Study protocol

Full title

Human Immune Response Variation in Tuberculosis

Short title

HIRV-TB

Chief Investigator and affiliations

Dr Mahdad Noursadeghi, PhD FRCP

Univeristy College London Division of Infection and Immunity,

Cruciform Building, Gower Street, London WC1E 6BT

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(delete as applicable)

Protocol version number and date

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R&D / Sponsor Reference Number(s)

18/0055

IRAS Registration Number:

242062

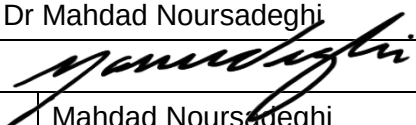
Protocol versions

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Final	2	14/09/2018	Dr Rishi Gupta (Clinical Research Fellow)	Substantial amendment

Declarations

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

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

Chief Investigator: Dr Mahdad Noursadeghi			
Signature: 		Date:	14/09/2018
Print Name(in full):	Mahdad Noursadeghi		
Position:	Senior Lecturer in Infection and Immunity Honorary Consultant in Infectious Diseases		

On behalf of the Study Sponsor:			
Signature: 		Date:	25/9/2018
Print Name(in full):	Pushpsen Joshi		
Position:	Research Governance Manager		

Summary information

IRAS Number	242062
REC Reference No	18/LO/0680
Sponsor Reference No	R&D 18-0005

Full (Scientific) title	Human Immune Response Variation in Tuberculosis	
Health condition(s) or problem(s) studied	Tuberculosis	
Study Type	Observational longitudinal and cross-sectional study	
Target sample size	1000	
Study Duration/length	5 years	
Expected Start Date	1st June 2018	
End of Study definition and anticipated date	31st May 2023	
Data and sample storage	Human tissue samples	UCL Division of Infection and Immunity, under custodianship of chief investigator
	Data collected / Storage	UCL Division of Infection and Immunity, under custodianship of chief investigator
Funding body	Wellcome Trust	
Grant number	207511/Z/17/Z	
Funding body	NIHR	
Grant number	DRF-2018-11-ST2-004	

Chief Investigator	Dr Mahdad Noursadeghi, University College London Division of Infection and Immunity, Crucifrom Building, Gower Street, London WC1E 6BT. Telephone: 0203 108 2128, Email: m.noursadeghi@ucl.ac.uk.
Study coordinator	Ms Zandile Maseko, Research Nurse, University College London Division of Infection and Immunity, 2BMaple House, 149 Tottenham Court Road, London Wc1T 7NF, Email:z.maseko@ucl.ac.uk

Key words

Tuberculosis; single nucleotide polymorphisms; tuberculin skin test.

List of abbreviations

Commonly used abbreviations – add or delete as applicable

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
GAfREC	Governance Arrangement for NHS Research Ethics
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IPR	Intellectual property rights
MD	Medical Device
ISRCTN	International Standard Randomised Controlled Studies Number
PI	Principle Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Clinical Study
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File
UCL	University College London
UIN	Unique Identification Number

Contents

1. Introduction

Mycobacterium tuberculosis (Mtb) remains a major threat to global health, causing 10 million new cases of active tuberculosis (TB) disease and 1.8 million deaths per year[1]. The prevalence of immunological memory for Mtb, detected by the tuberculin skin test (TST) or by interferon (IFN)γ release assays (IGRA), indicates that many more people experience asymptomatic or latent TB infection (LTBI). Of these, 10% go on to develop active TB[2–5]. In the remainder, successful host defence is primarily thought to be mediated by macrophage control of Mtb replication, augmented by IFNγ in T helper (Th)1 responses. The importance of immune defence is further highlighted by Mendelian Susceptibility to Mycobacterial Disease (MSMD) due to inherited deficiencies of IFNγ-associated signalling[6,7], and by increased risk of active TB associated with HIV infection[8] or anti-TNF therapy[9]. Yet, most individuals with active TB have none of these risks, indicating that other variations in immune responses determine outcomes in the majority.

The limitations in our understanding of immune protection against Mtb are a fundamental hurdle to identifying an individual's risk of active disease, and to harnessing the immune system to prevent or treat Mtb infection. On health economic grounds, systematic programs aim to prevent active TB by drug treatment of LTBI, 90% of whom do not need treatment because they will never develop disease[10,11]. There has been no improvement on the modest efficacy of BCG vaccination[12], and treatment of Mtb infection requires prolonged antimicrobial drugs, increasingly compromised by Mtb drug resistance[13]. Greater understanding of the immune mechanisms that determine the clinical outcome of Mtb infection is a global research priority. These will allow us to target preventative measures at those with the highest risk of active disease. In addition, they will focus attention on immune responses that could be modulated to enhance vaccine efficacy, and to develop host directed therapies in order to reduce the duration of antimicrobial treatment for TB or to mitigate against increasing drug resistance[14–17].

2. Background and rationale

TB disease arises from stochasticity in multivariate immune responses such that variation of any one of many components can tip the balance towards immunological protection or pathogenesis. Genome-wide transcriptional profiling of biopsies from the site of tuberculin skin test (TST) provides comprehensive molecular and systems level assessments of in vivo human immune responses to a standardised mycobacterial challenge, at the site of host-pathogen interactions[20,21]. This approach allows quantitation of cell-type specific recruitment, Mtb specific innate immune responses and the biological activity of specific cytokines in response to the TST[20,22,23], and has been shown to represent variations in molecular pathology at the site of active disease in human TB[20].

Transcriptional profiling of TST biopsies in LTBI patients with longitudinal follow up to identify immune response correlates of subsequent progression to active TB. This approach necessitates the ability to exclude active TB in patients at the time of TST challenge, to safely defer LTBI treatment, and to accurately identify individuals progressing to active TB before the onset of clinical disease. Blood transcriptomic biomarkers achieve these aims. They have been shown to accurately discriminate active pulmonary and extrapulmonary TB from LTBI or other infectious diseases[24]. Blood transcriptomic changes can also predate diagnosis of active disease[25]. Unpublished data has also shown that blood transcriptional signatures can identify patients who develop symptomatic active TB within 3 months, with positive and negative predictive values of 0.99-1 assuming cumulative 5% pre-test probability of progression to active disease in cohorts of TB contacts[10,26].

