TRIAL PROTOCOL

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

Protocol version 1.2

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Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

Protocol Approval/Sign-off

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

This protocol has been approved by:	
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Abbreviations and Definitions

Term	Description
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction (AR)	Any untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
ALT	Alanine aminotransferase
ATS	American Thoracic Society
ATT	Anti-tuberculosis Therapy
BTA	British Thoracic Society
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DMP	Data Management Plan
E	Ethambutol
EHR	E = ethambutol, H = isoniazid, R = rifampicin
EHRZ	E = ethambutol, H = isoniazid, R = rifampicin, Z = pyrazinamide
EoT	End of Treatment
H	Isoniazid
ICF	Informed Consent Form
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LFT	Liver Function Test
LTBI	Latent Tuberculosis Infection
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PHE	Public Health England
PI	Principal Investigator

PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QoL	Quality of Life
QALY	Quality Adjusted Life Year
R	Rifampicin
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** Comments: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SmPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

Z	Pyrazinamide

TRIAL SUMMARY

(This table shows the summary for the main trial only. For details of the cohort study see Appendix A).

Title	Reintroduction of anti-tuberculosis therapy following drug-induced liver injury: a randomised controlled trial
Trial Design	Pragmatic, individually randomised, parallel group, open randomised controlled superiority trial with concealed allocation (1:1) and minimisation
Objectives	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 objectives • To determine the cost-effectiveness of reintroducing a non-Z containing, versus Z-containing regimen Cohort study • To determine i) the frequency and ii) quality of life impacts of DILI episodes in adults being treated for latent TB infection
Eligibility 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
Intervention and control	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 Control • 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

Outcome Measures	Primary • DILI recurrence within 12 months following randomisation Secondary • Severity of DILI recurrence • Physician rated clinical cure at end of treatment (EoT) • Clinical cure at 12 months • Total number of days on ATT at EoT • ATT adherence at EoT • Adverse event rate at EoT or at 12 months whichever is sooner • Mortality at 12 months • Quality of life assessed by EQ-5D-5L and healthcare resource use
Sample Size	350 patients recruited across approximately 40 sites
Expected recruitment duration	48 months

Trial Flow Diagram:

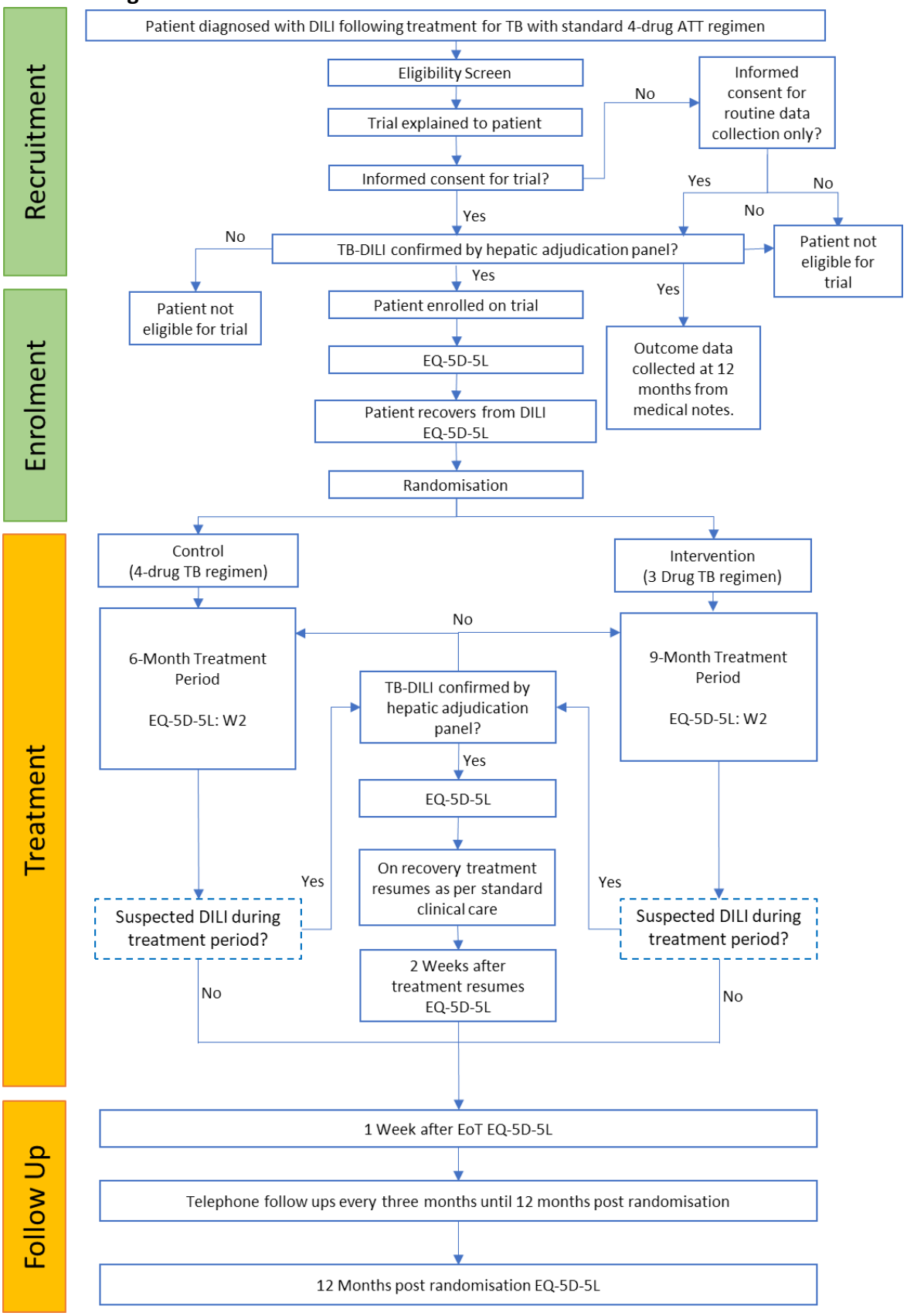

TABLE OF CONT*ENTS*

Contents

1 Background and Rationale

1.1. Background

In 2018, 4,655 people were diagnosed with tuberculosis (TB) in the UK, equivalent to a rate of TB of 8.3 per 100,000 population.[1] 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. Only 2.7% of people with TB were coinfected with HIV in 2018; most (81.7%) were born outside the UK. Early data from 2019 suggests that the rate of TB may be higher in 2019 compared to 2018.

The standard treatment of drug-sensitive TB involves a 4-drug combination of anti-TB therapy (ATT) for 2 months (intensive phase of treatment), followed by a 2-drug combination for 4 months (continuation phase of treatment), making a total treatment duration of 6 months. Cure rates are around 97%.[9]

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. Unpredictable or idiosyncratic reactions which develop acutely account for most types of DILI. These reactions are unpredictable based on the pharmacological action of the drug, independent of drug dose and are relatively unusual for each drug.

Among those who develop DILI on ATT, 16% develop jaundice and 5.3% acute liver failure; the latter is the most severe outcome of DILI, of which 22% can be fatal.[11] Most patients with DILI who report symptoms experience nausea, vomiting, anorexia and lethargy. Early detection of DILI with cessation of the inciting drug(s) serves to limit the severity of DILI and its consequences. Not all asymptomatic increases in liver enzymes while on ATT constitute DILI episodes. Some of the increase in liver enzymes are self-limiting or are attenuated through a process called hepatic adaptation (please see later). However, very high levels of liver enzymes (>5x upper limit of normal) in the absence of symptoms are thought to represent early DILI episodes that, if left untreated (ie. continued exposure to the inciting drug(s)), would progress to symptomatic DILI.

Apart from any symptoms and sequelae related to DILI, a patient who experiences a DILI episode also suffers delay in the treatment of their primary illness. When a patient with active TB has a DILI episode, the overarching strategy is to i) stop the inciting drug(s), ii) allow the liver to recover and then iii) reintroduce as many first-line ATT drugs as possible to enable the highest chance of clinical cure of TB disease in the shortest length of time. The median duration of cessation of ATT is 18 days while reintroduction of ATT drugs takes a further 10 -14 days (median).[2,12] Therefore, for each episode of DILI, a total of 28 days' delay can be expected before full ATT is re-started.[12]

Guiding the patient through recovery from DILI and re-establishment of ATT requires additional healthcare resources. In one study from Canada, 29 of 37 patients who developed serious ATT-related side effects made a total of 91 extra clinic visits, and the TB clinic nurses made an additional 30 home visits to 8 of these patients.[13] If full standard first-line ATT is not reintroduced following DILI, modified regimens may require extension of the treatment duration beyond 6 months to achieve acceptable rates of clinical cure. This adds to patient and healthcare costs.

