you are free to withdraw at any time without giving a reason. If you choose not to take part, your care will not be affected

2. A summary of the trial

In the UK, TB is routinely treated with a combination of four medicines, this is referred to as 4-drug treatment. Most patients can successfully complete their treatment course without any problems. Unfortunately, in some cases, the treatment can begin to cause damage to the liver, this is called drug-induced liver injury (DILI). To protect the liver and encourage it to recover, the TB treatment is stopped.

Once the liver has recovered doctors must decide how to restart TB treatment. There are two options that are used in the NHS. One is to re-introduce all 4 drugs again and complete 6 months of treatment, the other option is to re-introduce only 3 drugs, leaving out the drug pyrazinamide (Z), and complete 9 months of treatment.

Some research suggests that leaving out Z lowers the chance that a patient will experience another episode of DILI, it might be safer for the patient, and less disruptive to their TB treatment. The main aim of the trial is to find out the safest and most effective way to treat the patient; the trial information will also be used to see how benefits to the NHS can possibly be implemented.

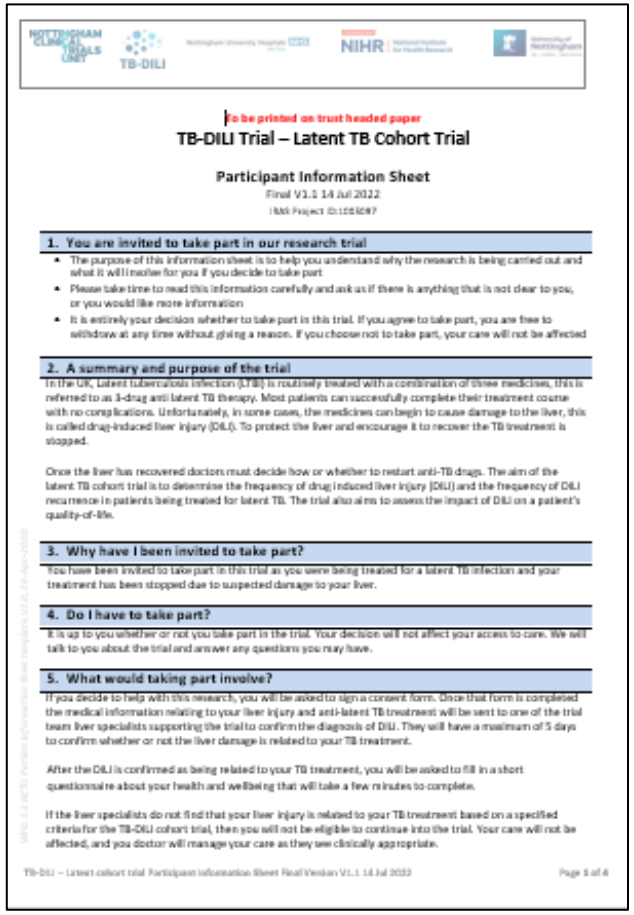
3. What is the purpose of the trial?

The main purpose of the TB-DILI trial is to determine whether restarting TB treatment with only 3 drugs is safer for patients than restarting with 4 drugs. We will determine this by looking at how many patients on each treatment (restarted with 3 or 4 drugs) go on to experience a reoccurrence of DILI. Participants on the trial will be randomly assigned one of the two treatment options. We will also perform an investigation to see which of the treatment options is more cost-effective for the NHS. At the end of this trial, we hope to be able to advise the NHS on the best way that doctors should treat future TB-DILI patients.

4. Why have I been invited to take part?

You have been invited to take part in this trial as you were receiving 4-drug treatment for an active TB infection and your treatment has been stopped due to suspected damage to your liver. Once you have recovered your doctor needs to decide how best to re-introduce your treatment, the TB-DILI trial is comparing the two options currently in use in the NHS. Instead of your doctor deciding between the two we would like to randomly assign one of the two treatment options to you.

