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# BMJ Open

## A feasibility study evaluating the uptake, effectiveness and acceptability of routine screening of pregnant migrants for latent tuberculosis infection in antenatal care: a research protocol

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Manuscripts

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3 **A feasibility study evaluating the uptake, effectiveness and acceptability of routine**  
4 **screening of pregnant migrants for latent tuberculosis infection in antenatal care: a**  
5 **research protocol**

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## Abstract

### Introduction

Globally, Tuberculosis (TB) is a leading cause of death in women of reproductive age and there is high risk of reactivation of latent tuberculosis infection (LTBI) in pregnancy. The uptake of routine screening of migrants for LTBI in the UK in primary care is low. Antenatal care is a novel setting which could improve uptake and can lend insight into the feasibility and acceptability of offering opt-out screening for LTBI.

### Methods and analysis

This is an observational feasibility study with a nested qualitative component. The setting will be the antenatal clinics in three hospitals of an NHS Trust. Inclusion criteria are pregnant migrant women aged 16-35 years attending antenatal clinics who are from countries with a TB incidence of greater than 150/100,000 including sub-Saharan Africa, and who have been in the UK for less than 5 years. Participants will be offered LTBI screening with an opt-out interferon gamma release assay (IGRA) blood test, and be invited to complete a questionnaire. Both participants and healthcare providers will be invited to participate in semi-structured interviews or focus groups to evaluate understanding, feasibility and acceptability of routine opt-out LTBI screening. The primary analysis will focus on estimating the uptake of the screening programme along with the corresponding 95% confidence interval. Secondary analysis will focus on estimating the test positivity. Qualitative analysis will evaluate the acceptability of offering routine opt-out LTBI screening to participants and healthcare providers.

### Ethics and dissemination

The study has received the following approvals: Health Research Authority (IRAS 247388) and National Health Service Ethics Committee (19/LO/0557). The results will be made available locally to antenatal clinics and primary care physicians, nationally to NHS England and Public Health England and internationally through conferences and journals.

**Trial Registration Number:** NCT04098341, pre-results.

## Article Summary

### Strengths and limitations of this study:

- This is the first study to investigate the uptake, feasibility and acceptability of routine opt-out screening for LTBI in antenatal care in the UK.
- The results will inform ways to increase uptake of LTBI screening in migrants in other settings such as primary care
- A primary limitation of this study is the difficulty in recruiting women who decline LTBI screening to semi-structured interviews and focus group, thereby losing valuable perspectives.

- Based on these results we will develop a definitive large-scale cluster randomized controlled trial to evaluate the effectiveness of LTBI screening in antenatal care.

## Introduction

### Context

Tuberculosis (TB) remains a significant global health problem affecting an estimated 10 million people worldwide in 2019 leading to 1.4 million deaths (1). TB is one of the top 10 causes of death globally and the leading cause from any single infectious agent (more than HIV/AIDS) (1). A quarter of the world's population is estimated to have latent TB infection (LTBI) (2). The World Health Organisation defines LTBI as a 'state of persistent immune response stimulation by *Mycobacterium Tuberculosis* antigens without evidence of clinically manifested active TB' (1). Individuals with LTBI have no signs and symptoms of active TB but remain at risk of developing active TB in their lifetime. LTBI acts as a reservoir for active TB and TB elimination requires strategies for LTBI control (3). Uptake of LTBI screening in primary care is low (4, 5). Antenatal care is a new setting for LTBI screening and understanding the factors affecting the feasibility and acceptability of LTBI screening in this setting are first steps towards developing effective interventions to improving LTBI screening uptake.

### Current knowledge

In women of childbearing age (16-45 years), TB is one of three leading causes of death globally (2). Diagnosis of TB in pregnancy is often delayed as pregnancy can mask some of the clinical manifestations of TB (6, 7). There is a higher risk of LTBI reactivation during pregnancy and postpartum likely due to T-cell suppression and reduced interferon-gamma production (8). TB in pregnancy is associated with poor perinatal, foetal and maternal outcomes (9, 10).

The UK has one of the highest TB incidence rates in Western Europe. The incidence of TB among those born outside the UK is 14 times higher at 39.0 per 100,000 population and accounting for 74% of all new cases of TB in England in 2019 (11). Public Health England's TB migrant health guide strategy recommends migrant screening for LTBI in high incidence areas in England such as the London Boroughs of Tower Hamlets, Newham and Waltham Forest (12, 13).