Globally, rates of DILI following TB therapy of 2 – 25% are reported .[14-18] In 2 UK studies, DILI was reported in about 7% of persons treated for TB; however, the definition of DILI differed between these studies.[12,19]
Roughly 53 – 57% of DILI episodes occur during the first 2 weeks of ATT, and 75 – 88% within the first 8 weeks, corresponding to the intensive phase of ATT.[12,19-21]

Our understanding of the differences in risk of DILI associated with individual ATT drugs comes from a range of studies including case-control studies, observational cohort studies, and clinical intervention trials. Most intervention trials have been designed primarily to test the efficacy of different ATT regimens with DILI measured as part of safety reporting (adverse events). DILI rates in efficacy trials have sometimes been noted to be lower than those observed under routine TB programmatic conditions and may reflect patients at higher risk of adverse effects not being recruited to intervention trials. Of the four standard first-line ATT drugs, ethambutol (E) very rarely causes DILI. Concerns centre mainly around isoniazid (H), rifampicin(R) and pyrazinamide (Z).

Isoniazid (H). Based on studies of the treatment of patients with latent TB infection (LTBI) where isoniazid was used as monotherapy for 6 to 9 months, H-related DILI occurred in 0.1% to 1% of cases.[22-24] In the REMOX trial (treatment for active TB), a H-free regimen had a numerically lower rate of DILI (2.2% versus 3.4%) than either the standard HRZE regimen or one where ethambutol (E) was replaced by moxifloxacin[15], suggesting that the independent contribution of isoniazid to DILI during multi-drug therapy may be similar to or slightly higher than that suggested by the data in LTBI studies.

Rifampicin (R). Based on studies of the treatment of patients with LTBI where rifampicin (R) was used as monotherapy or in combination with isoniazid (RH), DILI occurred in 0.3% to 0.4% of cases, and in general, no more frequently than for patients treated with H alone.[25] In two dose-ranging studies of rifampicin given as part of multidrug therapy for active TB, DILI occurred in up to 2% of participants at the standard 10 mg/kg dose, though data were not available on which drugs were implicated. Hepatotoxicity did not appear to be dose-related, supporting an idiosyncratic aetiology.[26,27]

Pyrazinamide (Z). The projected difference in event rates between groups (Z-containing vs non-Z-containing reintroduction regimens) rests on the premise that pyrazinamide poses a higher risk of DILI than other first-line ATT drugs. There is no evidence to suggest that hepatic adaptation (the process that permits the safe reintroduction of drugs following a DILI event, discussed in more detail below) occurs to different degrees for different ATT drugs. Therefore, our estimates for the event rate in both randomised groups are based predominantly on data from studies that have compared DILI event rates between different ATT drugs.

Following recovery from an episode of DILI, reintroduction (re-challenge) of ATT drugs is safe for most patients. This is due to a process called **hepatic adaptation.** Hepatic adaptation after DILI might allow 75% - 90% of patients to be re-challenged with the same drugs, and ultimately continue taking these drugs.[2,3] Initial description of this phenomenon involved 218 patients receiving isoniazid for latent TB; 20% developed raised liver enzymes including 3 with elevated bilirubin and despite continuation of the drug, none developed liver failure.[28,29] The mechanism for hepatic adaptation is not fully known.[30] In terms of recurrence of DILI due to all drugs after re-challenge, a systematic review did not show any significant difference between those who have recurrence of DILI (called positive re-challenge) and those who do not (negative re-challenge) which can effectively stratify patients based on risk of recurrent DILI.[31] There is no evidence that severity of original DILI and recurrence of DILI are correlated.[31]

We are aware of only 2 intervention trials that address the issue of ATT reintroduction following DILI.

- *Sharma et al* was a 3-arm trial (n= 175) designed to test different modes of reintroduction.[2] All 3 regimens in the trial contained pyrazinamide (HRZ regimens). Patients aged >65 years were excluded because the authors felt the risk of DILI was increased in those who are older. Although point-estimates for DILI recurrence rates differed slightly across the 3 arms (13.8%, 10.2% and 8.6%), 95% confidence intervals (CIs) for between group effects were wide and provided no strong evidence in favour of any regimen.
- *Tahaoglu et al* was a 2-arm trial (n=45) designed to test reintroduction of a Z-containing versus non-Z-containing regimen (EHRZ vs EHR + Streptomycin).[3] There was no age restriction for enrolment. DILI recurrence in the Z-containing arm was 25% (95% CI 9 to 45%) vs 0% in the non-Z containing arm. In addition, post-trial, all patients who had experienced DILI recurrence (all in the Z-containing arm) were safely re-challenged with the non-Z regimen. The authors interpreted this as further evidence of Z-related DILI. Of these 2 trials, only *Tahaoglu et al* provides data on Z vs non-Z regimens but it is limited by the small sample size. Nevertheless, the lower bounds of the event rate for the Z-containing regimen is similar to the overall event rate reported by *Sharma et al* (~10%) and is consistent with the observation that patients at higher risk of DILI were not enrolled by *Sharma et al*.

Four retrospective cohort studies report DILI recurrence frequencies following ATT reintroduction. It is very difficult to compare across these studies due to variations in a) patient cohorts, b) definitions of DILI used and c) methods for detection of DILI. *Costiniuk et al* (2015) studied 53 individuals with ATT-DILI (48 HIV co-infected).[21] DILI recurrence occurred in 12% of the cohort; no association was observed with the mode of reintroduction (sequential (n=12) vs parallel (n=30)). *Natarajan et al* (2016) reported results in a conference abstract concerning 50 patients with DILI in whom HRZ was reintroduced with 10% DILI recurrence.[32] *Abbara et al* (2017) described 105 patients with ATT-DILI, using a less strict definition of *possible DILI*. A non-Z regimen was reintroduced in all patients with 12.4% recurrence of *possible* DILI.[12] *Shamaei et al* (2017) reported on 135 patients with ATT-DILI; 109 (80.7%) were re-challenged with a non-Z regimen and 26 (19.2%) with a Z-containing regimen.[33] Patients in the non-Z group were highly selected for an increased risk of potential DILI (eg. 12.6% HIV positive vs 0%; viral hepatitis 11.4% vs 3.8%). DILI recurrence rates for non-Z vs Z-containing regimens were 17.4% vs 15.4% respectively).

1.2. Trial Rationale

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.[8,9]

The NICE TB Guideline (2016), section 1.7.4.1, recommends clinicians "*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*." The NICE Guideline Development Group (GDG) acknowledged that the evidence supporting this recommendation was of very low quality; based on 2 trials (Sharma *et al.,* 2010, and Tahaoglu *et al.*, 2001). The recommendation was mainly developed by expert consensus.

The American TB Guideline (2006) also recommends 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.*

Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge."

These two Guidelines are interpreted variously by clinicians, in the NHS and globally, resulting in a range of clinical practice. Some clinicians prefer to routinely avoid reintroducing pyrazinamide (Z), aiming instead for a 9-month non-Z containing regimen. Others consider the severity of DILI in deciding on reintroduction of Z; however, the threshold for classifying 'milder DILI' also varies. It is equally difficult for patients to make informed choices. There are no data on patient-related costs or quality of life (QoL) measures to inform the balance between risk of recurrent DILI versus extension of treatment duration.

1.2.1. Justification for participant population

The target population comprises of adults treated within the NHS for active TB with standard 4-drug ATT who have experienced an episode of DILI requiring these drugs to be stopped.

The main trial will determine the risk of recurrence and health economic impacts of a pyrazinamide (Z)-containing versus non-Z containing reintroduction regime following a DILI episode. Pyrazinamide (Z) is not a component of treatment for latent TB infection (LTBI). Therefore, including patients with LTBI in the main trial is not appropriate. Furthermore, anecdotal evidence suggests DILI occurrence (from treatment with R or H) in these patients, who are usually clinically well, is likely very low (<1.5%). A separate clinical trial to determine the safest and most effective drug reintroduction strategy in these patients is not feasible in the UK because of the very large sample size needed for a definitive study. Instead, we propose a cohort study to provide firmer estimates of the frequency of DILI occurrence and recurrence, and the quality-of-life impacts arising. The cohort study involving patients with latent TB infection (LTBI) will also benefit the current trial because it will keep sites actively recruiting into the programme of research. We provide further details of the cohort study in Appendix A.

1.2.2. Justification for design

This trial will provide reliable data on DILI recurrence rates and QoL for the 2 main reintroduction options in current practice in the NHS. These data will enable patients and their clinicians to make informed choices regarding the most appropriate strategy to adopt. We anticipate results from this trial to directly inform future clinical practice within the NHS and globally.

1.2.3. Choice of treatment

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).

1.2.4. Cohort Study: Patients with LTBI

Patients with LTBI who develop DILI while on anti-LTBI drugs comprise a separate target population. They will be approached to participate in a prospective observational cohort study. See Appendix A for full details of this cohort study.

2. Aims, Objectives and Outcome Measures

2.1. Aims

To compare the relative safety and effectiveness, including cost, of two different drug reintroduction strategies in adults with TB following an episode of anti-TB DILI.

2.2. Objectives and outcome measures

2.2.1. Primary

- DILI recurrence within 12 months following randomisation.