Latent TB



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TB-DILI Trial – Latent TB Cohort Trial

Participant Information Sheet

Final V1.1 14 Jul 2022

IRAS Project ID: 1018097

1. You are invited to take part in our research trial

- The purpose of this information sheet is to help you understand why the research is being carried out and what it will involve for you if you decide to take part
- Please take time to read this information carefully and ask us if there is anything that is not clear to you, or you would like more information
- It is entirely your decision whether to take part in this trial. If you agree to take part, you are free to withdraw at any time without giving a reason. If you choose not to take part, your care will not be affected

2. A summary and purpose of the trial

In the UK, Latent tuberculosis infection (LTBI) is routinely treated with a combination of three medicines, this is referred to as 3-drug anti latent TB therapy. Most patients can successfully complete their treatment course with no complications. Unfortunately, in some cases, the medicines can begin to cause damage to the liver, this is called drug-induced liver injury (DILI). To protect the liver and encourage it to recover the TB treatment is stopped.

Once the liver has recovered doctors must decide how or whether to restart anti-TB drugs. The aim of the latent TB cohort trial is to determine the frequency of drug induced liver injury (DILI) and the frequency of DILI recurrence in patients being treated for latent TB. The trial also aims to assess the impact of DILI on a patient's quality-of-life.

3. Why have I been invited to take part?

You have been invited to take part in this trial as you were being treated for a latent TB infection and your treatment has been stopped due to suspected damage to your liver.

4. Do I have to take part?

It is up to you whether or not you take part in the trial. Your decision will not affect your access to care. We will talk to you about the trial and answer any questions you may have.

5. What would taking part involve?

If you decide to help with this research, you will be asked to sign a consent form. Once that form is completed the medical information relating to your liver injury and anti-latent TB treatment will be sent to one of the trial team liver specialists supporting the trial to confirm the diagnosis of DILI. They will have a maximum of 5 days to confirm whether or not the liver damage is related to your TB treatment.

After the DILI is confirmed as being related to your TB treatment, you will be asked to fill in a short questionnaire about your health and wellbeing that will take a few minutes to complete.

If the liver specialists do not find that your liver injury is related to your TB treatment based on a specified criteria for the TB-DILI cohort trial, then you will not be eligible to continue into the trial. Your care will not be affected, and you doctor will manage your care as they see clinically appropriate.

TB-DILI – Latent cohort trial Participant Information Sheet Final Version V1.1 14 Jul 2022 Page 1 of 4

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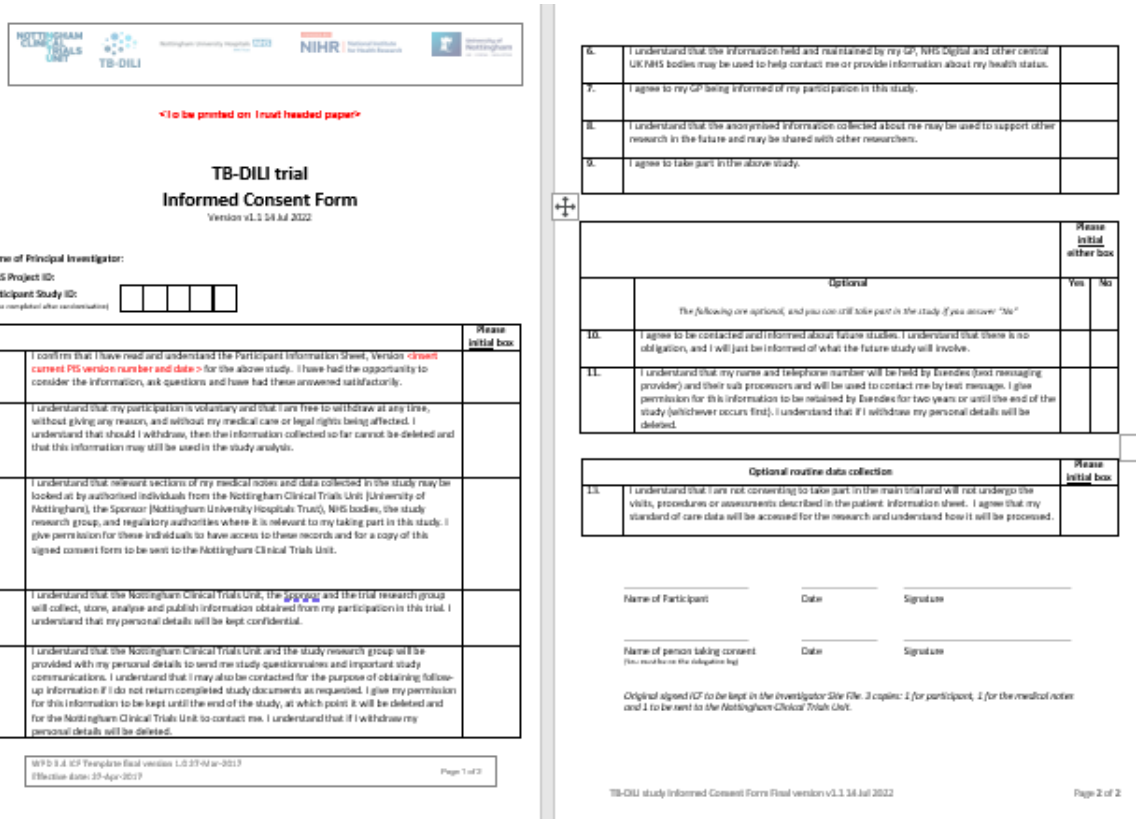
Patient information and consent