Twin studies indicate that the risk of active TB has a host genetic component. Candidate gene association studies focussing on innate immune responses have reported putative TB susceptibility loci[40–49]. Given the complexity of integrated innate and adaptive cell-mediated immunolgical systems, these studies do not offer the comprehensive approach required to identify the constellation of genetic polymorphisms that may affect TB risk. Conventional genome-wide association studies (GWAS) of active TB have not replicated the findings of candidate gene studies and generally lacked sufficient power[50–55]. Expression quantitative trait loci (eQTL) studies, in which genome-wide single nucleotide polymorphisms (SNPs) are associated with quantitative differences in transcriptional responses to a stimulus offer substantially greater power to identify the genetic correlates of variation in immune responses[56–59]. They also provide the fundamental advantage of directly

identifying the functional impact of genetic polymorphisms on both specific molecules and molecular pathways. An eQTL study of TST transcriptional responses offer an important opportunity to identify the genetic correlates of variation in anti-Mtb immune responses.

3. Objectives

3.1. Primary Objective

- Identification of TST immune responses that are associated with increased the risk of active TB.

3.2. Secondary Objectives

- Identification of host-genetic polymorphisms associated with transcriptional variation in the TST.
- In vitro functional validation of eQTL associations and investigation of how they impact on Mtb growth in macrophages.
- To test whether expression of a whole blood transcriptional biomarker for subclinical TB resolves with LTBI therapy (LTBI treatment sub-study).

4. Study design

This is an observational study incorporating longitudinal cohort and cross-sectional components. 400 participants will be recruited to the longitudinal cohort with two year follow up, to identify TST immune responses that increase the risk of active TB (primary objective). Cross-sectional analysis of data from these 400 participants will be combined together with the data obtained from an additional 600 participants, giving a sample size of 1000 recruited over four years in total, to identify host-genetic polymorphisms associated with transcriptional variation in the TST. In vitro functional validation of eQTL associations and investigation of how they impact on Mtb growth in macrophages will be conducted in peripheral blood cells collected from selected participants. Finally, a subset (n=80) of these 1,000 participants who express a blood transcriptional biomarker for subclinical TB will be enrolled in a parallel cohort study, to test whether resolution of biomarker expression is expedited by LTBI therapy. These individuals will be offered treatment for LTBI as per national guidance, but we know that only approximately 40-60% accept this treatment. All patients will be followed up with interval blood sampling. Expression of the 3 gene biomarker will be compared at 4, 8, 12 and 24 weeks between individuals who accept and decline treatment.

5. Study schedule

The longitudinal study will recruit individuals with LTBI from the existing UK contact screening program[11,27]. The additional individuals for the cross-sectional study will be recruited from the Public Health New migrant screening program referrals to LTBI clinics. Clinical staff at each participating site (Appendix 1) will introduce potentially eligible individuals (Section 7) to the study team, who will seek to obtain informed written consent (see Section 6). The study schedule for participants who give consent is summarised in Appendix 2. They will undergo a chest radiograph (provided by the routine NHS Trust clinical service) and screening blood tests (Appendix 3) and, followed by one tuberculin skin test in each arm. One TST site will biopsied at 48 hours and the second TST site will be biopsied at seven days (Appendix 4). All blood tests, chest radiography, TSTs and biopsies will be performed within the TB clinic the participant was recruited from.

Participants who have a positive blood transcriptional biomarker will then enter the LTBI treatment sub-study. In the absence of clinical evidence of active TB, they will be offered LTBI therapy as part of their usual NHS care, and asked to attend appointments after 4, 8, 12 and 24 weeks for clinical review and repeat blood sampling (the 4, 8 and 12 week time points are aligned with those required in routine clinical care for monitoring). Adherence to LTBI therapy will be measured by self-report questionnaire, pill counts, urine testing and/or medication boxes, depending on local site availability and practice.

Participants with a negative blood transcriptional biomarker and who meet the eligibility criteria for the longitudinal study will be asked to attend follow up clinic appointments with the study team at three monthly intervals for two years. These additional appointments will take place at the TB clinic the participant was recruited from. At each appointment they will complete a questionnaire (Appendix 5), undergo blood sampling

and a chest radiograph. Participants can withdraw at any time without giving a reason. Participants will also be consented for recall by selected genotype or phenotype to obtain additional peripheral blood samples within the five-year lifetime of this study for in vitro mechanistic studies (see secondary objectives).

Participants who request to withdraw from the study or are lost to follow up will be referred back to the routine clinical service by the study team. Participants who develop a positive blood transcriptional biomarker at any point during longitudinal follow-up will then enter the LTBI treatment sub-study. Participants who develop a positive blood transcriptional biomarker or reach a study end point (Appendix 6) as a surrogate for progressive TB before 2 years, will be identified as progressors. Participants who complete 2 years follow up will be identified as non-progressors. Progressors and non-progressors will undergo routine clinical assessments to evaluate the need for any TB treatment when their participation in the study ends.

6. Recruitment and consent

Potential participants who meet the eligibility criteria will be identified by the routine tuberculosis clinical service and introduced to the study team. The study team will describe the study to these individuals, provide them with the participant information sheet, and answer their questions, in person, by telephone, by post or by email according to the participant's preferences. After at least 24 hours to consider this information, the study team will invite those who agree to participate to provide written informed consent.

For non-English speakers the study team will communicate with telephone translation services and provide translations of the participant information sheet and consent form. The original signed consent form will be filed in the study master file and a copy will be provided to the participant. All participants who are referred to the study team will be entered into a screening log with a record of their eligibility criteria, their decision to participate or reasons for declining to participate as appropriate.