The London Borough of Newham was spearheading large-scale LTBI screening programme in anticipation of the national programme. A total of 20,905 LTBI tests were reported between July 2014 and June 2017 across England with nearly half of the tests taking place in Newham (4, 5). Between April 2015 and June 2016, 5,622 eligible migrants in England were offered an LTBI test, 2,904 (51%) of whom attended for the test (4).

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2  
3 Effective screening for LTBI is key to reducing TB incidence in the UK. There is good  
4 evidence that screening and treatment of LTBI is a cost-effective intervention that  
5 significantly reduces the risk of developing active disease and the risk of onward  
6 transmission (14, 15). The national LTBI migrant screening programme has been  
7 rolled out but there is insufficient evidence on the best setting for uptake of LTBI  
8 screening.  
9

## 10 11 Rationale for LTBI screening in antenatal care 12

13  
14 Pregnancy can predispose to reactivation of LTBI and diagnosis can be delayed due  
15 to reduced awareness among healthcare providers and reluctance to investigate non-  
16 specific TB symptoms by chest radiography (16). Risks of LTBI reactivation and delays  
17 in diagnosis of TB can be mitigated by screening an at-risk pregnant migrant  
18 population for LTBI. A simple clinical algorithm recommended by the WHO based on  
19 absence of current cough, fever, weight loss, and night sweats can help to exclude  
20 active TB disease. Moreover, healthcare professionals will have a higher index of  
21 suspicion for active TB in IGRA positive pregnant migrant women presenting with  
22 symptoms suggestive of TB, thus preventing a delay in diagnosis (17).  
23

24  
25 Pregnant migrants may not be accessing routine health care and often do not have a  
26 GP. Antenatal care may therefore be a key opportunity to assess the woman's health  
27 and screen for TB. Antenatal care provides an opportunity for health promotion such  
28 as advocating GP registration and is a time when parents may be particularly receptive  
29 to public health information and promotion.  
30

31  
32 LTBI screening for migrants from high TB incidence countries in antenatal care has  
33 shown high uptake in the U.S. but feasibility of LTBI screening in antenatal clinics in  
34 the UK has not been evaluated (18).  
35

## 36 37 Research hypothesis and aims 38

39  
40 We hypothesise that offering routine opt-out LTBI screening to an at-risk pregnant  
41 migrant population in antenatal care will be feasible and acceptable to pregnant  
42 migrant women and healthcare providers.  
43

44  
45 There is limited qualitative research about the acceptability to women of LTBI  
46 screening in pregnancy. Reasons for low uptake may be due to stigma of having active  
47 TB or fear of a positive test result affecting their immigration status. An opt-out  
48 approach to LTBI screening may normalise the process and has the potential to  
49 reduce barriers such as stigma, as well as practical barriers (19).  
50

51  
52 Provider knowledge and understanding of the risks of TB, screening and treatment  
53 can be a major predictor of successful management of TB (20). Data from Newham's  
54 LTBI screening programme has highlighted that offer of screening varies amongst GP  
55 practices indicating that health care provider knowledge and attitude may influence  
56 offer of screening (21).  
57

58  
59 Evaluating the impact of healthcare provider training to improve TB management has  
60 mainly been performed in low-income countries and there are only a few rigorous TB  
training evaluation studies available. E-learning modules use pre- and post- training

1  
2  
3 tests to evaluate acquired knowledge. A GP E-learning module has been developed  
4 by TB Alert to enhance knowledge of GPs responsible for screening and treatment of  
5 LTBI but the effectiveness of the module has not been formally evaluated.  
6

7  
8 Routine opt-out testing has proven effective for other diseases (HIV / Hepatitis B, C)  
9 (22). Factors affecting successful uptake of screening programmes include how the  
10 test is offered, by whom, to whom, and in what setting (23). Pregnant women screened  
11 for HIV during pregnancy perceived routine opt-out HIV testing as beneficial for both  
12 women and their unborn babies (23). Globally, some countries offer routine screening  
13 for TB in pregnancy mainly through symptom screen and sputum examination (15).  
14