- Verbal explanation of trial
  - Opportunity to ask any questions
  - Informed they may withdraw at any time if they change their mind

- Provide patient with a copy of current Patient Information Sheet (PIS) and Informed Consent Form (ICF)

Consent form

- ✓ Consent can only be taken by trained and delegated Investigators (*or Research Nurse – if nurse consent is approved at your Trust*)
- ✓ Investigator / RN **must** sign and date ICF in presence of participant (i.e. on same day)
- ✓ Ensure participant enters initials and does not tick or cross any of the boxes
- ✓ Participant **must** complete name and date section themselves at the time of signing – this should not be prepared in advance
- ✓ Completed paper ICFs must be uploaded to the NCTU and retained as source data



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TB-DILI trial

Informed Consent Form

Version v1.1 14 Jul 2022

Name of Principal Investigator:

IRAS Project ID:

Participant Study ID:

		Please initial box
1.	I confirm that I have read and understand the Participant Information Sheet, Version <insert current PIS version number and date> for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw, then the information collected so far cannot be deleted and that this information may still be used in the study analysis.	
3.	I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the Nottingham Clinical Trials Unit (University of Nottingham), the Sponsor (Nottingham University Hospitals Trust), NHS bodies, the study research group, and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and for a copy of this signed consent form to be sent to the Nottingham Clinical Trials Unit.	
4.	I understand that the Nottingham Clinical Trials Unit, the Sponsor and the trial research group will collect, store, analyse and publish information obtained from my participation in this trial. I understand that my personal details will be kept confidential.	
5.	I understand that the Nottingham Clinical Trials Unit and the study research group will be provided with my personal details to send me study questionnaires and important study communications. I understand that I may also be contacted for the purpose of obtaining follow-up information if I do not return completed study documents as requested. I give my permission for this information to be kept until the end of the study, at which point it will be deleted and for the Nottingham Clinical Trials Unit to contact me. I understand that if I withdraw my personal details will be deleted.	

WFD 3.4 ICF Template final version 1.0 27-Mar-2017
Effective date: 19-Apr-2017

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6.	I understand that the information held and maintained by my GP, NHS Digital and other central UK NHS bodies may be used to help contact me or provide information about my health status.	
7.	I agree to my GP being informed of my participation in this study.	
8.	I understand that the anonymised information collected about me may be used to support other research in the future and may be shared with other researchers.	
9.	I agree to take part in the above study.	