2.2.2. Secondary

- Severity of DILI recurrence
- Reported clinical cure at end of treatment (EoT)
- Reported clinical cure at 12 months
- Total number of days on ATT at EoT
- ATT adherence at EoT
- Adverse event rate at 12 months
- Mortality at 12 months
- Quality of Life using EQ-5D and healthcare resource use

3. Trial Design and Setting

3.1. Trial Design

Phase III, multi-centre, randomised, open-label, parallel group, superiority trial with concealed allocation (1:1) and minimisation to receive either the intervention, sequential full-dose reintroduction of non-Z-containing 3-drug ATT (compromising EHR) or the control sequential full-dose reintroduction of a Z-containing 4-drug ATT (comprising EHRZ).

3.2. Trial Setting

Patients will be recruited through secondary NHS TB centres across the UK. It is anticipated that at least 40 recruiting sites will be required to achieve the target sample size during a recruitment period lasting 48 months.

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

1. During routine outpatient clinics/consultations
2. Community clinics and mobile clinics
3. Hospital in-patients

In light of the COVID-19 pandemic and revisions being made to clinical pathways within the NHS, it is expected that some routine clinic appointments may be carried out remotely via telephone/video call in place of a face-to-face visit. However, no major changes in the care pathway of patients who develop DILI are expected.

4. Eligibility

Potential participants will be identified at the time of DILI occurrence by the site PI and TB team. During the DILI recovery period (median 18 days from cessation of ATT drugs)[12], eligibility screening, recruitment and randomisation will be carried out by research staff. Patients who require alternative 'bridging' TB drugs *during DILI recovery* will be eligible for trial participation. Only patients who are deemed suitable for reintroduction of standard 4-drug ATT after recovery from DILI will be enrolled and randomised.

In order to take part in the TB-DILI trial, patients must meet all of the listed inclusion criteria and none of the exclusion criteria at this baseline visit.

4.1. Inclusion Criteria

- Adult 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

4.2. Exclusion Criteria

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

To obtain a realistic estimate of safety and tolerability, no adult will be excluded on the basis of (older) age, liver disease, alcohol use, HIV status or other medication use.

The NICE TB Guideline does not outline a specific LFT monitoring plan. Participating sites will be encouraged to adopt a preferred monitoring plan with flexibility for local practice variations across hospitals. Sites will be requested to upload all LFTs performed onto the eCRF.

Definition of DILI. This will be based on internationally recognised criteria that take into account baseline measurements.[34]

Table 1. Clinical chemistry criteria for DILI in those with normal liver enzymes at baseline.

Any one of the following- • >3-fold elevation in ALT and either bilirubin elevation exceeding 2 x upper limit of normal (ULN) or presence of hepatitis symptoms (anorexia, nausea, vomiting, abdominal pain) • >5-fold elevation above ULN of alanine aminotransferase (ALT) • >2-fold elevation above the ULN for alkaline phosphatase (ALP), particularly with accompanying 5'-nucleotidase or gamma-glutamyl transpeptidase (GGT) elevations and when there is no known bone pathology driving the rise in ALP.

Isolated hyperbilirubinemia or raised GGT in the absence of other liver enzyme elevations will not qualify as DILI. These case definitions are in agreement with those from the American Thoracic Society TB Guideline, but also include a cholestatic pattern of DILI (with elevation of ALP) which is observed in

up to 17% of ATT DILI cases. Case definitions for DILI in patients who have elevations of ALT or ALP ≤1.5 x ULN prior to the onset of ATT would be the same as those with normal ALT or ALP at the onset of ATT. In patients with ALT or ALP elevation ≥1.5 x ULN prior to ATT, it is important to distinguish natural fluctuations in ALT/ALP levels from DILI. For the TB-DILI trial, the following will apply:
in patients with ALT or ALP elevations ≥1.5 x ULN prior to ATT, DILI will be defined as

- ALT ≥3 x upper limit of baseline levels or
- ≥ 300 U/L or
- ALP ≥ 2 x upper limit of baseline,

irrespective of bilirubin elevation or hepatitis symptoms.
(criteria based on consensus guideline for the management of patients with chronic liver disease) .[35]

Severity of DILI will be graded according to the international expert working group as shown in Table 2.

Table 2. DILI Severity scale[34]

Category	Severity	Description
1	Mild	Elevated ALT/ALP reaching criteria for DILI but bilirubin <2x ULN
2	Moderate	Elevated ALT/ALP reaching criteria for DILI and bilirubin ≥2x ULN or symptomatic hepatitis
3	Severe	Elevated ALT/ALP reaching criteria for DILI and bilirubin ≥2x ULN and one of the following: • International Normalised Ratio (INR) ≥1.5 • ascites[36] and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis[37] • Other organ failure considered due to DILI
4	Fatal or transplantation	Death or transplantation due to DILI

Definition of Recovery from DILI:

1) in those who had normal baseline LFTs - return of liver enzymes to less than 2 x ULN ALT plus bilirubin in normal range,
2) in those who had elevated baseline LFTs – either i) return of liver enzymes to less than 2X ULN ALT plus bilirubin in normal range or, ii) return to baseline levels, whichever is the greater; *PLUS* resolution of signs and symptoms of hepatotoxicity after withdrawal of ATT drugs (criteria based on the American Thoracic Society TB Guideline and NICE TB Guideline).

Hepatic Adjudication Panel. Liver enzyme elevation in isolation is not a sufficient criterion to confirm a diagnosis of DILI. Other factors to consider are i) temporal association of ATT with elevation of liver tests, and ii) exclusion of alternative explanations.

A blinded Hepatic Adjudication Panel will review all relevant data relating to possible DILI episodes. The panel will judge the probability of ATT-related DILI and DILI severity according to defined criteria. Differences will be resolved by consensus, with the option of co-opting a third panel member as needed.

5. Screening and Consent

5.1. Screening

All trial activity must be recorded in the patient's NHS medical notes in each of the pathways. It is important that a record of the consultation, trial information and eligibility reviews are documented in the patient's medical notes and each entry dated and signed by the individual completing the activity.

Screening data

Sites will be required to provide a summary of screening data on an ongoing basis during the recruitment period, which will be reviewed regularly by the Trial Management Group (TMG) and oversight committees.

5.2. Consent

Written informed consent for each participant must be obtained prior to performing any trial related procedure.

The potential participant will be given the opportunity to ask questions throughout the process. Consent will be obtained by a member of the research team in accordance with the delegation of responsibilities authorised by the Principal Investigator on the site delegation log. This will usually be by a medically qualified doctor, or where local Trust policy allows this may be a research nurse. **Eligibility for the trial must always be confirmed by a medically qualified doctor using the eligibility checklist.**

Consent for the trial will be taken in writing. In light of the COVID-19 pandemic, alternative methods (e.g. remote consent) may be used where a baseline face-to-face visit is not possible; local NHS policy will dictate the method of consultation/visit and all consent taking will be in accordance with trial approvals, applicable regulatory policies and NHS guidelines.

All patients identified as being potentially eligible for the trial will be given a Participant Information Sheet (PIS) and a member of the site research team will explain the trial to the patient. Where a face-to-face visit is not possible e.g., due to social distancing measures, a copy of the PIS may be posted or provided electronically, whichever is convenient to the patient. The potential participant will also be given contact details so that they can ask any questions they may have. A signed consent form must be sent electronically or via post to the clinical team.

The consent documentation will also inform participants that their General Practitioner (GP) will be made aware of their participation in the trial.

5.2.1. Responsibilities

It remains the responsibility of the Principal Investigator to ensure informed consent is obtained appropriately. A Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators or "delegate(s)" will ensure that they adequately explain the aim, trial treatment, anticipated benefits, and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary. Any potential participant is free to decline participation and may withdraw from the trial at any time. Every potential participant should be given 24 hours to

read the PIS and, if they wish, to discuss their participation with others, such as family members, their GP or other healthcare professionals outside of the site research team.

5.2.2. Obtaining consent

Patients who are identified as being potentially eligible for the trial will be asked by the investigator or delegate if they are interested in participating and will be given a copy of the PIS to read. Patients attending a consultation by telephone or video call, will be given the same information about the trial and if interested, sent a copy of the PIS by post or electronically. The PIS will also be available online.

If a patient expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the informed consent form (ICF). Details of the trial and the participants participation including date of consent should be recorded in the medical notes.

The participant must give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the participant's medical records, and a copy of the signed ICF to be sent to the Nottingham Clinical Trials Unit (NCTU).

The consent form will include consent for the collection of contact details for the purpose of obtaining follow-up information and receiving trial communications.

The Investigator or delegate will then sign and date the form. Copies of consent forms should be filed in the participant's medical notes (where medical notes are electronic, a copy must be scanned (where paper) and uploaded into the patient's notes, or digitally uploaded (where electronic)), and the original kept in the Investigator Site File (ISF). Once the participant is enrolled onto the trial, the participant's unique trial identification number will be entered on the ICF maintained in the ISF.