15  
16 To test our hypothesis, we will assess the uptake, feasibility and acceptability of  
17 screening an at-risk pregnant migrant population for LTBI at routine antenatal booking  
18 visits in secondary care, using opt-out IGRA testing. The results from this feasibility  
19 study will allow us to develop a definitive large-scale cluster randomised controlled  
20 trial (RCT) evaluating the effectiveness of a LTBI screening in antenatal care, the  
21 effectiveness of interventions used to maximise migrant screening for LTBI in  
22 pregnancy and to increase uptake of LTBI treatment postpartum.  
23

## 24 25 **Methods and analysis**

### 26 27 **Study protocol**

28  
29 This is a prospective observational feasibility study with nested qualitative research  
30 involving three hospitals (The Royal London Hospital, Newham University Hospital  
31 and Whipps Cross University Hospital). Study participants will enter the cohort when  
32 they attend the antenatal clinic for their booking appointment, after they meet inclusion  
33 criteria (Table 1). Midwives will offer LTBI screening as an opt-out IGRA blood test  
34 alongside other routine investigations for blood borne viruses at the initial booking  
35 appointment. The study will assume valid implied consent for participation if women  
36 undertake an IGRA test at the time it is offered by the midwife on an opt-out basis.  
37 Participants will leave the cohort 6 weeks post-delivery of the baby or at the time of  
38 miscarriage if they have had a miscarriage.  
39  
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42

43 At the time of offer of LTBI screening, we will record routine clinical data of all eligible  
44 pregnant migrant women including those who do not accept screening. Data on age,  
45 ethnicity, year of entry to the UK, pre-existing medical conditions and antenatal history  
46 which is routinely recorded in the medical notes will be collected.  
47

48 All eligible pregnant migrant women will be screened for active TB by their midwives  
49 using a standardised symptom assessment questionnaire that includes the WHO  
50 recommended TB symptoms screen during their booking appointment. Study  
51 participants with a positive IGRA blood test will undergo screening for active TB using  
52 the WHO recommended TB symptoms screen at 20 weeks, 30-34 weeks, delivery and  
53 post-partum. Data on symptoms of active TB will be collected at each time point (see  
54 Figure 1).  
55  
56

57 All eligible pregnant women will be asked to complete a short questionnaire on  
58 acceptability of LTBI screening, knowledge about TB/LTBI, and barriers to screening.  
59 At the end of pregnancy, women will be asked to complete the same questionnaire to  
60

1  
2  
3 compare the perception and knowledge of active TB/LTBI before and after the  
4 screening intervention. Trained research personnel will obtain written informed  
5 consent from the participant for the questionnaire.  
6

7  
8 We have used the SPIRIT reporting guidelines for this paper (24).  
9

## 10 11 12 13 Outcomes

14  
15  
16 Our primary outcomes are (i) the uptake of screening for LTBI in antenatal care  
17 assessed by the proportion of eligible migrant women offered a test who accepted  
18 LTBI screening, and (ii) the offer of IGRA blood test screening by healthcare providers  
19 assessed by the proportion of migrant women eligible for screening who were offered  
20 an IGRA test.  
21

22  
23 Secondary outcomes are: rates of LTBI and active TB identified in pregnant migrant  
24 women during the study period, time to diagnosis, understanding and acceptability of  
25 LTBI screening and acceptability of interventions to increase screening uptake,  
26 perceived facilitators and barriers influencing uptake of LTBI screening and treatment  
27 uptake post-partum, increase in knowledge and awareness about active TB/ LTBI  
28 amongst pregnant migrant women and healthcare providers and evaluation of cost-  
29 effectiveness of LTBI screening in antenatal care compared to primary care.  
30

31  
32 Process outcomes of the study are the numbers of eligible participants and screening  
33 acceptance rate, proportion of eligible pregnant migrant women who were offered  
34 LTBI screening, views and experiences of participants on study recruitment methods,  
35 data collection methods, and retention in the study and level of NHS support required  
36 for the proposed definitive cluster RCT.  
37  
38  
39