		Please initial either box	
	Optional *The following are optional, and you can still take part in the study if you answer "No"*	Yes	No
10.	I agree to be contacted and informed about future studies. I understand that there is no obligation, and I will just be informed of what the future study will involve.		
11.	I understand that my name and telephone number will be held by Esendex (text messaging provider) and their sub processors and will be used to contact me by text message. I give permission for this information to be retained by Esendex for two years or until the end of the study (whichever occurs first). I understand that if I withdraw my personal details will be deleted.		

	Optional routine data collection	Please initial box
13.	I understand that I am not consenting to take part in the main trial and will not undergo the visits, procedures or assessments described in the patient information sheet. I agree that my standard of care data will be accessed for the research and understand how it will be processed.	

Name of Participant | Date | Signature

Name of person taking consent | Date | Signature

Original signed ICF to be kept in the Investigator Site File. 3 copies: 1 for participant, 1 for the medical notes and 1 to be sent to the Nottingham Clinical Trials Unit.

TB-DILI study Informed Consent Form Final version v1.1 14 Jul 2022

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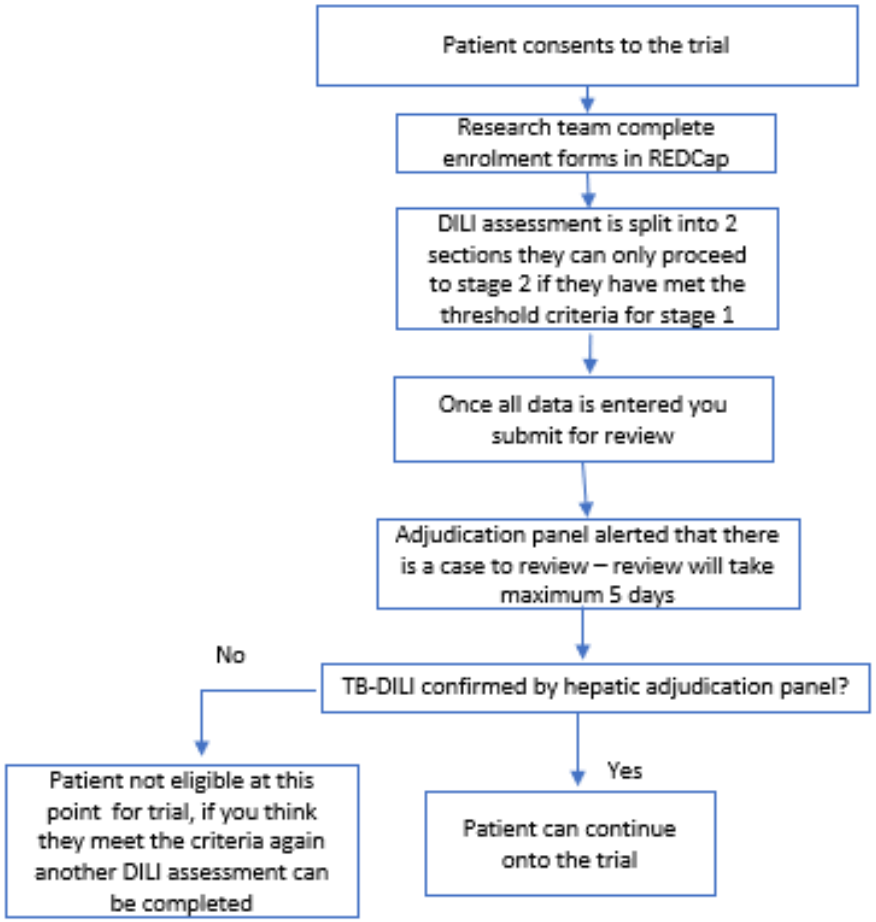
Adjudication panel