Throughout the trial, the participant will have the opportunity to ask questions. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect a participant's decision to continue, the participant will be given time to consider this and if they are happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the NCTU and via the trial website. It is the responsibility of the local site research team to ensure that all copies available locally are printed or copied onto the headed paper of the local institution.

5.3. Optional consent for sub-study

Potential participants who do not enter the trial will be approached for consent to use their routinely collected data. These data will complement results from the main trial and provide additional valuable data on DILI occurrence and recurrence.

Documentation of consent will be the same as outlined in section 5.2.2

5.4. GP Notification

Following randomisation and with the participant's consent, their GP will be informed that the participant is taking part in the trial.

6. Enrolment and Randomisation

6.1. Enrolment

Following informed consent, baseline data will be collected by a member of the site research team and the participant will be enrolled using the secure online trial database. Further information on baseline data collection requirements is detailed in section 8.2.

An authorised member of the site research team will log into the secure randomisation system and randomise the participant.

6.2. Randomisation

Eligible patients will be individually randomised on a 1:1 ratio to one of the treatment groups using an online randomisation system developed and maintained by the NCTU. Access to the system will be granted by the NCTU in accordance with the roles delegated by the Principal Investigator on the Site Delegation Log.

Treatment will be assigned using a minimisation algorithm balancing on the following factors:

- Recruitment site
- Participant's age (≤ 35 and >35 years)
- Participant's worst severity of DILI up to randomisation (mild and moderate/severe)

The randomisation algorithm will include a probabilistic element to allocation making prediction of the allocated group virtually impossible.

6.3. Blinding and concealment

Allocation will be concealed to trial staff prior to randomisation using REDCap, an automated web system operated by the NCTU.

Blinding of the participants and site research team following randomisation is not possible due to the nature of the interventions.

Table 3 provides an overview of the blinding status of all individuals involved in the management and delivery of the trial.

Table 3: The blinding status of individuals involved in the trial

Trial role	Blinding status	Comments
Participant	Not blinded	Not possible due to the nature of the intervention. Participants will be informed which arm of the trial they have been randomised to immediately after randomisation.

Trial role	Blinding status	Comments
Principal investigator and site research staff	Not blinded	Not possible due to the nature of the intervention. Following randomisation, an e-mail will be sent to the PI (unblinded for participants they PI randomise only) and/or member of the site research team performing the randomisation (as delegated) confirming treatment allocation.
Chief Investigators	Blinded	The Chief investigator and Deputy Chief investigator will remain blinded to treatment allocation overall (knowledge of treatment allocation is limited to participants at their own site). In instances where serious adverse events are reported, the CIs will become unblinded to complete the full causality assessment.
Adjudication Panel	Blinded	The adjudication panel will remain blinded to treatment allocation overall when performing adjudication for a potential DILI during various timepoints within the trial.
Software programmer	Not blinded	The software programmer is responsible for the management of the randomisation system and database and will have access to all unblinded datasets within both systems.
TB-DILI Trial Management staff within NCTU	Not blinded	Blinding of trial Management staff within NCTU impractical due to the range of potentially unblinding data collected during the trial. For example, Serious Adverse Event reports will be handled by the trial management team who may become unblinded to a participant's treatment allocation.

Trial role	Blinding status	Comments
Data management	Not blinded	Data management staff will have access to the unblinded datasets within the trial randomisation system and database to ensure data quality and undertake central monitoring activities.
Trial statistician	Not Blinded	The trial statistician will remain blinded (they will not have access to treatment allocations or data which has the potential to unblind) prior to approval of the statistician analysis plan. After approval of the analysis plan the trial statistician will be able to access potentially unblinding data. They will also be able to request treatment allocation data where necessary (e.g. for the purposes of preparing interim reports).
Senior Trial Statistician	Blinded	Where possible the senior trial statistician will remain blinded and not have access to treatment allocations or data which has the potential to unblind until after the final database lock.
Independent statistician	Not blinded	A statistician independent of the trial management team will be responsible for validating statistical analysis and will therefore be unblinded to trial interventions.
Health Economist	Blinded	The health economist will not have access to treatment allocations or data which has the potential to unblind until after the final database lock.

7. Trial treatment / intervention

7.1. Treatment

Patients will be randomised to one of the following treatment arms:

ARM	TREATMENT	FORMULATION AND DOSE
CONTROL	**EHRZ**	**See NICE Guideline (standard dosing as per BNF Guidelines)**
INTERVENTION	**EHR**	**See ATS TB Guideline (standard dosing as per BNF Guidelines)**

7.2. Treatment Supply and Storage

7.2.1. Treatment Supplies

Following randomisation and treatment allocation, trial treatment will be dispensed to participants from standard clinical stocks in accordance with the usual site supply procedures.

7.2.2. Packaging and Labelling

Trial specific labelling will not be required as all IMPs have a marketing authorisation in the UK and are being used within their licensed indication.

The IMP will be dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/31 94) Marketing Authorisations Etc. Regulations 1994 that apply in relation to relevant dispensed medicinal products.

7.2.3. Storage of Treatment

There are no trial-specific requirements for the storage of any of the IMPs used in this trial. All treatment prescribed and dispensed for the purpose of the trial will originate from standard clinic stock which will be stored in accordance with the manufacturer's storage instructions as detailed in the applicable Summary of Product Characteristics (SmPC). Sites will follow their own local policies for storage of medication.

7.3. Dosing Schedule

In accordance with standard practice, participants will be instructed to start their allocated treatment on the day they receive their treatment, this will be 1-3 days from the date of randomisation. Start and stop dates of medication will be included in the eCRF.

7.4. Accountability Procedures

Sites will follow their own local procedures for recording medication dispensed to trial participants. There are no additional trial-specific accountability requirements.

7.5. Treatment Modification

7.5.1. Missed Doses

In the case of any missed doses, participants will be advised to continue their treatment course until it is completed. If the clinician feels too many doses have been missed then treatment will be restarted. This is in line with standard care. Information on compliance with allocated treatment will be collected in the eCRF.

7.5.2. Adherence

For the purposes of assessing adherence to the interventions in the internal pilot, adherence will be defined as treatment prescription consistent with randomised allocation. For participants for whom treatment is prematurely stopped or modified because of a suspected DILI recurrence, then these cases will be reviewed to ascertain adherence to randomised allocation up until the point of DILI recurrence.

8. Trial procedures and assessments

8.1. Summary of assessments

A summary of trial procedures is shown in figure 2. A detailed description of each procedure can be found in section 8.2.

Figure 2: Summary of trial procedures time point

	TRIAL PERIOD																							
TIMEPOINTS	**E**	**R**	**Phase A**							**Phase B**					**Phase C**			**DILI Recurrence**		**EoT**			**Follow-up Post R**
Timepoint [Weeks]	W-2	W-1	W0							W1	W2	W4	W6	W8	W16	W24	W32	Diagnosis of DILI	2-Weeks after treatment re-start	W25	W33	*	W52
Timepoint [Days]		-1	0	1	3	4	6	7	9														
Tolerance [Days]	**a**	±2	±1	±1	±1	±1	±1	±1	±1	±4	±4	±4	±4	±4	±14	±14	±14	-	-	-	-		-
ENROLMENT:																							
Eligibility screen	X																						
Informed consent	X																						
Baseline Assessments																							
Adjudication panel confirmation	X																	X					
EQ-5D-5L	X																						
Randomisation		X																					
CONTROL ARM																							
Drug Re-Introdcution																							
Reintroduce EH				X																			
Reintroduce R						X																	
Reintroduce Z								X															
Drug Discontinuation																							
Discontinue Z+R														X									
Assessments																							
LFT (suggested not mandated)			X		X		X		X	X	X	X	X	X	X	X	X	X	X				
EQ-5D-5L			X								X							X	X	X			X
Follow-Up post EoT																							
Follow-up telephone call																				X		X	
INTERVENTION ARM																							
Drug Re-Introdcution																							
Reintroduce EH				X																			
Reintroduce R						X																	
Drug Discontinuation																							
Discontinue R														X									
Assessments																							
EQ-5D-5L			X								X							X	X		X		X
Follow-Up post EoT																							
Follow-up telephone call																					X	X	

E = Enrolment

R = Randomisation

EoT = End of Treatment

a. The enrolment period will occur at the onset of DILI, the period between E & R will be variable dependent upon patient recovery. Predicted average time is 2 weeks
* Every 12 weeks after EoT until 12 months post R

9. Schedule of Assessments

9.1. Eligibility Screen

The designated clinician will confirm discontinuation of standard 4-drug ATT due to a suspected DILI event. They will check the patient against the eligibility criteria, and they will approach the patient about the trial.

9.1.1.Informed Consent

Any patient identified as being potentially eligible for the trial will be given a PIS by a member of their usual care team and a member of the site research team will explain the trial the patient. Where a face-to-face visit is not possible e.g. due to social distancing measures, a copy of the PIS may be posted or provided electronically whichever is convenient to the patient and contact details provided so that the potential participant has the opportunity to discuss the study and ask questions before providing their consent to participate.