## 40 41 Patient and Public Involvement

42  
43 Healthwatch Newham conducted a survey to evaluate patient experiences of the LTBI  
44 screening programme in Newham, to identify the key factors that influence the uptake  
45 of screening, and to understand why patients decline screening. The results of this  
46 survey have influenced the design of this study, and migrants with LTBI has provided  
47 useful information about how LTBI screening could be better conducted. Evaluation of  
48 patient experiences demonstrated that migrants would like to be offered a LTBI test  
49 directly by their GP or nurse and that the test should be part of a general check-up.  
50 Our intervention has been designed to provide this by incorporating the offer of an  
51 Interferon-gamma release-assay (IGRA test) into routine antenatal care check-ups by  
52 midwives. The concept and the study design has been developed in close  
53 collaboration with TB Alert (UK TB charity), with the support of the East London  
54 Katherine Twining network PPI group (Katie's Team) and the Centre for Maternal and  
55 Child Health Research at City, University of London's service user panel and former  
56 TB/ LTBI patients. PPI members felt that testing for LTBI as an opt-out approach is an  
57 acceptable intervention for pregnant migrant women.  
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60



## Sample size

A sample of 200 pregnant migrant women offered testing allows this study to estimate the screening uptake rate (key primary outcome for the feasibility study) with adequate precision across a range of possible values of the rate. If the uptake rate is 50% (at which precision is lowest) then this can be estimated within 6% either side, i.e., a 95% confidence interval of 54-66%. If, however the rate is as high as 80% (or equivalently as low as 20%) then the rate can be estimated within 5%.

## Statistical analysis

The primary analysis will focus on estimating the uptake of the screening programme along with the corresponding 95% confidence interval. Secondary analysis will focus on estimating the test positivity. Associations between uptake and potential explanatory variables will be assessed using the Chi squared test, and the strength of association will be presented as an odds ratio with 95% confidence interval. Identification of which characteristics are associated after adjusting for others will be performed using multiple logistic regression, and adjusted odds ratios will be presented.

## Nested qualitative research

Study participants will be invited to participate in semi-structured interviews or focus groups to explore acceptability of LTBI screening in antenatal care, understanding of LTBI amongst eligible pregnant women and health care providers, potential use of educational resources in each of these groups and potential barriers/facilitators to LTBI screening and treatment uptake.

A theoretical framework derived from the literature, survey and demographic data will be used to select a purposive sample to explore a range of relevant opinions and experiences. This will include interviewing women who have taken up screening as well as those who have not, or where this is not practicable, those within communities that might be offered screening. Sample size is guided by data saturation: for thematic analysis of semi-structured interviews this is likely to occur between 10 and 40 participants and for focus groups 24-32 participants. Trained research personnel will obtain written informed consent from the participant for the semi-structured interviews and focus groups.

Study participants will be invited to take part in two interviews. The first will take place early in the study (see Figure 1) and will explore participants' understanding of LTBI, along with perceived acceptability of the study and intervention, participants' perceptions of their own risk of TB, their understanding of the prevention of TB and their views on the opt-out screening. The interview will also explore factors that influence participants' decision to be screened and suggestions for what might motivate them or other women to be screened, and their perspectives on the study

1  
2  
3 data collection methods. Furthermore, participants' views and attitudes to LTBI  
4 treatment during or immediately after pregnancy will be assessed.  
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6

7 A second follow-up interview will take place towards the end of the study (see Figure  
8 1) with those participants who test IGRA positive to discuss their response to receiving  
9 a positive screening result, feelings around future treatment and explore what factors  
10 might encourage/ discourage women from taking up treatment post-partum. Themes  
11 and concepts identified from the first set of interviews will inform the topics raised in  
12 the second interviews. This iterative approach will allow follow-up interviews to build  
13 on and explore further the participant experience, and to incorporate issues raised by  
14 other participants.  
15  
16

17 Women who decline participation in LTBI screening will be asked by recruiting  
18 midwives whether they consent for an independent researcher to contact them for an  
19 interview to explore their views. If few 'declining' women consent, up to three  
20 community-based focus groups will be conducted with migrant women of childbearing  
21 ages, and if appropriate men, in relevant populations to explore their awareness and  
22 their views about screening.  
23  
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25

26 Semi-structured interviews will also be conducted with 6-8 healthcare providers,  
27 including those who are involved in delivering the intervention, those who have  
28 expertise in managing pregnant women and local GPs to whom pregnant women may  
29 seek advice about screening and treatment for LTBI.  
30  
31

32 Two further focus groups with midwives, physicians and nurses, each involving around  
33 8-12 participants will add a different perspective to that of the women. Their views and  
34 experiences on approaches to screening for TB/ LTBI in antenatal care, along with  
35 perceived barriers/ facilitators to LTBI screening and treatment, from a service or  
36 community perspective, will be explored.  
37  
38