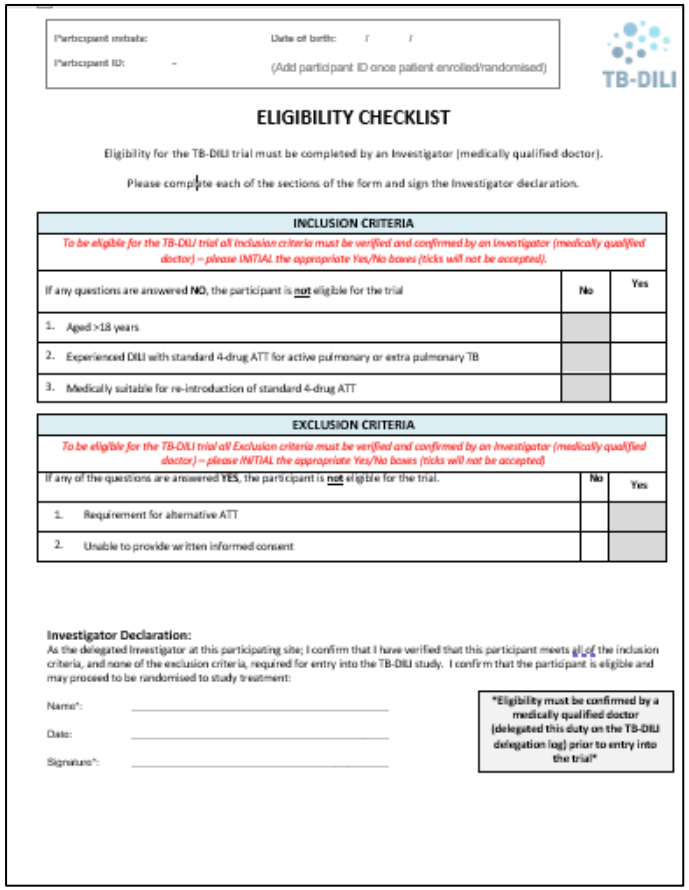
- A blinded hepatic adjudication panel will review all relevant data relating to possible DILI episodes.
- The panel will adjudicate as to whether the episode meets the trial definition of a DILI
- Differences will be resolved by consensus, with the option of co-opting a third panel member as needed.
- Patients cannot be randomised into the trial until the adjudication panel have confirmed that they are eligible.

Adjudication process



Eligibility checklist

- ✓ Eligibility must be confirmed after consent has been obtained and ***prior*** to randomisation
- ✓ Eligibility must be confirmed by a ***medically qualified doctor*** – i.e. can only be confirmed by delegated investigator(s)
- ✓ Investigator must initial against each inclusion/ exclusion criterion verified and then sign and date investigator declaration to confirm participant is eligible prior to randomisation
- ✓ Completed paper eligibility checklists should be uploaded to the NCTU and retained as source data



Participant initials: Date of birth: / /

Participant ID: - (Add participant ID once patient enrolled/randomised)

TB-DILI

ELIGIBILITY CHECKLIST

Eligibility for the TB-DILI trial must be completed by an Investigator (medically qualified doctor).

Please complete each of the sections of the form and sign the Investigator declaration.

INCLUSION CRITERIA

To be eligible for the TB-DILI trial all inclusion criteria must be verified and confirmed by an investigator (medically qualified doctor) – please INITIAL the appropriate Yes/No boxes (ticks will not be accepted).

If any questions are answered **NO**, the participant is not eligible for the trial	No	Yes
1. Aged >18 years		
2. Experienced DILI with standard 4-drug ATT for active pulmonary or extra pulmonary TB		
3. Medically suitable for re-introduction of standard 4-drug ATT		

EXCLUSION CRITERIA

To be eligible for the TB-DILI trial all Exclusion criteria must be verified and confirmed by an investigator (medically qualified doctor) – please INITIAL the appropriate Yes/No boxes (ticks will not be accepted)

If any of the questions are answered **YES**, the participant is not eligible for the trial.	No	Yes
1. Requirement for alternative ATT		
2. Unable to provide written informed consent		

Investigator Declaration:

As the delegated Investigator at this participating site; I confirm that I have verified that this participant meets all of the inclusion criteria, and none of the exclusion criteria, required for entry into the TB-DILI study. I confirm that the participant is eligible and may proceed to be randomised to study treatment:

Name*: _____

Date: _____

Signature*: _____

Eligibility must be confirmed by a medically qualified doctor (delegated this duty on the TB-DILI delegation log) prior to entry into the trial