7. Eligibility criteria

7.1. Inclusion Criteria

- Peripheral blood IGRA positive
- Contact of new case of pulmonary tuberculosis (for longitudinal study only)

7.2. Exclusion Criteria

- Age <18 or >60 years
- Unable to give written consent
- Clinical or radiographic features of active tuberculosis
- HIV-1 infection
- Active hepatitis B or C infection
- Pregnancy
- History of autoimmune disease
- History of skin disease
- History of malignancy
- Immunomodulatory drugs (Appendix 6)
- History of allergy to local anaesthetics
- History of keloid scarring

8. Clinical governance and indemnity

The risks for participants in the present study are summarised in Appendix 8.

Participants' General Practitioners will be notified of their patient's involvement in this study, subject to written informed consent by the patient.

All participants will be contacted 1 week after their final visit to check that the TST biopsy wounds have healed as expected. Where necessary, participants will be offered a further appointment for clinical review of the biopsy sites and to instigate appropriate clinical management under the supervision of the Chief Investigator.

Any participants who develop evidence of active tuberculosis will be referred for urgent review by routine clinical TB services.

All adverse events will be recorded as described in Appendix 9. All complaints and adverse events will be reported immediately to the sponsor by email (research-incidents@ucl.ac.uk) and using the on line incident reporting form (https://opinio.ucl.ac.uk/s?s=17671). If the adverse event takes place within a UCLH Trust site, the event will be reported through the Trust incident reporting system (Datix). Annual progress reports will be submitted to the Research Ethics Committee.

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

9. Statistical methods

9.1. Sample size and statistical power

We will recruit 400 LTBI contacts of active pulmonary TB cases to address the primary objective. This sample size is derived from estimated progression from LTBI to active TB within 2 years of 5%, giving 20 progressors and 380 non-progressors. Progressive disease may be due to a range of different immune responses, and each variation may only be evident in a subset of cases. Therefore, conventional differential gene expression analysis in the TST between groups of progressors and non-progressors, may not identify statistically significant differences. Instead, we will undertake supervised outlier profile analysis to identify gene expression among subsets of progressors, which lies outside the normal range measured in non-progressors. These methods provide robust statistical confidence by incorporating multiple testing corrections[32–36], and have been successfully applied to discovery of novel oncogenic pathways[32,37]. Using preliminary TST transcriptomic data from HIV negative individuals in computational simulations, we estimate >0.8 statistical power in this sample size to detect significant outlier traits among progressors (false discovery rate <0.05) when the outlier trait is shared by 5 or more progressors (Figure 2A). In order to identify eQTLs of TST transcriptomic data, we estimate that a sample size of 1000 is required to give >90% power to detect statistically significant correlations ($p<10^{-8}$) for allelic frequencies ≥5% depending on the correlation coefficients, as a composite measure of effect size and variance[61]. Finally, from our pilot data, we estimate that 15% of these individuals will express the blood transcriptional biomarker at time of recruitment to the study. Of these estimated 150 participants, 80 will be recruited to the LTBI treatment sub-study. Conservatively assuming that only 25% of patients decline LTBI therapy, a sample size of 68 participants will provide 80% power to detect a difference of 0.8 standard deviations (SDs) in signature scores between those who accept and decline treatment at each time point. This calculation assumes similar standard deviations among individuals in both groups. We have estimated 0.8SDs as the minimum difference in signature scores that is likely to be of clinical significance (based on the difference in mean scores between IGRA-positive and IGRA-negative TB case-contacts in our pilot data. To allow for losses to follow-up, 80 participants will be recruited.

9.2. Experimental approaches and data analysis

Bioinformatic pathway enrichment analysis of outlier gene expression amongst all progressors will be used to identify common immune correlates of risk of progression to active TB at the systems level. To complement this approach, we will also reduce the dimensions of data in the TST transcriptome of all non-progressors, from individual genes into co-correlated clusters as a surrogate for immune networks[38]. We will compare the expression of each cluster to identify statistically significant differences between progressors and non-progressors. We will then undertake pathway analysis of each differentially expressed cluster to identify the immune pathways that may influence risk of progression to active TB. Data from participants in the cross-sectional study, and those in the longitudinal study who withdraw from the study or are lost to follow up before completing 2 years follow up will be included by identifying any progressors amongst these groups by linkage to national TB surveillance records, held at Public Health England.

All 1000 participants undergoing TST transcriptional profiling will be genotyped for >1.7 million genome wide SNPs using the Illumina Infinium Multi-Ethnic Global-8 array, with additional imputation of >4 million SNPs to allow fine mapping of associations. Statistically significant SNP associations with quantitative variation in the TST transcriptome will be identified as previously described[57]. Iterative eQTL analyses will be performed in year 3 after the first 400 recruits, in year 4 after 750 recruits and in year 5, using data from all 1000 individuals. In addition, we will assess whether any eQTLs are associated with immune response variation that correlate with progression to active TB, thereby identifying potential genotypic susceptibility loci via their association with a functional impact on anti-Mtb immune responses. Where possible, we will assess whether the eQTLs identified in the present study represent significant susceptibility loci for active TB using a targeted (statistically more powerful) analysis approach to re-examine previously published GWAS data. In order to make maximum use of the novel data, we will also identify eQTLs which coincide with loci associated with any phenotypic/disease traits in GWAS catalogues (www.genome.gov/gwastudies/), thereby offering novel mechanistic insights into the associations.

For in vitro mechanistic studies participants will be selected for recall by genotype (5-10 per group) to obtain peripheral blood T cells, monocytes and monocyte derived macrophages (MDM). SNP genotypes will be selected, which are associated with variations in TST response that do not correlate with IFNγ and are implicated in macrophage control of Mtb growth. We will prioritise the most tractable responses involved in cell-mediated Mtb killing mechanisms, and pathways that may affect macrophage viability. Selected cell types will be stimulated with live Mtb or Mtb-derived antigens to validate the eQTL associations by quantitative PCR and to establish the cell-type specificity of these associations. Where eQTL data suggest novel molecular interactions, we will test the predicted interaction in cells from subjects with the relevant genotypes, using lentiviral vectors to overexpress specific genes or small molecule and antibody blocking reagents as appropriate. To complement this approach, we will use CRISPR editing to reproduce genetic variants of interest in model cell lines. Finally, we will assess bacterial growth in MDM cultures, using flow cytometric quantitation of intra and extracellular Mtb. We will test Mtb growth in MDM cultures ±selected T cell subtypes using cells from subjects with targeted genotypes.