39 Interview and focus group data will be analysed thematically, using constant  
40 comparison techniques, to identify, interpret and report patterns (themes) representing  
41 beliefs and experiences that participants share (or differ on) in relation to the research  
42 questions. The interviews and focus groups will also assess the views and  
43 experiences of participants and healthcare providers on study recruitment methods,  
44 data collection methods, facilitators and barriers to involvement, and compliance to  
45 study procedures.  
46  
47  
48

## 49 Data management

50  
51 All study data will be managed according to the Clinical Effectiveness Group (CEG)  
52 data management policy. Data will be entered directly onto a purpose-built database  
53 where possible (paper CRFs will be used as a backup if required).  
54  
55

56 Source data will be taken from the women's antenatal records and entered directly  
57 onto a database. Questionnaire data will be generated directly and then entered into  
58 the database.  
59  
60

1  
2  
3 The Investigator will ensure that patient anonymity is protected and maintained. They  
4 will also ensure that patient identities are protected from any unauthorised parties.  
5 Information with regards to study patients will be kept confidential and managed in  
6 accordance with the Data Protection Act, NHS Caldicott Guardian, The Research  
7 Governance Framework for Health and Social Care and Research Ethics Committee  
8 Approval.  
9

10  
11 The study will collect personal data and information about the participants either  
12 directly or from their clinical team. Routine clinical data will be entered onto a secure  
13 computer database, either by the research team or directly via a secure internet  
14 connection. The data will be pseudoanonymised. Any data processed by those outside  
15 the research team (research registrar, nurse or project coordinator) will be  
16 anonymised. All personal information obtained for the study will be held securely and  
17 treated as (strictly) confidential. All staff share the same duty of care to prevent  
18 unauthorised disclosure of personal information. No data that could be used to identify  
19 an individual will be published.  
20  
21

22  
23 Transcripts from interviews and focus groups will be archived securely and audio-  
24 records destroyed securely following study closure in accordance with City, University  
25 of London's data management and retention policy. As all transcripts are de-identified  
26 at transcription stage to ensure confidentiality, and personal data will be securely  
27 destroyed one year after study closure, no personal data will be included in archived  
28 records.  
29

### 30 31 32 Ethics and Dissemination: 33

34 The study has received approval from The Health Research Authority (IRAS 247388)  
35 and London- City & East Research Ethics Committee (19/LO/0557). The study has  
36 been registered with clinicaltrials.gov (NCT04098341, pre-results). The results will be  
37 made available locally to antenatal clinics and primary care physicians, nationally to  
38 NHS England and Public Health England and internationally through conferences  
39 and journals.  
40  
41

### 42 43 44 Discussion 45

46 Systematic national implementation of the LTBI screening programme is essential to  
47 achieving the aims of the collaborative strategy and support the WHO goal of TB  
48 elimination. The uptake of LTBI screening amongst migrants is low. This study seeks  
49 to provide patient-centred, migrant-inclusive evidence of the uptake, feasibility and  
50 acceptability of routine opt-out LTBI screening amongst pregnant migrants in antenatal  
51 care. It also seeks to understand potential facilitators and barriers from a healthcare  
52 provider perspective. We will assess whether this site of screening results in higher  
53 rates of LTBI screening uptake. The results of this study will inform the design of a  
54 cluster RCT I trial evaluating the effectiveness of acceptable interventions to maximise  
55 migrant screening for LTBI in pregnancy, and to increase uptake of LTBI treatment  
56 postpartum.  
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60

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## Authors' contributions

HK, ST, CMcC, AC, ZD, PJW, CG and IA designed the study and secured funding. AR trained healthcare providers and recruited participants for the study. AR wrote the first draft of the manuscript. All other authors reviewed drafts of this manuscript and commented upon them.

## Conflict of Interest

PJW acknowledges funding from the MRC Centre for Global Infectious Disease Analysis (grant number MR/R015600/1); this award is jointly funded by the MRC and Foreign, Commonwealth and Development Office (FCDO) under the MRC/FCDO Concordat agreement and is also part of the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme supported by the EU. PJW is also supported by the NIHR Health Protection Research Unit (HPRU) in Modelling and Health Economics, which is a partnership between Public Health England (PHE), Imperial College London, and LSHTM (grant code NIHR200908). The views expressed are those of the authors and not necessarily those of the UK Department of Health and Social Care, FCDO, EU, MRC, NIHR, or PHE.