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Retention

Retention is just as important as recruitment

- Follow-up will be a mixture of data entry from medical notes by research team and patient reported by the completion of the EQ-5D-5L

Ways you can help us improve retention

- ✓ Ensure patient is aware of importance of us collecting the EQ-5D-5L questionnaire data
- ✓ Explain processes clearly to them
- ✓ Ensure correct contact details are recorded

Safety reporting

Adverse Events (AE): any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have a causal relationship with this treatment

Serious Adverse Event (SAE): is an AE which:

- Results in death
- Life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Congenital anomaly/birth defect
- Other medically important event

'Important medical events' are considered serious if they jeopardise the patient's health or require an intervention to prevent any of the above consequences

Safety reporting

Serious Adverse Events (SAEs):

- SAE's should only to be reported if the PI deems that particular SAE unexpected and potentially due to the intervention drug (i.e. a SUSAR)
- Reporting period : Date of Randomisation to 12 months post randomisation. If participants are still being treated at the 12-month follow-up, the reporting period will be extended to 3 months post the 12-month follow-up.
- Planned hospital admissions will **not** be reported as SAEs

Adverse events (AEs):

- Adverse event rate is one of our secondary outcomes
- Events should be reviewed against the SmPC for the drugs being used
- The data should be entered onto REDCap

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To report a SAE, email the SAE Form to:

nctu-SAE@nottingham.ac.uk

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Study procedures

Assessments

PROCEDURE	PRE-RANDOMISATION	POST-RANDOMISATION
Eligibility screen	X	
Informed consent	X	
Baseline data collection	X	
Adjudication Panel	X	
EQ-5D-5L Questionnaire	X	
Randomisation	X	
Issue randomised trial treatment		X

Liver Function Testing (LFT)

- The NICE TB guidelines does not outline a specific LFT monitoring plan
- Sites will be encouraged to adopt a preferred monitoring plan with flexibility for local practice variation across hospitals.
- Sites will be requested to upload all LFTs performed into REDCap.

Primary Outcome

- Could occur at any time point during treatment period
- Any suspected DILI should be reported on the REDCap database
- Discontinuation of control or intervention ATT regimen
- The suspected DILI will be confirmed by the adjudication panel against the trial definition of a DILI
- If DILI confirmed then patient will complete 2 additional EQ-5D-5L

Follow-up

- The patient will complete the EQ-5D-5L at the following timepoints
  - Baseline DILI assessment
  - Baseline DILI recovery
  - Week 2 post randomisation
  - 1 week end of treatment
  - Follow-up 12 months post randomisation

  If the patient has a recurrence then they will complete 2 additional questionnaires
  - Recurrence
  - DILI recurrence post recovery

- Participants will receive text, email phone call reminders (as necessary) to remind them to complete their questionnaires
- For non-English speakers EQ-5D-5L will be sent via post in their preferred language


EQ-5D-5L

ONCE COMPLETED PLEASE ENTER DATA ONTO THE REDCAP DATABASE

PID - Initials

Date / /

TB-DILI

Anti-TB therapy following drug-induced liver injury

Health Questionnaire

English version for the UK

Source Data

- Most data for TB-DILI will be captured directly within the database, where this is not possible a TB-DILI workbook will be available to record information for the baseline visit
- Medical records, screening log and the TB-DILI workbook (where used) will be considered source data (details in Data Location Log)
- Medical records must evidence
  - ✓ Discussions about the trial
  - ✓ Consent process, consent form and confirmation of consent
  - ✓ Sample results
  - ✓ Randomisation and confirmation of treatment allocation
  - ✓ Treatment dispensed/prescribed (if different to allocated treatment, reason why a different treatment was prescribed)

Discontinuations

- If a patient withdraws their consent prior to randomisation, they will not be randomised and no follow up data will be collected

- Participants may also withdraw their consent for follow-up and/or other trial-related activities e.g.receiving trial-related communications after randomisation. They can still remain in the trial with us collecting data directly from their medical notes