10. Patient and public involvement (PPI)

All project staff will undergo UCL training in Public Engagement (www.ucl.ac.uk/publicengagement/training). We will take advantage of an established lay patient panel within the UCLH/UCL Biomedical Research Centre to preview and feedback on all patient information sheets and recruitment strategies. We will liaise with the UCL Public Engagement Unit (www.ucl.ac.uk/publicengagement) to describe our research to the general public and patients. We will specifically target those attending TB clinical services and migrant communities involved in the new migrant screening programme in collaboration with Public Health England, ensuring that information is presented in the range of appropriate languages. To do so, we will offer annual educational meetings for interested groups to provide information on research developments in tuberculosis and address their questions. We will optimise the value of these events using established UCL toolkits for planning and evaluation (www.ucl.ac.uk/publicengagement/evaluation/toolkits). In addition, we will take advantage of UCL resources such as the iTunes online lecture facility to broadcast seminars and lectures to a varied audience. For valuable research findings that may be of interest to the wider public including patient communities, commercial clinical services or government policy makers, we will liaise with the UCL Media Office at the time of publication to maximize opportunities for media coverage and ensure timely press releases. In line with Wellcome Trust open access policies, we will make all scientific publications derived from this project freely available by submission to Pubmed Central and the UCL Research Publications Service at the time of publication.

11. Sample management

All samples will be collected from patients in accordance with the patient consent form and patient information sheet and shall include all tissue samples or other biological materials and any derivatives, portions, progeny or improvements as well as all patient information and documentation supplied in relation to them. Samples will be processed, stored and disposed in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter.

All research samples will be labelled with the UIN at the point of collection. All research sample collection, transportation storage and processing will be performed by designated staff under the supervision of the Chief Investigator. Designated project staff will transport research samples (by road or rail in UN approved category B triple layered packaging) from the TB clinics on the day of collection to designated secure restricted access laboratories within the UCL Division of Infection and Immunity for storage or processing by designated laboratory staff. The collection, transfer, storage location and processing events related to each research sample will be recorded in a password protected electronic sample log. Any transfer of samples to other UK or non-UK research institutions, for additional analyses related to the present study will be subject to a material transfer agreement in which the new user will be responsible for restricting use of the data to agreed purposes, maintenance of confidentiality and data security, reporting publications and other outputs to the Chief Investigator of this study and restricting onward transfer of samples to a third party.

12. Data management

12.1. Data outputs

A case record form (CRF, Appendix 10) will be completed for each study participant. The CRF will be the only document with participant identifiable data. The CRF's will be kept in the study master file which will be stored in secure UCL offices with restricted access under the custodianship of the Chief Investigator. All study data will be linked to the participant UIN only without any participant identifiers. This project will generate 1000 genome-wide transcriptional profiles of the in vivo human immune response to the tuberculin test, using RNA sequencing at a depth of 20-30 million reads, as a model for in situ host-pathogen interactions in tuberculosis as well as a prototypic model of cell mediated immune responses in general. 1000 SNP genotype profiles will also become available from the same individuals using the most comprehensive multi-ethnic SNP array currently available. In addition a subset of 400 individuals within this cohort will generate longitudinal data on blood transcriptomic biomarkers of active TB data combined with high resolution clinical metadata. We will also seek to share anonymised linked clinical metadata. Each data set and the combination of linked data will be of exceptional value to discovery science in tuberculosis specifically and infection/immunology research more broadly, as well to the translational applications of blood transcriptional profiling. Data analysis will be conducted by designated research staff under the supervision of the chief investigator. Specific analysis will include the transfer of anonymised electronic data to designated collaborators under the terms of data transfer agreements, in which collaborating partners will be responsible for restricting use of the data to agreed purposes, maintenance of confidentiality and data security, reporting publications and other outputs to the CI of this study and restricting onward transfer of samples to a third party.

12.2. Data sharing

The data will be made available at the time of peer-reviewed publications, or by 12 months after completion of the project. Raw transcriptomic, genotyping data and linked phenotypic data will be made available through quality controlled public repositories to maximise their use by the scientific community. Specifically, European Bioinformatics Institute Array Express repository (http://www.ebi.ac.uk/arrayexpress), for genome-wide transcriptomic data, and the European Bioinformatics Institute Genome-Phenome arcive (https://www.ebi.ac.uk/ega) for genotypic and phenotypic data. Processed/analysed data sets will also be made available through supplementary on-line content associated with peer-reviewed scientific publications.

Potential users of the research data will be able to find out about our data through peer reviewed research publications, presentations at seminars or international conferences in the field of study and through institutional press releases where appropriate. Accession numbers to our data within public repositories will be provided in research papers and identifiable through conventional search facilities provided by each facility.

The terms of participant consent, restrictions resulting from intellectual property rights and prior collaborations or the lack of good quality metadata are all potential restrictions to data sharing. Specifically, we will not share ant data from which individual patients can be identified directly or through association with other data sources.

12.3. Data security and governance

We will minimise risk of deficiencies in data collection and storage. We will obtain specific consent from participants to include provision for data sharing. All electronic data will be stored in password encrypted computer facilities, maintained by information technology services within the Division of Infection & Immunity at UCL, and backed up by automated synchronisation within dedicated divisional servers with password protected access. Paper records will be kept in locked research offices within the Division of Infection & Immunity at UCL, within research buildings subject to secure electronic card or code access. All processes and events related to the projected will be logged in laboratory records, including provenance of data, their coding and detailed descriptions for variables. Personal identification information will be restricted to the study master file in hard copy and password encrypted electronic database, annotated with UIN codes to link to experimental data. Instrument metadata will be collected in curated electronic archives, annotated with relevant information for each experiment including UIN for specific experiments and study participants. All procedural and data analysis protocols (including amendments) will be stored as curated electronic files. At the end of the study, data will be fully anonymised by unlinking the UIN from identification information for each participant. Long-term storage will be undertaken in the UCL digital data repository (http://www.ucl.ac.uk/library/digital-collections) as well as the public repositories specified above.