**Word count: 3661**

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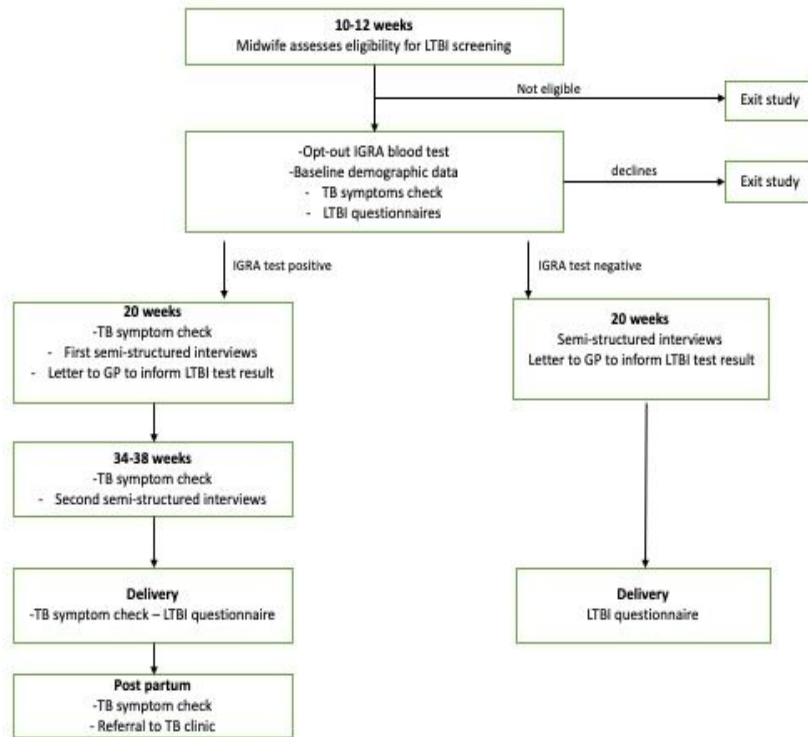
For peer review only

**A feasibility study evaluating the uptake, effectiveness and acceptability of routine screening of pregnant migrants for latent tuberculosis infection in antenatal care: a research protocol**

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>- Pregnant migrant women aged 16-35 years</li> <li>AND</li> <li>- from high TB incidence countries (incidence of TB of &gt;150/100,000 including sub-Saharan Africa)</li> <li>AND</li> <li>- who have been in the UK for less than 5 years</li> </ul>	<ul style="list-style-type: none"> <li>- Previous history of TB or LTBI</li> <li>- Individuals who are unable to consent</li> <li>- Evidence of current active TB (based on history, examination, blood tests, chest X-ray findings or other radiological findings)</li> </ul>

Figure 1. Timeline of study project (Assessment and follow-up of migrant women)







Dr Heinke Kunst  
Senior Lecturer  
Queen Mary University  
Blizard Institute  
4 Newark Street  
London  
E1 2AT

Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)  
[Research-permissions@wales.nhs.uk](mailto:Research-permissions@wales.nhs.uk)

29 April 2019

Dear Dr Kunst

**HRA and Health and Care  
Research Wales (HCRW)  
Approval Letter**

**Study title:** Uptake, effectiveness and acceptability of routine screening of pregnant migrants for latent tuberculosis infection in antenatal care: a feasibility study

**IRAS project ID:** 247388

**REC reference:** 19/LO/0557

**Sponsor** Queen Mary University of London

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

**How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?**

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

1  
2  
3 Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern  
4 Ireland and Scotland.  
5  
6

### 7 **How should I work with participating non-NHS organisations?**

8 HRA and HCRW Approval does not apply to non-NHS organisations. You should work with  
9 your non-NHS organisations to [obtain local agreement](#) in accordance with their procedures.  
10  
11

### 12 **What are my notification responsibilities during the study?**

13  
14  
15 The document “*After Ethical Review – guidance for sponsors and investigators*”, issued with  
16 your REC favourable opinion, gives detailed guidance on reporting expectations for studies,  
17 including:  
18

- 19 • Registration of research
- 20 • Notifying amendments
- 21 • Notifying the end of the study
- 22