- **The NCTU must be informed of all requests by participants to stop their involvement in the trial as soon as possible**; appropriate action will be taken to ensure that the participant's wishes are followed

Investigator Site File (ISF)

- NCTU will provide site with an Investigator Site File ISF
- Maintenance of the ISF should be delegated on the site delegation log

The ISF must contain all trial records for the site:	
• Protocol	• Signed paper consent forms
• Participant documents	• Study logs
• Approvals	• Delegation log, CVs/ GCPs and trial training records
• Agreements	• Monitoring records
• SAE documentation	• Investigator Meeting/ Initiation reports and monitoring reports

Role and Responsibilities

Site responsibility:

- Medical care of participants and ensuring patient safety
- Work in accordance with the approved trial protocol, trial manual and SOPs
- Comply with all ethical and legal requirements
- Ensure consistency and completeness of data
- Keeping and retaining accurate records
- Using secure storage facilitates for participant and trial documents

Co-ordinating centre – Nottingham Clinical Trials Unit:

- Trial Management
- Data Management
- Study oversight and monitoring
- Participant follow-up
- SAE handling and reporting

PI Responsibilities

- ✓ Legal responsibility for trial conduct and safety reporting at site
- ✓ Trial-related medical decisions
- ✓ Participant confidentiality
- ✓ Source document retention
- ✓ Investigator site file maintenance
- ✓ Safety reporting
- ✓ Protocol deviations
- ✓ Maintain a list of staff and delegated duties
- ✓ Ensure new staff are trained on the current trial protocol (document on training/delegation logs)
- ✓ Ensure staff changes are reported to the Trial Manager
- ✓ Ensure adequate lines of communication with the Trial Manager and NCTU
- ✓ eCRF final sign off
- ✓ Permit monitoring, audit and inspection
- ✓ Archiving (retain all documents and records; NCTU will communicate re archiving towards end of study)

Evidence of PI oversight

Site responsibility:

- PI protocol signature page
- Available and responsive
- Up-to-date delegation log & training records
- Meeting notes in ISF filed
- Medical records:
  - Consent process well documented
  - Confirmation of eligibility
  - Review of sample results
  - Decisions on treatment
  - Adequate source data
- SAEs (causality/relatedness assessment)
- Adequate source data

Research Nurse responsibilities

- ✓ Maintain:
  - ✓ ISF and trial related documents
  - ✓ Patient identification/enrolment log/ screening log and monthly summary update into the database
- ✓ Instruct participant with sample collection
- ✓ Completion of eCRFs
- ✓ SAE reporting
- ✓ Prepare for monitoring visits
- ✓ Manage and implement trial amendments
  - – version control

Monitoring

- No routine onsite monitoring visits will take place
- Triggered monitoring visits may take place if necessary
- Central monitoring of the following data will be performed remotely by NCTU continuously throughout the trial:
  - Screening data
  - Informed consent forms
  - Eligibility checklists
  - eCRF data
  - Sample results
  - Medication tracking

TB-DILI Cohort Study

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Aim

Determine with greater precision the frequency of DILI recurrence under standard care conditions in the NHS, and the quality of life impacts arising. If possible, we will determine independent risk factors for DILI recurrence.

Outcome measures

Primary outcome

- DILI recurrence at end of treatment

Secondary outcome

Measured at end of treatment:

- Severity of DILI recurrence
- Total number of days on anti-LTBI drugs
- Adverse event rate
- QoL using ED-5D-5L and healthcare resource use