12.4. Document archiving

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study. The CI confirms that he/she will archive the study master file through the UCL Library Records Office (http://www.ucl.ac.uk/library/about/records-office) for 25 years and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive the respective site's study documents for 25 years and in line with all relevant legal and statutory requirements.

12.5. Intellectual property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights (IPR) to UCL, and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL, execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

Intellectual property protection will be undertaken through collaboration with UCL Business (http://www.uclb.com/).

13. Funding

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by a Wellcome Trust Investigator Award to Dr Mahdad Noursadeghi (reference number: 207511/Z/17/Z)

The research costs for the LTBI treatment sub-study have been supported by an NIHR Doctoral Research Fellowship Award to Dr Rishi Gupta (reference DRF-2018-11-ST2-004).

Participant costs for extra attendances to clinic for research purposes will be met by flat rate re-imbursement of £10 per extra attendance, covered by the research funding.

14. Peer and regulatory review

The study has been peer reviewed in accordance with the requirements outlined by UCL. The sponsor considers the procedure for obtaining funding from Wellcome Trust and NIHR to be of sufficient rigour and independence to be considered an adequate peer review.

15. Monitoring and auditing

The CI will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality. The CI will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

16. Training

The CI will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files.

17. Publication and dissemination policy

The CI will be responsible for ensuring that this study conforms to sponsor (UCL) and funder (Wellcome Trust, NIHR) policies on open access publishing (http://www.ucl.ac.uk/library/open-access and https://wellcome.ac.uk/funding/managing-grant/open-access-policy. In addition, the CI will ensure that this study will conform to ICJME policy on authorship and non-author contributors for publications (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html)

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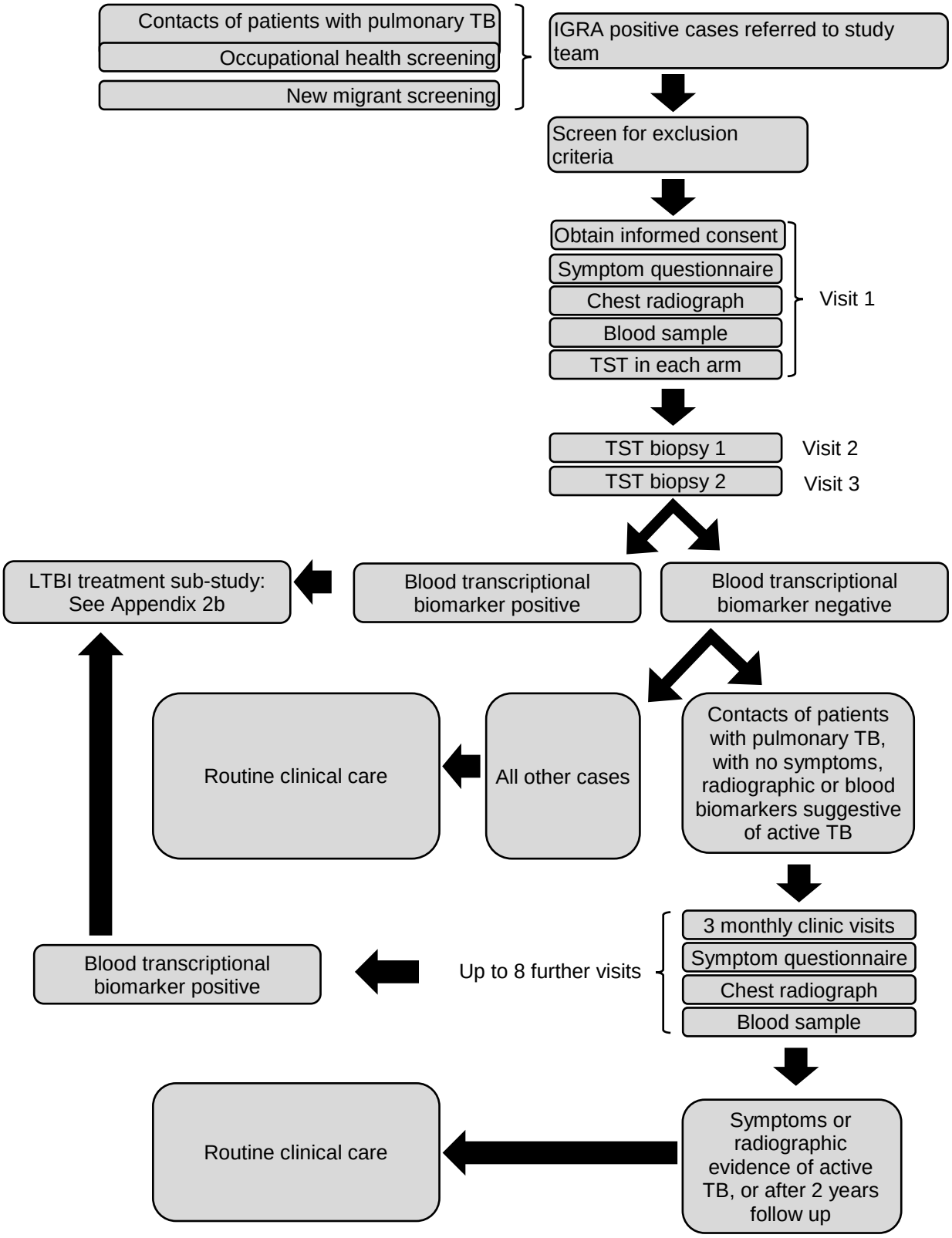
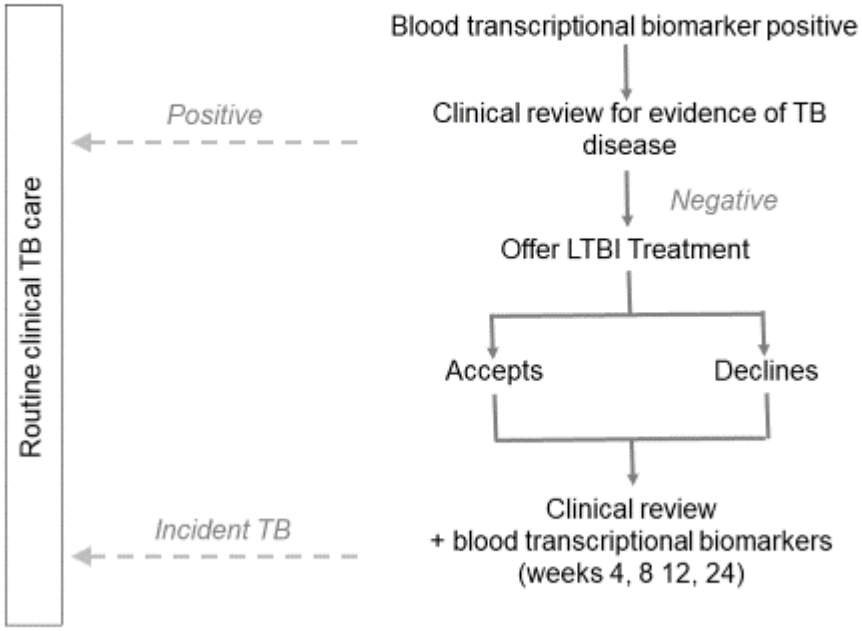
Appendix 1: Participating NHS sites