23 The [HRA website](#) also provides guidance on these topics, and is updated in the light of  
24 changes in reporting expectations or procedures.  
25  
26

### 27 **Who should I contact for further information?**

28 Please do not hesitate to contact me for assistance with this application. My contact details  
29 are below.  
30  
31

32  
33 Your IRAS project ID is **247388**. Please quote this on all correspondence.  
34  
35

36 Yours sincerely,  
37  
38

39 Kevin Ahmed  
40 HRA Approvals Manager  
41  
42

43  
44 Telephone: 0207 104 8171

45 Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)  
46  
47

48  
49 *Copy to: Dr Mays Jawad, Sponsor Contact, Queen Mary University of London*  
50  
51  
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## List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

<i>Document</i>	<i>Version</i>	<i>Date</i>
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		27 July 2018
GP/consultant information sheets or letters [GP letter]	1	01 March 2019
HRA Schedule of Events	1.0	05 April 2019
HRA Statement of Activities	1.0	05 April 2019
IRAS Application Form [IRAS_Form_04032019]		04 March 2019
Letter from funder [Intent to Fund]		23 March 2018
Non-validated questionnaire [Knowledge questionnaire]	1	01 March 2019
Other [HP quiz]	1	01 March 2019
Other [Poster]	1	01 March 2019
Participant consent form [Healthcare Workers Interview]	2.0	15 April 2019
Participant consent form [Healthcare Workers Knowledge Questionnaire]	2.0	15 April 2019
Participant consent form [Patient Focus Groups]	2.0	15 April 2019
Participant consent form [Patient Interviews]	2.0	15 April 2019
Participant consent form [Focus Groups]	2.0	15 April 2019
Participant consent form [Patient Questionnaires]	2.0	15 April 2019
Participant information sheet (PIS) [PIS for pregnant women]	1	01 March 2019
Participant information sheet (PIS) [Healthcare Workers]	2.0	15 April 2019
Participant information sheet (PIS) [Patients]	2.0	15 April 2019
Research protocol or project proposal	2.0	15 April 2019
Summary CV for Chief Investigator (CI) [HK CV]	Version 1	03 March 2019

## Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	A statement of activities has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No study funding will be provided to sites as per the statement of activities	A Principal Investigator should be appointed at study sites	Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

## Other information to aid study set-up and delivery

*This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.*

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Health Research  
Authority

**London - City & East Research Ethics Committee**

Bristol Research Ethics Committee Centre  
Whitefriars  
Level 3, Block B  
Lewins Mead  
Bristol  
BS1 2NT

**Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval**

12 April 2019

Dr Heinke Kunst  
Senior Lecturer  
Queen Mary University  
Blizard Institute  
4 Newark Street  
London  
E1 2AT

Dear Dr Kunst

**Study title:** Uptake, effectiveness and acceptability of routine screening of pregnant migrants for latent tuberculosis infection in antenatal care: a feasibility study  
**REC reference:** 19/LO/0557  
**IRAS project ID:** 247388

The Research Ethics Committee reviewed the above application at the meeting held on 04 April 2019. Thank you and Ms Ananna Rahman for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact [hra.studyregistration@nhs.net](mailto:hra.studyregistration@nhs.net) outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

**Ethical opinion**

1  
2  
3 The members of the Committee present gave a favourable ethical opinion of the above  
4 research on the basis described in the application form, protocol and supporting  
5 documentation, subject to the conditions specified below. .  
6  
7

8 Management permission must be obtained from each host organisation prior to the start of  
9 the study at the site concerned.  
10

11 *Management permission should be sought from all NHS organisations involved in the study*  
12 *in accordance with NHS research governance arrangements. Each NHS organisation must*  
13 *confirm through the signing of agreements and/or other documents that it has given*  
14 *permission for the research to proceed (except where explicitly specified otherwise).*  
15

16 *Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission*  
17 *for research is available in the Integrated Research Application System, at [www.hra.nhs.uk](http://www.hra.nhs.uk)*  
18 *or at <http://www.rdforum.nhs.uk>.*  
19

20  
21 *Where a NHS organisation's role in the study is limited to identifying and referring potential*  
22 *participants to research sites ("participant identification centre"), guidance should be sought*  
23 *from the R&D office on the information it requires to give permission for this activity.*  
24