If a patient is interested in taking part, written informed consent will be obtained before any trial procedures are carried out, as described in section 5.2. If a face-to-face visit does not take place and consent is obtained remotely, site staff must have received the completed informed consent form (ICF) before issuing baseline questionnaires. This may be electronically or by post.

9.1.2. Baseline Assessments

Prior to randomisation, all relevant clinical data will be submitted to the DILI-adjudication panel. The panel will review the clinical information to determine that the patient is experiencing/has experienced a DILI event related to treatment of TB with standard 4-drug ATT. The patient will also be asked to complete the EQ-5D-5L, a quality-of-life questionnaire.

9.1.3.Randomisation

Upon confirmation of DILI by the adjudication panel, randomisation will occur after the patient has recovered, and the attending clinician is prepared to re-commence treatment. The Principal Investigator or delegated site staff will randomise the patient using the online randomisation system via a secure website developed and maintained by NCTU.

9.1.4.Prescribe/ issue trial treatment

Phase A

[Begins within 2 days of randomisation]

- Reintroduction of treatment regimen (anticipated duration):
    - 9 days for control arm
    - 7 days for intervention arm

Phase B

- EQ-5D-5L completion at W2 for both arms
- Discontinuation of Drug(s) at W8:
    - Control Arm: E and Z
    - Intervention Arm: E

DILI Recurrence
[Could occur at any timepoint during treatment period]

- EQ-5D-5L questionnaire
- Discontinuation of control or intervention ATT regimen

DILI Recovery

- EQ-5D-5L questionnaire

EoT

- EQ5D questionnaire is completed one week after the end of treatment: This is expected to be W25 for control arm and W37 for intervention arm

12 Months Post Randomisation
[±28 days]

- EQ-5D-5L
- Collection of outcome data

9.2. Treatment discontinuation

Participants who discontinue the study treatment or change treatment for any reason will continue to be followed up in accordance with the trial schedule and continue to provide trial data, including completion of follow-up questionnaires for use in the analysis, unless they are unwilling to do so. All the data collected will be used, and any participant who discontinues study treatment will be reminded of the importance of continuing to complete study questionnaires/assessments.

Reasons for trial treatment discontinuation may include participant decision or significant adverse events.

9.3. Withdrawal Procedures

Participants who do not adhere to allocated trial treatment are not required to withdraw.

9.3.1. Withdrawal prior to randomisation

Any patients that request to withdraw their consent prior to randomisation will be withdrawn completely from the trial; they will not be randomised, and follow-up questionnaires will not be issued. They will be offered the opportunity to provide consent for their routine data to be used; see section 5.3.

9.3.2. Discontinuation from trial follow-up/ other trial-related activities post randomisation

Participants may discontinue their contribution to follow-up and/or other trial-related activities, including receiving trial-related communications. The NCTU must be informed of all requests by participants to stop their involvement in the trial and appropriate action will be taken to ensure that the participants wishes are followed.

Sites will be trained to determine which activities the participant may wish to discontinue from

Participants may discontinue one or all of the following activities:

Discontinuation type	Discontinuation procedure	Use of data that are already collected
Discontinue follow-up questionnaires	Any participant that requests to discontinue from trial follow-up procedures will still have their routine clinical data obtained.	N/A discontinue from follow-up procedures only
Discontinue from other trial communications	Any patient who requests to be withdrawn from other trial communications will be removed from all mailing lists for ongoing trial contact (e.g. newsletters and reminders) but will still receive trial questionnaires.	N/A withdrawal from communications only
Collection of data from medical records and/or NHS Digital	Any participant that requests to discontinue collection of routine data will be directed to the national data opt out service.	Any data collected prior to participant withdrawal will be retained and used.
Full trial withdrawal	Any participant that requests to have no further involvement in the trial will be marked as withdrawn on the trial database.	Any data collected prior to participant withdrawal will be retained and used unless the participant specifically requests that all their data is removed

If site staff are made aware of a participant's discontinuation from any trial activities, the PI or delegate should record this in the CRF as soon as possible to ensure the correct procedures are followed by NCTU and the site team. Participants will be asked their reason(s) for withdrawal but are not obliged to provide these.

Withdrawn participants will not be replaced. Data collected prior to withdrawal will be retained and used in the analysis as per described in the PIS. It should be made clear to any participant withdrawing consent for further data collection that data pertaining to safety will continue to be collected for regulatory purposes and will be included in any safety analysis and the final analysis. In addition, if any significant new information becomes available with regard to the treatment they received in the trial, it may be necessary to contact them in the future.

9.4. Losses to follow-up

If contact cannot be made and the participant has not withdrawn their consent to participation in the trial, outcome data will be obtained from medical records by the research team and/or NHS Digital where possible. If it is not possible to obtain the primary outcome, the participant will be designated as lost to follow-up for the primary outcome

9.5. Protocol non-compliance

Protocol compliance will be assessed via central monitoring of eCRF data in accordance with the trial monitoring and data management plans. If a member of site staff is made aware of a non-compliance, they are advised to report this to the NCTU who can assess and record in the eCRF where appropriate.

10. Adverse Event Reporting

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction (AR)	Any untoward and unintended responses to an IMP related to any dose administered. An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event

Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

10.1. Adverse Events (AEs) and reporting requirement/ procedures

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 (and subsequent amendments).

All IMPs being used in this trial are being used within license and have well characterised safety profiles.

The treatments provided to both randomised groups are widely available within the NHS, used in standard care and considered to be safe. Expected adverse events (listed in the table below) are as per the SmPC for trial treatments. These events are secondary outcomes and will be collected as part of the eCRF. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) as per NCTU standard practice and the number of occurrences reviewed throughout the trial by the TMG and the Data Monitoring Committee (DMC).

Table 4. Expected Adverse Events Associated with the Study Medication

Body system	**Adverse event**
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Thrombocytopenia
	Thrombocytopenia with purpura
	Neutropenia
	Eosinophilia
	Leukopenia
	Haemolytic anaemia
	Disseminated intravascular coagulation
	Vitamin K dependent coagulation disorders
Congenital, familial, and genetic disorders	Porphyria
Ear and labyrinth disorders	Deafness
	Tinnitus
	Vertigo
Endocrine disorders	Adrenal insufficiency
Eye disorders	Tear discolouration
	Optic neuritis
	Pyrexia

General disorders and administration site conditions	Chills
	Edema
	Malaise
	Fever
Hepatobiliary disorders	Hepatitis
	Hyperbilirubinemia
Immune system disorders	Anaphylactic reaction
	Hypersensitivity
Infections and infestations	Pseudomembranous colitis
	Influenza
Investigations	Hepatic enzyme increased
	Blood bilirubin increased
	Aspartate aminotransferase increased
	Alanine aminotransferase increased
	Blood creatinine increased
	Blood pressure decreased
Metabolism and nutrition disorders	Acidosis
	Hypoglycaemia
	Nicotinic acid deficiency
	Decreased appetite
	Hyperuricaemia
	Gout
Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus
	Muscle weakness
	Myopathy
	Bone pain
	Joint pains
Nervous system disorders	Peripheral Neuropathy
	Dizziness
	Headache
	Cerebral haemorrhage
	Numbness
	Paraesthesia of the extremities
	Disorientation
Pregnancy, puerperium and perinatal conditions	Post-partum haemorrhage
	Fetal-maternal haemorrhage
Psychiatric disorders	Elevated mood
	Psychotic disorder
	hallucinations
	mental confusion
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
	Dyspnoea
	Wheezing
	Sputum discoloured
	pulmonary infiltrates
	Pneumonitis,
Vascular Disorders	Vasculitis
	Shock
	Flushing

	Vasculitis
	Bleeding
Gastrointestinal disorders	Constipation
	Dry mouth Nausea
	Pancreatitis acute
	Nausea
	Vomiting
	Diarrhoea
	Gastrointestinal disorder
	Abdominal discomfort
	Tooth discoloration
	anorexia
Hepatobiliary disorders	Hepatitis
	Acute hepatic failure
	Liver injury
	Jaundice
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis
	eosinophilia systemic symptoms
	Erythema multiforme
	Stevens-Johnson syndrome
	Rash
	Pruritus
	Urticaria
	Dermatitis allergic
	Pemphigoid
	Sweat discoloration
	Acute generalized exanthematous pustulosis (AGEP)
Renal and urinary disorders	Dysuria
	Acute kidney injury
	Chromaturia
	Interstitial nephritis
Reproductive system and breast disorders	Gynaecomastia
	Menstrual disorder

10.2. Serious Adverse Events and reporting requirements

Due to common use of these drugs in treating this disease, there is already an immense volume of safety data collected on these drugs. It is improbable that new SUSARs will be identified for the drugs in this trial. Data collection in TB-DILI will operate entirely from patient reported outcomes and there is no clinical routine follow-up once medication has been dispensed. As such, it is not likely that further details of any SAE will be available to the central study team, and any action/outcomes may only be known at the next data collation point. Although this limits the value of expedited reporting from either a safety or regulatory perspective, the processes in place still meet the Sponsor's legal obligations in terms of SUSAR reporting.