NHS Trust	Local PI	Contact details
Whittington Health Care Trust	Dr Mahdad Noursadeghi	m.noursadeghi@ucl.ac.uk
Royal Free London NHS Foundation Trust	Dr Marc Lipman	marclipman@nhs.net
North Middlesex University Hospital NHS Trust	Dr Stefan Lozewicz	s.lozewicz@nhs.net
Barts Health NHS Trust	Dr Heinke Kunst	Heinke.Kunst@bartshealth.nhs.uk
Homerton University Hospital NHS Foundation Trust	Dr Graham Bothamley	Graham.Bothamley@homerton.nhs.uk

Appendix 2a: Summary of study schedule



Appendix 2b: Summary of schedule for LTBI treatment sub-study



Appendix 3: Summary of research samples tests at each study visit

Sample		Purpose	Processed by
Blood samples			
Pre-TST only	10 mL EDTA sample for DNA	DNA genotyping	UCL study research laboratory
Pre-TST and all follow-up visits up to 2 years	2 mL serum	C-reactive protein	NHS clinical laboratory
	3 mL Tempus RNA tube	RNA profiling	UCL study research laboratory
	3 mL Quantiferon Gold Test	IGRA	UCL study research laboratory
	20 mL heparinised blood	Storage of peripheral blood mononuclear cells for mechanistic studies	UCL study research laboratory
LTBI treatment sub-study visits	2 mL serum	C-reactive protein	NHS clinical laboratory
	3 mL Tempus RNA tube	RNA profiling	UCL study research laboratory
Recall visit	Up to 120 mL heparinised blood sample	Isolation of immune cells for in vitro mechanistic studies	UCL study research laboratory
Skin biopsies			
3mm punch biopsy at one TST site		RNA profiling	UCL study research laboratory
3mm punch biopsy at second TST site		RNA profiling	UCL study research laboratory

Appendix 4: Standard operating procedure for TST and biopsies

1. **At time 0**
   - Before administration of intradermal tuberculin, take following blood samples
   - Administer 2U Mantoux (Tuberculin) by intradermal injections into volar surfaces of each forearm
   - Mark the injection site blebs with indelible ink
2. **At 48 hours**
   - Measure induration and take clinical photograph at both TST sites.
   - At one TST injection site, infiltrate the injection site with local anaesthetic (2% lignocaine) and wait for 5 minutes.
   - Perform one 3mm punch skin biopsy at the anaesthetised site and place sample into 1 mL RNALater buffer.
   - Transfer samples to research laboratory for storage- store RNA sample at -80°C
3. **At 1 week**
   - At the second TST injection site, infiltrate the injection site with local anaesthetic (2% lignocaine) and wait for 5 minutes.
   - Perform one 3mm punch skin biopsy at the anaesthetised site and place sample into 1 mL RNALater buffer.
   - Transfer samples to research laboratory for storage- store RNA sample at -80°C
4. **At 2 weeks**
   - Contact patient to ensure biopsy sites are healing well

Appendix 5: Participant symptom questionnaire

1. Have you had a persistent cough for more than two weeks?
2. Have you lost weight in the last 3 months?
3. Have you experienced any drenching night sweats during the last 3 months?

Appendix 6: Study end points

Participation in the study will end with any one of the following events and participants will go on to have routine clinical assessments to evaluate the need for LTBI or active TB treatment.

1. 2 year follow up completed
2. Changes in chest radiography (airspace shadowing or lymphadenopathy) consistent with progressive/active TB with at least one yes answer in the symptom questionnaire.
3. Two yes answers in the symptom questionnaire.

Appendix 7: Screening and consent log

Name	DOB	Eligible	Consented	Reasons for declining consent	Signed	Date

Appendix 8: Immunomodulatory drugs

Systemic corticosteroids

Azothioprine

Corticosteroids

Cycolsporin,

FK506

Methotrexate

Tacrolimus

Anti-TNF (adalimumuab, etanercept)

Appendix 9: Risks to participants

Severity score- Low=can cause discomfort but unlikely to have an impact on health, Moderate=potential impact on health but unlikely to be life-threatening, Severe=definite impact on health and significant potential to be life-threatening.