If possible we will determine independent risk factors for DILI recurrence

Trial entry criteria

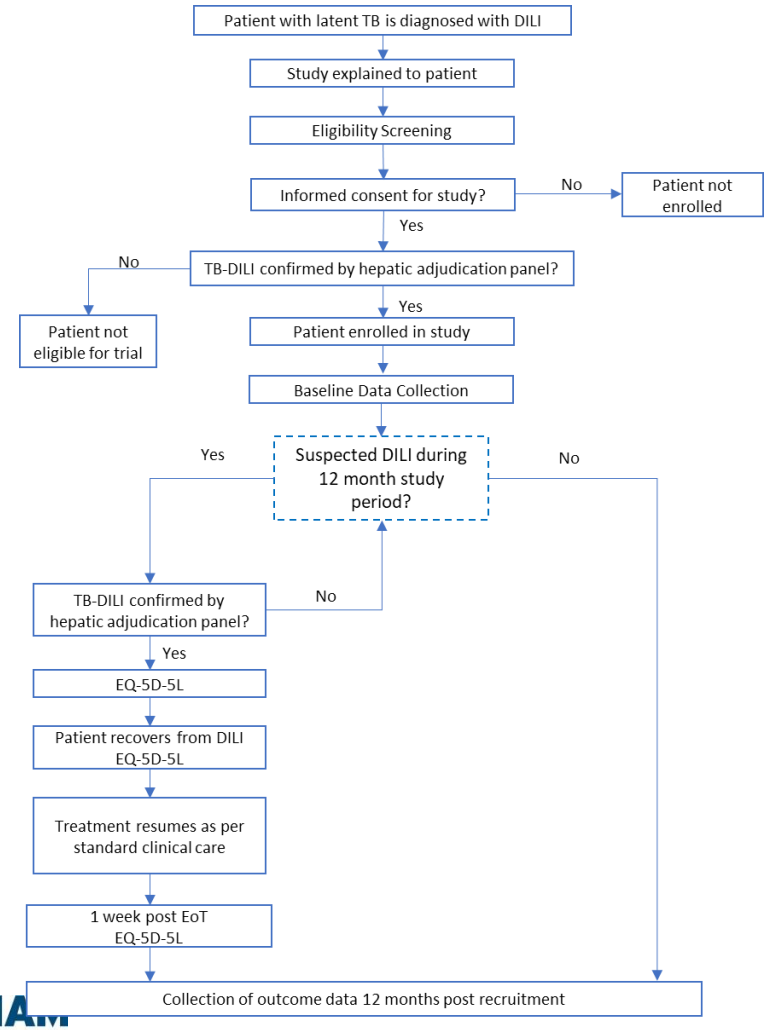
Inclusion criteria

- Adult aged ≥ 18 years
- Experienced DILI with anti-LTBI drugs
- Medically suitable for re-introduction of anti-LTBI drugs.

Exclusion criteria

- Unable to provide written informed consent

Patient pathway



Study Procedures

- Patient screened
- Consented
- Baseline data collection
- Adjudication panel confirm eligibility/ recurrences
- EQ-5D-5L will be taken at 3 junctures
  - DILI occurrence
  - DILI recover
  - 1 week post EOT

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Data collection only

Patient pathway

- Participants who do not enter the main trial should be considered for the data collection arm only
- Trial entry criteria is the same as the main trial however patients will not be randomised
- The main ICF should be used for consent and they should also complete section B of the ICF
- Participants will be enrolled onto REDCap and the adjudication will confirm eligibility before any further data can be collected

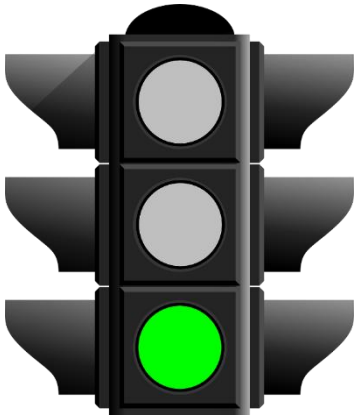
Next steps

What happens next?

Your site cannot open to recruitment until NCTU have issued you with the 'green light'

Documents needed:

- ✓ PI protocol signature page
- ✓ Delegation Log with PI signature
- ✓ Training logs and CV/GCP certificates
- ✓ Signed site agreement (mCNA)
- ✓ Completed database access requests



Processes needed:

- ✓ Local R&D approval
- ✓ Ensure local stock of TB drugs

When all documents and approvals are in place,
NCTU will then issue a "Green-light letter"
and you are ready to go!

Thank you and good luck with recruitment

Please contact us if you need any support with any trial related activities

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