If an Investigator believes a particular SAE in a participant receiving the drugs is both unexpected and potentially due to the interventional drug (i.e. a SUSAR), they will be asked to complete a SAE report as soon as possible after becoming aware of the event.

Following review by the Chief Investigator/delegate, all confirmed SUSARs will be reported to the Chair of the DMC and to relevant regulatory authorities, Sponsor, ethics committees, and investigators in an expedited manner in accordance with regulatory requirements.

Safety information relating to adverse events not subject to expedited reporting that are captured as trial endpoints will be closely monitored by the DMC throughout the trial. The DMSC will be provided with a report (at a frequency [at least annual] specified by the DMSC) which will include the key safety-related trial outcomes.

10.3. Events that do not require reporting

Individuals who develop a DILI significant enough to require hospital admission are at high risk of developing other adverse events. To this end, anticipated events that are consequences of the underlying disease, common events in the study population, or are part of the primary and secondary outcomes will be exempt from expedited reporting. Adverse events that are not listed as expected events (table 4) and are not deemed as serious and related to trial treatment (i.e. a SUSAR) by the assessing clinician are also exempt from reporting.
A SAE judged by the Investigator or medical monitor (in this case the CI), to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The medical monitor will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information (RSI) –see Section 10.1) it will be classified as a SUSAR.

10.4. SAE reporting Procedure – NCTU trial Office

Only SAEs that are deemed related by the assessing clinician (i.e. a SUSAR) need reporting. When completing the SAE form, the Investigator will be asked to define the causality and severity of the AE. The SAE form must be sent to the NCTU as soon as possible and no later than 24 hours after first becoming aware of the event (or obtaining the follow-up information from the participant).

On receipt, NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. If confirmation is not received within 1 working day, the site should contact the NCTU. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the Site File and TMF.

Sites
For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE form to confirm agreement with the causality and severity assessments. The form should then be returned to NCTU and a copy kept in the Site File. Investigators should also report SAEs to their own Trust where required by local practice.

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete, date and sign a SAE form. The form should be e-mailed to NCTU using the following e-mail address:

FOR SAE REPORTING ONLY: nctu-sae@nottingham.ac.uk

NCTU
On receipt of a SAE Form, seriousness and causality will be reviewed independently by the medical monitor responsible for determining causality assessments.

10.4.1. Provision of follow-up information

Follow-up information should be provided on a SAE Follow-up form. Only events deemed to be related to trial treatment will be followed up to resolution or stabilisation of the event.

10.5. Reference Safety Information

The Reference Safety Information (RSI) will be the SmPC as described in the table below.

Drug	SmPC
Ethambutol	Ethambutol 100mg film coated tablets. Intrapharm Laboratories Limited.
Isoniazid	Isoniazid, each ampoule contains 50mg Isoniazid in 2ml of solution. Alliance Pharmaceuticals Limited.
Rifampicin	Rifampicin 300mg gelatin capsules. Generics [UK] Limited t/a Mylan.
Zinamide	Zinamide 500mg white tablets. Genus Pharmaceuticals Limited.

Treatment for this condition varies across clinical practice in both dosage and formulation therefore we have included the SmPC for all active drugs being used in the trial. Due to the treatment schedule, relatedness will be assessed against the appropriate SmPC(s) for the drug(s)s that the participant has been administered at the time of the event.

Any updates to the RSI will be reviewed annually in line with the Development Safety Update Report (DSUR).

10.6. Reporting period

Details of unexpected AEs (except those listed is section 10.1) will be documented and reported from the date of commencement of protocol defined treatment 12 months after randomisation. In the case where 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.

10.7. Monitoring pregnancies for potential serious adverse events

The safety profile of the drugs being used are well known therefore there is no requirement to monitor pregnancies for potential SAEs.

10.8. Reporting to the Competent Authority and Research Ethics Committee

10.8.1. Suspected Unexpected Serious Adverse Reactions

On becoming aware of a SUSAR, the Trial Manager (or delegate) will notify the Sponsor as soon as possible. The Sponsor will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days. All other events categorised as SUSARs will be reported within 15 days.

SUSARs will be unblinded to allow reporting to REC and the MHRA.

10.8.2. Serious Adverse Reactions

The NCTU will report details of all SAEs and SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

10.8.3. Adverse Events

Details of all AEs will be reported to the MHRA on request.

10.8.4. Other safety issues identified during the course of the trial

If any urgent safety measures are taken, the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and the sponsor, of the measures taken and the circumstances giving rise to those measures.

10.9. Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

10.10. Data Monitoring Committee (DMC)

The independent DMC will review all SAEs.

10.11. Reporting to third parties

No reporting of adverse events to third parties is expected. Any safety issues identified during the course of the trial will be notified to the MHRA.

11. Data Handling and Record Keeping

11.1. Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

In order to allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Each site will record the location of source data at their site using a source data location log prior to commencing recruitment and signed by the Principal Investigator. For the TB-DILI trial, source data refers to, but is not limited to, the participant's medical notes, data recorded directly into the eCRF, baseline paper questionnaires and source data worksheets (when direct entry to the eCRF is not possible), and follow-up questionnaires.

All data collected directly from participants will be considered as source data within the eCRF. Where paper questionnaires are issued to participants these will be returned to the NCTU for data entry and will be considered source data. Where questionnaire data is obtained via telephone, these data will be entered directly into the eCRF or collected on paper proforma (where direct eCRF is not possible) by a member of the NCTU and will be considered source data.

11.2. Electronic Case Report Form (eCRF) Completion

Data reported within the eCRF may comprise or will be consistent with, the source data, and any discrepancies will be investigated. Staff delegated to complete eCRFs will be trained to adhere to ICH-GCP guidelines and trial-specific guidance on the completion of the eCRF.

Where necessary, paper SAE forms will be completed by site staff and a copy scanned and emailed to NCTU for data entry.

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the eCRF has been completed correctly and that the data are accurate. This will be evidenced by the electronic signature of the site's Principal Investigator on the eCRF. It is the responsibility of the Principal Investigator to ensure there are site staff in place locally to complete data entry into the eCRF in a timely manner.

11.3. Data Management

Details about data handling will be specified in the Data Management Plan (DMP). This will include the agreed validation specification which will validate data for consistency and integrity as it is entered.

All trial data will be entered onto the REDCap database through the eCRF with participants identified only by their unique trial number and initials The REDCap eCRF database will be developed and maintained by NCTU. Access to REDCap will be restricted and secure. Any missing or ambiguous data will be queried with the site via the eCRF. Sites should respond to data queries in a timely manner, ideally within 2 weeks of the query being raised. All access and data transactions will be logged in a full audit trail.

Data will be held on clinical trial servers. These servers are located within The University of Nottingham data centres, which are managed and monitored 24/7. Security is both physical (secure limited access) and electronic (behind firewalls, access via user accounts (user name and password)), restricted access (e.g. site users only have access to their site's data, and by user type/role). All access and data transactions will be logged in a full audit trail.

Participants' eCRF data will be reviewed and soft-locked) on an ongoing basis once they are deemed to have a complete set of data that has passed data validation checks (i.e. there are no data queries outstanding). Once all participants' data have been soft-locked and the statistical analysis plan has been finalised, the trial database will be hard locked (set to read only). This will be done prior to the final data analysis.

11.4. Archiving

It is the responsibility of the Sponsor to ensure that all documents in the Sponsor file are retained for 25 years after the end of trial. It is the responsibility of the NCTU to ensure that all documents in the TMF are retained for at least 25 years after the end of trial and that Principal Investigators ensure all essential trial documentation contained within the Investigator Site Files and participant source data worksheets at their site are securely retained for at least 25 years after the end of the trial. The end

of the trial is defined in section 13. No documents will be destroyed without prior approval from the Sponsor.

The Trial Master File and trial documents held by NCTU on behalf of the sponsor shall be archived at secure archive facilities deemed appropriate for research data archive by the University of Nottingham. All trial databases and associated meta-data encryption codes will be appropriately archived and the details documented within NCTU.

Documents will be archived following any regulatory requirements and any local procedures. No documents will be destroyed without prior approval from the Sponsor.

11.5. Data sharing

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Participants' contact details, including name, address, telephone/mobile number and email will be shared between participating sites and NCTU for the purposes of follow up, issuing questionnaires and electronic reminders (text/email) for the trial. The University of Nottingham's approved provided of SMS texting services eSendex (https://www.esendex.co.uk/) will be used to message participants. This means that participants mobile numbers will be shared with eSendex via a secure data transfer in order to run the service, and all appropriate security steps are taken to ensure the confidentiality and protection of the data in their care. Participants have an optional consent to have there information held by essendex in order to be contacted via text message.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files.