Description of risk	Estimated incident rate	Severity	Justification
Progressive active TB as a result of deferring LTBI treatment in the longitudinal study.	<1%	Moderate	The two year cumulative risk of progressive TB in individuals being recruited to this study (IGRA positive contacts of active pulmonary TB) is estimated to be 5%. In routine clinical practice LTBI treatment is commonly offered to all such individuals. On the basis that this treatment is in fact not necessary for the vast majority, clinical review at 3-6 monthly intervals is widely used as an alternative approach. In the present study, we will undertake enhanced follow up at 3 monthly intervals with the addition of novel blood biomarkers with the potential to identify subclinical active TB representing an end point in their participation, when individuals will be offered treatment in line with standard clinical care. The available data on the predictive value of these biomarkers indicates that this approach minimises the 2 year cumulative risk of the development of symptomatic TB disease <1%. On the basis subclinical active TB will not meet conventional criteria for the diagnosis of symptomatic TB disease requiring full TB treatment, we expect that most participants who develop biomarkers of subclinical TB will be offered LTBI treatment. On the basis of being IGRA positive, all participants who complete 2 year follow up will be considered for LTBI treatment as per routine clinical practice. The risk of active TB is substantially lower after 2 years follow up, therefore these participants may opt not to accept LTBI treatment.

Description of risk	Estimated incident rate	Severity	Justification
Increased radiation exposure due to repeated chest radiographs	100%	Low	Participants may have up to 8 extra chest radiographs. Each of these is equivalent to 10 days of natural background radiation exposure, associated with a negligible additional cancer risk of <0.01%. This risk is substantially outweighed by the benefits of chest radiographic monitoring for evidence of progressive TB.
Discomfort during phlebotomy	10%	Low	The overall risk of harm is very low.
Brief discomfort during local anaesthetic injection	10%	Low	The overall risk of harm is very low.
Allergic reaction to local anaesthetic (Peolple with a history of allergic reaction to local anaesthetics will be excluded)	<1%	Moderate	People with a history of allergic reaction to local anaesthetics will be excluded. The overall risk of harm is very low.
Pain at the biopsy site	5%	Low	The overall risk of harm is very low.
Bleeding at the biopsy site	<5%	Low	The overall risk of harm is very low.
Infection of the biopsy site	<1%	Moderate	The overall risk of harm is very low.
Minor residual (after 3-6 months) scarring of the biopsy site	10%	Low	People with a history of keloid scarring will be excluded. The overall risk of harm is very low.

Appendix 10: Adverse events

Definitions

Term	Definition
"Adverse Event (AE)"	Means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
"Adverse Reaction (AR)"	Means any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
"Serious Adverse Event (SAE), "Serious Adverse Reaction, or Unexpected Serious Adverse Reaction"	means an adverse event, adverse reaction or unexpected adverse reaction respectively that − results in death − is life threatening − requires hospitalisation or prolongation of existing hospitalisation − results in persistent or significant disability or incapacity or − consists of a congenital anomaly or birth defect
"Suspected Serious Adverse Reaction (SSAR)"	means an adverse reaction that is classed in nature as serious and which <u>is consistent</u> with the information about the medicinal product in question set out
	in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
	(b) in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question
"Suspected Unexpected Serious Adverse Reaction (SUSAR)"	means an adverse reaction that is classed in nature as serious and which <u>is not consistent</u> with the information about the medicinal product in question set out
	in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
	in the case of any other investigational medicinal product, in the IB relating to the trial in question

Adverse event reporting form

Study sponsor ID number	
Subject initials	
Subject (study) UIN	

Description of Adverse Event			
Date of onset			
Outcome	Resolved without residual effect	☐	
	Resolved with residual effect	☐	
	Continuing	☐	
	Death	☐	
Date of Resolution			
Severity Grade	Mild	☐	
	Moderate	☐	
	Severe	☐	
Casualty Assessment	Not related	☐	
	Possibly related	☐	**These qualify an Adverse event (AE) as an Adverse Reaction (AR)**
	Probably related	☐	
	Definitely related	☐	
Is it Serious	Results in death	☐	**Please complete SAE reporting form and email to UCL Biomedicine R&D Unit within 24hrs:** randd@uclh.nhs.uk
	Is life threatening	☐	
	Requires hospitalisation or prolongation of existing hospitalisation	☐	
	Results in persistent or significant disability or incapacity	☐	
	Consists of congenital anomaly or birth defect	☐	
	No	☐	

Serious Adverse Event Reporting Form

Definition of SAE:
An SAE can be defined as: an untoward medical occurrence in a subject during clinical research involving a pharmaceutical product, medical device, or clinical intervention that: is fatal; is life threatening; results in persistent or significant disability / incapacity; requires inpatient hospitalisation or prolongs a current hospitalisation; results in a congenital anomaly in offspring; or an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above.
Initial Reporting:
For all initial reporting of any Serious Adverse Events / Incidents this form must be completed **fully** and sent to the UCL Joint Research Office (randd@uclh.nhs.uk) within 24 hours of the incident occurring or being known.
Follow-up Information:
For subsequent follow-up reporting of an SAE, a new SAE reporting form should be completed with just administration details and sections A, D, E and G **only** and forwarded to the UCL Biomedicine R&D Unit as soon as possible. All SAEs must be followed up until closure.
SUSARs/Expedited Reporting:
For any Suspected Unexpected Serious Adverse Reactions (SUSARs) which are life threatening/fatal, initial reports must be sent to the Competent Authority and the Main Ethics Committee by the sponsor within 7 days of being aware of the event. Follow-up information must be sent to the Competent Authority and Main Ethics Committee within 8 days after initial reporting. All other SUSARs must be reported within 15 days and any follow up information sent to the Competent Authority and Main Ethics Committee as soon as possible. A copy of these reports must be sent to the UCL Biomedicine R&D Unit if this duty has been delegated by the sponsor to the CI.