Data generated as a result of this trial will be available for inspection on request by the sponsor local R&D departments and the NCTU.

Anonymised participant data may be shared with researchers external to the trial research team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the NCTU.

12. Quality control and quality assurance

12.1. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current curriculum vitae (CV) to the NCTU. All members of the site research team will also be required to be entered onto a site delegation log signed by the individual staff member and the Principal

Investigator. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed appropriate GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The NCTU must be informed immediately of any change in the site research team.

12.2. Monitoring

12.2.1. On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Any on site monitoring activities will be reported to the Sponsor and any issues noted will be followed up to resolution. On-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, lower than expected SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, the NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the TB-DILI trial staff access to source documents as requested.

12.2.2. Central Monitoring

The NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming eCRF data against the criteria for monitoring outlines in the monitoring plan. Sites will be requested to send in copies of signed ICFs and other documentation for internal review a predefined number of participants. All details of proposed central monitoring will be detailed in the monitoring plan.

12.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify the Trials Office of any MHRA inspections. The trial will be subject to internal audit (system and trial level) on a risk basis.

The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

12.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments) the Sponsor of the trial is responsible for the oversight of notification to the licensing authority of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. It is the responsibility of NCTU to notify the licensing authority, in writing within 7 days of becoming aware of a breach and confirm this has been communicated with the Sponsor.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify the NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the NCTU is investigating whether or not a

serious breach has occurred sites are also requested to cooperate in providing sufficient information to report the breach to the MHRA and REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the trial oversight committees (Trial Management Group, Trial Steering Committee, DMC), the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

13. End of Trial Definition

The end of trial will be the date of final database lock. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the NCTU will inform the MHRA and REC within 15 days of the end of trial and provide them with a summary of the clinical trial report within 12 months of the end of trial.

14. Statistical Considerations

14.1.1. Power Calculations / sample size calculation

Assuming 10% of participants in the 4-drug group and 1.5% in the 3-drug group experience DILI recurrence, then a recruited sample size of 175 per arm would provide 90% power to detect this difference (with a two-sided type-I error of 5%), allowing for up to 10% non-collection of primary outcome data due to loss-to-follow-up and mortality giving 157 per arm for analysis$_{2,3}$. This calculation is based on a two-sided Z-Test with pooled variance.

Table 5 describes the smallest detectable absolute difference in proportions for a trial randomising 175 participants per group with varying rates of loss to follow-up, with a power of either 80% or 90% (and a two-sided type-I error of 5%), and assuming various rates of DILI recurrence.

Table 5: Smallest detectable absolute reduction in risk for a trial randomising 175 participants per group with varying rates of loss to follow-up (LTFU) and assuming various proportions of DILI recurrence.

Loss to follow-up	Effective sample size per group	Power (%)	Percentage of DILI recurrence in 4-drug group (%)				
			10	**15**	**20**	**25**	**30**
10%	157	80	7.6	9.6	11.1	12.3	13.3
		90	8.5	10.7	12.5	14.0	15.2
5%	166	80	7.4	9.3	10.8	12.0	13.0
		90	8.3	10.5	12.2	13.6	14.8
None	175	80	7.3	9.1	10.6	11.7	12.7
		90	8.1	10.3	12.0	13.3	14.5

14.2. Analysis of Outcome Measures

14.2.1. Planned Interim Analysis

No formal interim analyses are planned. However, an internal pilot has been built into the trial to allow a feasibility assessment which will examine recruitment and retention. This will be continually monitored, and a formal review will take place 18 months after the first participant has been randomised. Recruitment will be measured against the overall recruitment target at 18 months. To assess retention in the maximum number of participants at 18 months, retention is defined as the proportion of participants for whom the primary outcome is evaluable a) at 12 months for participants recruited within the first six months, b) at end of treatment for subsequent recruits.

Table 6: Internal pilot progression criteria.

	Black (stop the study)	**Red (proceed with recovery plan)**	**Amber (proceed with changes)**	**Green (proceed)**
% Threshold				
Trial recruitment	<50%	50 – 79%	80- 99%	≥100%
Recruitment rate (site/month)	<0.12	≥0.12 - ≤0.18	≥0.18 – <0.23	≥0.23
Retention (primary outcome obtained)	<50%	50-79%	80 – 99%	≥100%
Adherence*	<50%	50-74%	75-89%	≥90%

*Adherence defined in section 7.5.2.

14.2.2. Planned Final Analyses

The analysis and reporting of the trial will be in accordance with CONSORT guidelines, with the primary comparative analyses being conducted according to randomised allocation with due emphasis on confidence intervals for between-arm comparisons. A full statistical analysis plan will be developed prior to unblinding the trial statistician.

Descriptive statistics of demographic and clinical measures will be used to assess balance between the randomised arms at baseline, but no formal statistical comparisons will be made. Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages.

The primary comparative analysis will employ generalised linear mixed effects regression modelling to compare the proportion with a DILI recurrence at 12 months in each group, adjusting for minimisation variables. The comparison will be presented as both an absolute (risk difference) and relative (risk ratio) effect, along with 95% confidence intervals. Secondary outcomes will be analysed using appropriate mixed effects regression models dependent on data type (binary, continuous, survival etc.), adjusting for minimisation variables.

The primary approach to between-group comparative analyses will be by intention-to-treat, that is including all participants according to randomised allocation regardless of adherence. Participants

who complete treatment without DILI recurrence will be assumed to not meet the primary outcome (i.e., no recurrence of DILI), unless there is evidence to the contrary. All available evidence indicates the risk of ATT-DILI following cessation of drugs can be assumed as zero (no published reports known). Using this approach, we expect there to be very little missing primary outcome data but will use multiple imputation if required so that all randomised participants may be included in the primary analysis.

14.2.3. Planned Subgroup Analyses

Appropriate interaction terms will be included in the primary regression analyses in order to conduct subgroup analyses according to DILI severity.

Between-group treatment effects will be provided for each subgroup, but interpretation of any subgroup effects will be based on the treatment-subgroup interaction and 95% confidence interval, estimated by fitting an appropriate interaction term in the regression models. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses will be regarded as exploratory.

15. Health Economics

Quality of Life will be measured using an online questionnaire to collect EQ-5D-5L data, with patients prompted by email / text message, and/or telephone. Patients who cannot use the online system will provide information by telephone

Quality of Life will be measured at 5 junctures for all participants: i) during initial DILI, ii) after DILI recovery prior to start of ATT, iii) 2 weeks after starting ATT, iv) one week after the end of ATT and v) at 12 months post-randomisation (the primary outcome). Participants with a DILI recurrence will have 2 additional measurements, vi) during DILI recurrence and vii) after recovery from DILI recurrence when on ATT. This is to enable assessment of the QoL impact of initial DILI (against a background of QoL detriment due to active TB and ATT, comparing i and ii), recurrent DILI (comparing vi and vii), TB disease under treatment (comparing ii and iii), and ATT (comparing iii and iv, and iii and v). The two arms of the trial will be compared using measurements i and v.

To enable healthcare resource costs to be calculated based on staff costs (determined by time and grade), drugs costs (from the British National Formulary), and costs of tests (NHS tariffs), we will record information on health services used by participants relevant to TB care during treatment and follow-up. This will include clinic visits, home visits, additional drugs used, and additional clinical resources required to manage recovery from DILI (e.g. ICU care). Relevance of services used to TB care will be determined by the attending TB team.

16. Trial Organisational Structure

16.1. Sponsor

Nottingham University Hospitals NHS Trust will undertake the role of Sponsor as defined by the UK Policy Framework for Health and Social Care Research. Delegated responsibilities will be assigned to the Chief Investigator, participating NHS Trusts and Nottingham Clinical Trials Unit.

16.2. Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU).

16.3. Trial Management Group

The TMG will be responsible for the day-to-day management of the trial. Membership includes (but is not limited to) the CI, Deputy Chief Investigator, Trial Manager, Trial Statistician and other members of the NCTU multidisciplinary team as appropriate. The TMG will ensure high quality trial conduct, to time and within budget, monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will also be responsible for ensuring project milestones are achieved. The TMG will meet regularly during the entire course of the trial.

16.4. Trial Steering Committee (TSC)

A TSC will be established which includes an independent chair, independent and non-independent members and patient representatives. The role of the TSC is to provide oversight of the trial. A meeting will take place 6 months and 18 months after the first participant is recruited with all meetings thereafter taking place approximately every six months during the recruitment phase of the trial.

TSC members will be asked to sign the TB-DILI TSC Charter which will outline their roles and responsibilities. The TSC will consider and act, as appropriate, upon the recommendations of the DMC, and in accordance with the TSC Charter, and ultimately carries the responsibility for deciding whether the trial needs to be stopped on the grounds of safety or efficacy.

The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC).

16.5. Data Monitoring Committee

Reports will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

During the recruitment phase of the trial, the DMC is scheduled to meet 6 months and 18 months after the recruitment of the first participant and annually thereafter.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC who will convey the findings of the DMC as appropriate (e.g. MHRA, funder, and/or Sponsor).