Initial report	☐	Follow up report	☐	Reporting date	
Study Title					
Ethics Ref No					
R&D Ref No					

Section A – Details of subject affected by Serious Adverse Event					
Has the chief Investigator been informed of this event prior to completion of this form?					
Subject initials		Subject DOB		Subject UIN	
Gender		Height		Weight	

Section B – Details of the Serious Adverse Event			
Date of event onset		Time of event onset	
Site		Exact location	
Study intervention			
Time of intervention			
Type of serious adverse event			
Subject died	☐		

Life threatening	☐
In-patient hospitalisation or prolongation	☐
Persistent or significant disability/incapacity	☐
Congenital anomaly/ birth defect	☐
Medically important event	☐
Other	☐

Describe Event: Give a summary of signs and symptoms including vital signs, diagnosis, treatment of event, concurrent treatment and other relevant medical history. Please include the point in the study at which the event occurred.

Section C – Relationship To Study Involvement				
Was the incident related to the subject's involvement in the study?	Yes	☐	No	☐
Is the event related to the study intervention?	Yes	☐	No	☐
Was this expected by the Chief Investigator?	Yes	☐	No	☐
Was this expected by the Sponsor?	Yes	☐	No	☐
Is the event related to the study intervention?	Yes	☐	No	☐

Give details if sponsor's and CI/PI evaluation of expectedness differ						
Severity grading	Mild	☐	Moderate	☐	Severe	☐
Action taken regarding subject's participation in the study						
Temporarily discontinued	☐	Permanently discontinued	☐	Subject continued	☐	
Date		Decision taken by				
Explain the reasons for the decision						

Section D – Outcome of Serious Adverse Event	
Recovered	☐
Not yet recovered	☐
Alive with sequelae	☐
Subject died	☐
Give details	

Section E – Details of Reporter and Site Chief Investigator	
Name of person completing this report	
Role	
Affiliation	
Contact details (email)	
Reporter signature	Date

Chief investigator signature	Date

Section F – Circulation				
Date form completed				
Date CI informed				
Date Ethics Committee informed				
Did this event require an expedited report?	Yes	☐	No	☐
If yes please provide date reported to the Competent Authority (ies)/Main Ethics Committee				
Please list name(s) of the Competent Authority(ies)/Main Ethics Committee reports sent to				

Section G – Follow-up Information	
Date completed	
Additional information to describe progress of event	

Please forward a copy of this form to the UCL Joint Research Office (randd@uclh.nhs.uk). The original form should be kept in the Study/Trial Master File.

UCL Joint Research Office use only			
R&D Reference No			
Date received		Date reviewed	
Did this event require further action		Yes	No
If yes, provide details of action taken:			
Reviewed by			
Signed		Date	

Appendix 11: Participant case record form

Participant details

Name		UIN	
NHS no.		Hospital Site	
DOB	Age	Gender	Ethnicity
Address			

Screening questions

Could you be pregnant (if applicable)?	
Do any of the following diagnostic categories apply to your past medical history? (please circle):	
HIV infection, diabetes, malignancy, autoimmune diseases, keloid scarring, any skin disease, allergy to local anaesthetic injection	
Do you take any of the following medication? (please circle):	
Anti-TNF, Corticosteroids, Azothioprine, Cyclosporin, FK506, Methotrexate, Tacrolimus	
Why were you referred to the TB clinic? (please circle):	
Recent TB contact, recent migration to the UK, occupational health screening, other ……....	
Country of birth	
Date of entry to UK, if non-UK born	
If you have recently had contact with someone with TB, where was this? (please circle):	
Household, work, healthcare setting, transport, social contact, other ……	
If you have recently had contact with someone with TB, what was the date of the most recent contact?	
Have you been vaccinated with BCG? If so, what year was this?	
Have you been diagnosed with TB disease before? If so, what year was this?	
Have you recently had a tuberculin skin test done? If so, what date was this?	
Date of consent	

Pre-TST		Persistent cough for more than two weeks?	☐	Continue ☐
Blood	☐	Weight loss in the last 3 months?	☐	End study ☐
CXR	☐	Drenching night sweats during the last 3 months?	☐	

Visit 1: Tuberculin skin test in each arm

Lot number	Date	Administered by	Signed

Visit 2: Read TST induration, local anaesthetic, TST biopsy 1

TST L induration	TST L photograph ☐	TST R induration	TST R photograph ☐
Lot Number (48hr)	Date	Administered by	Signed
TST biopsy 1 ☐		Signed	

Visit 3: Local anaesthetic, TST biopsy 2

Lot Number (Day 7)	Date	Administered by	Signed
TST biopsy 2 ☐		Signed	

Eligibility for cohort studies					
LTBI treatment study?	Yes ☐	No ☐	Longitudinal contact study?	Yes ☐	No ☐
Accepted and commenced LTBI treatment?				Yes ☐	No ☐

Longitudinal study follow up assessments (mark with tick or cross)				**Outcome (circle)**
3 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
6 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
9 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
12 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
15 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
18 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
21 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
24 months		Persistent cough for more than two weeks?		Continue Treatment study End study
Blood		Weight loss in the last 3 months?		
CXR		Drenching night sweats during the last 3 months?		
Notes				

LTBI treatment study follow up assessments (mark with tick or cross)					**Outcome (circle)**
4 weeks		Persistent cough for more than two weeks?			Continue End study
Blood		Weight loss in the last 3 months?			
		Drenching night sweats during the last 3 months?			
Missed doses in last 4 weeks?			Pill count?		
8 weeks		Persistent cough for more than two weeks?			Continue End study
Blood		Weight loss in the last 3 months?			
		Drenching night sweats during the last 3 months?			
Missed doses in last 4 weeks?			Pill count?		
12 weeks		Persistent cough for more than two weeks?			Continue End study
Blood		Weight in the last 3 months?			
		Drenching night sweats during the last 3 months?			
Missed doses in last 4 weeks?			Pill count?		
24 weeks		Persistent cough for more than two weeks?			Continue End study
Blood		Weight loss in the last 3 months?			
		Drenching night sweats during the last 3 months?			
Missed doses in last 4 weeks?			Pill count?		

Notes