At the first DMC meeting, the committee will be presented with the data required to assess the stop-go criteria for the internal pilot phase of the trial (see section 14.2.1). The DMC and TSC will review the data against the stop-go criteria and advise whether the trial should continue, outlining any concerns/modifications required for continuation (if applicable).

16.6. Finance

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (funder reference: 12/95/15).

17. Ethical Considerations

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2018, the applicable UK Statutory Instruments, which include the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, the Data Protection Act 2018, The Human Tissue Act 2008 and Human Tissue (Scotland) Act 2006 (if applicable) and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use (Clinical Trials) regulations. The protocol will be submitted to and approved by the MHRA and REC prior to circulation.

18. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using their initials and unique trial identification number on the eCRF and correspondence between the NCTU and the participating site.

Participants will give their explicit consent for a copy of their ICF to be shared with the NCTU. This will be accessible via the trial randomisation system and will be used by the NCTU to monitor the consent process.

The Investigator must maintain documents not for submission to the NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The NCTU will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. competent authority, Sponsor). Representatives of the NCTU and Sponsor may be required to have access to a participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

19. Insurance and Indemnity

Nottingham University Hospitals NHS Trust will act as Sponsor for the trial. Delegated responsibilities will be assigned to the NHS Trusts taking part and NCTU.

Insurance and indemnity for trial participants and NHS trial staff are covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48. There are no special compensation arrangements, but trial participants may have recourse to the NHS complaints procedure.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

The Nottingham University Hospitals NHS Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20. **Publication Policy**

The dissemination of the proposed research findings will be via a published NIHR HTA monograph, research papers for publication in peer reviewed journals, presentation at medical conferences and communication of our findings to groups involved in guideline development.

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Chief Investigator and Trial Management Group and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator and NCTU. Manuscripts must be submitted to either party in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the Nottingham University Hospitals NHS Trust.

During the course of the trial, press releases may be issued from NCTU. Presentations or other material prepared by local investigators to publicise the trial must be reviewed by the Chief Investigator and NCTU. No party will be entitled to submit any publicity material without prior approval from NCTU.

Trial participants will be asked whether or not they would like to receive a summary of the research findings and invited to leave contact details by which they will be contacted with the research summary at the end of the project, following the publication of results.

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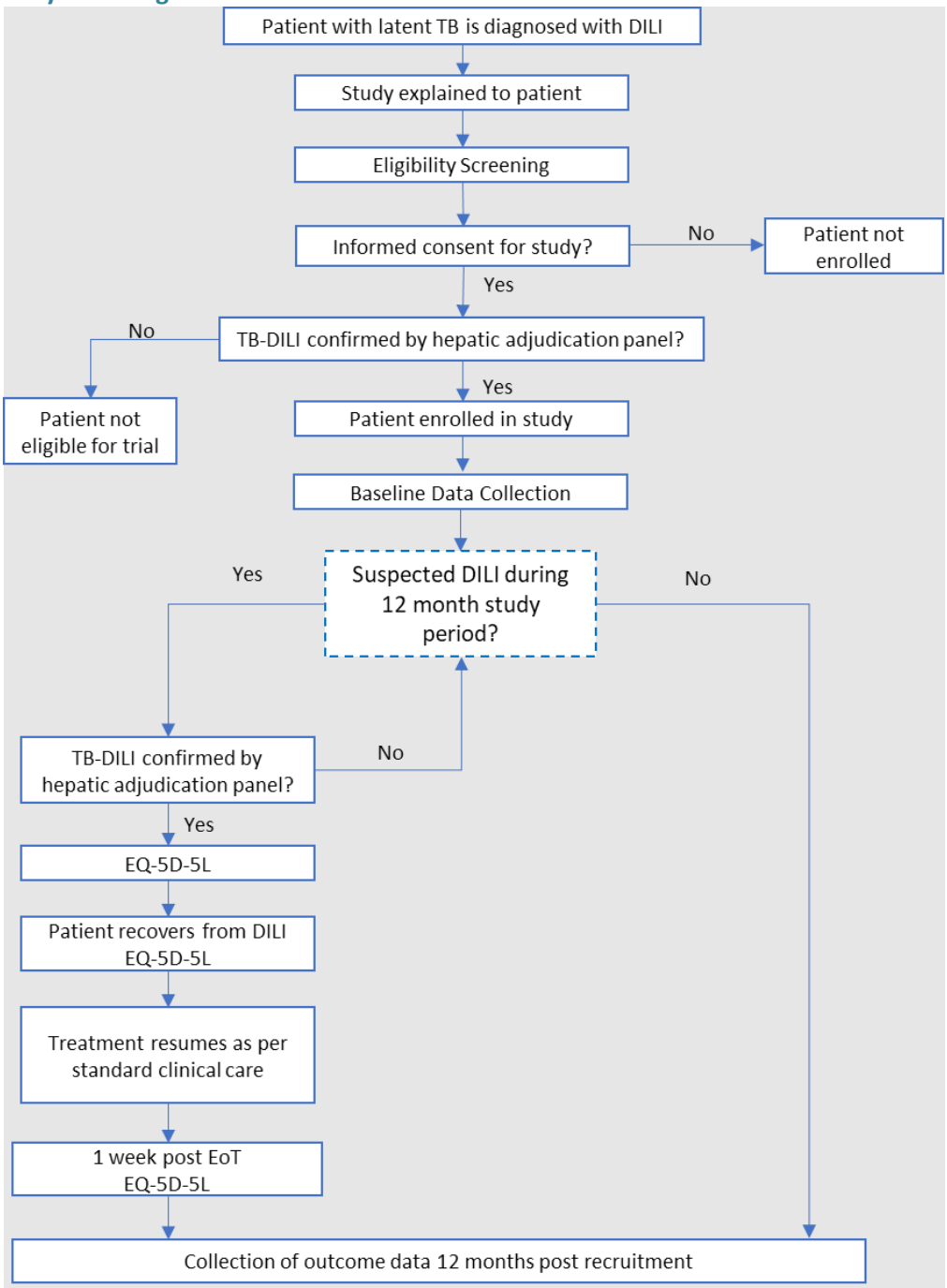
Appendices

Appendix A: Prospective cohort study: Patients with latent TB infection (LTBI)

Patients with LTBI who develop DILI while on anti-LTBI drugs comprise a separate target population. They will be approached to participate in a prospective observational cohort study.

Cohort study flow diagram



Aim

The aim of this cohort study will be to 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. (Based on an estimate of 1.5% DILI recurrence, 1300 participants would be required to determine two independent risk factors for DILI recurrence).

Primary outcome

- DILI recurrence at end of treatment

Secondary outcome

Measured at EOT:

- severity of DILI recurrence,
- total number of days on anti-LTBI drugs,
- adverse event rate,
- quality of Life using EQ-5D-5L and healthcare resource use.

If possible, we will determine independent risk factors for DILI recurrence.

Eligibility 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.

Attending clinicians will have full discretion regarding whether or not to reintroduce anti-LTBI drugs post-DILI, and if so, which regimen to use. We will suggest the same LFT monitoring schedule post-DILI is followed as for the main trial; this schedule mirrors standard clinical practice.

Outcome measures

The primary outcome (DILI recurrence) is an important clinical event that will be evident to the TB team, results of which will be obtained from the medical notes. EQ-5D-5L measurements will be taken at 3 junctures: i) DILI occurrence, ii) DILI recovery, iii) 1 week post-EOT. At each DILI recurrence, EQ-5D-5L will be measured during DILI and upon recovery.

The following parts of the cohort study will be conducted the same as the main trial:

- Screening and consent – section 5
- Trial treatment intervention – section 7
- Adverse event reporting – section 9
- Data handling and record keeping section 10

Sample size and expected recruitment

Annually, of 15,000 patients treated for LTBI in the UK, and based on a DILI occurrence of 1.5%, we may be able to recruit up to 75 participants (33% of eligible patients) per year, but estimates

are highly indeterminate. We propose a pilot phase of 18 months. If pilot data confirm very low DILI occurrence and recurrence, further recruitment may not be justified.

Based on an estimate of 1.5% DILI recurrence, 1300 participants would be required to determine two independent risk factors for DILI recurrence.

Statistical analysis

Descriptive statistics of demographic and clinical measures will be used to describe the characteristics of participants upon entry to the cohort study. The following outcomes at 12 months will be described descriptively with 95% confidence intervals where appropriate:

a) DILI recurrence,
b) severity of DILI recurrence,
c) total number of days on anti-LTBI drugs,
d) adverse event rate,
e) quality of Life using EQ-5D and healthcare resource use.

Descriptive statistics of baseline characteristics and DILI severity will be presented for participants with and without a DILI recurrence during the follow-up period. If feasible, an exploratory analysis will employ logistic regression modelling to identify potential candidate risk factors for DILI recurrence.