25 *For non-NHS sites, site management permission should be obtained in accordance with the*  
26 *procedures of the relevant host organisation.*  
27

28 *Sponsors are not required to notify the Committee of management permissions from host*  
29 *organisations.*  
30

### 31 Registration of Clinical Trials

32

33 All clinical trials (defined as the first four categories on the IRAS filter page) must be  
34 registered on a publically accessible database. This should be before the first participant is  
35 recruited but no later than 6 weeks after recruitment of the first participant.  
36

37  
38 There is no requirement to separately notify the REC but you should do so at the earliest  
39 opportunity e.g. when submitting an amendment. We will audit the registration details as part  
40 of the annual progress reporting process.  
41

42 To ensure transparency in research, we strongly recommend that all research is registered  
43 but for non-clinical trials this is not currently mandatory.  
44

45 If a sponsor wishes to request a deferral for study registration within the required timeframe,  
46 they should contact [hra.studyregistration@nhs.net](mailto:hra.studyregistration@nhs.net). The expectation is that all clinical trials  
47 will be registered, however, in exceptional circumstances non registration may be  
48 permissible with prior agreement from the HRA. Guidance on where to register is provided  
49 on the HRA website.  
50

51  
52 **It is the responsibility of the sponsor to ensure that all the conditions are complied**  
53 **with before the start of the study or its initiation at a particular site (as applicable).**  
54

### 55 **Ethical review of research sites**

56

57 *NHS Sites*  
58  
59  
60

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

### *Non NHS sites*

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

### **Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		27 July 2018
GP/consultant information sheets or letters [GP letter]	1	01 March 2019
Initial Assessment for REC		21 March 2019
IRAS Application Form [IRAS_Form_04032019]		04 March 2019
Non-validated questionnaire [Knowledge questionnaire]	1	01 March 2019
Other [PIS for healthcare workers]	1	01 March 2019
Other [Consent form interviews]	1	01 March 2019
Other [Consent form focus groups]	1	01 March 2019
Other [Consent form interviews healthcare workers]	1	01 March 2019
Other [Consent form knowledge questionnaires healthcare workers]	1	01 March 2019
Other [Consent form focus groups healthcare workers]	1	01 March 2019
Other [HP quiz]	1	01 March 2019
Other [Poster]	1	01 March 2019
Participant consent form [Consent form]	1	01 March 2019
Participant information sheet (PIS) [PIS for pregnant women]	1	01 March 2019
Research protocol or project proposal [Protocol]	1	01 March 2019
Summary CV for Chief Investigator (CI) [HK CV]	Version 1	03 March 2019

### **Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### **After ethical review**

### Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

### **User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

### **HRA Learning**

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities— see details at: <https://www.hra.nhs.uk/planning-and-improving-research/learning/>

**19/LO/0557**

**Please quote this number on all correspondence**

With the Committee’s best wishes for the success of this project.

Yours sincerely



**Dr John Keen**  
**Chair**

E-mail: [nrescommittee.london-cityandeast@nhs.net](mailto:nrescommittee.london-cityandeast@nhs.net)

*Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments*

*“After ethical review – guidance for researchers”*

*Copy to: Dr Mays Jawad, Queen Mary University of London*

*Lead Nation*  
*England: [HRA.Approval@nhs.net](mailto:HRA.Approval@nhs.net)*



**London - City & East Research Ethics Committee**  
**Attendance at Committee meeting on 04 April 2019**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Dr Marie E Bardsley	Director (Pharmaceutical Publication)	Yes	
Ms Clare Barron	Solicitor – in-house legal department	No	
Dr Ayse Baxter	Pharmaceutical Physician	No	
Dr Luis Beltran	Consultant Histopathologist	No	
Ms Ann Black	Health Economist/Psycho-social Researcher	Yes	
Mr Frank Cross	Consultant General and Vascular Surgeon	Yes	
Mr Fasahat Hussain		Yes	
Mrs Lisa Johnson	Head of Clinical Operations	Yes	
Dr John Keen	GP (REC Chairman)	Yes	
Mr Rajat Khullar	REC Manager	No	
Dr Kieran McCafferty	Nephrologist Consultant/ Hon Senior Lecturer	No	
Dr Paul Metcalfe	Research Scientist - immunohaematology	Yes	
Ms Anna (Renqian) Song	Pharmacist	No	

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Mr Kevin Ahmed	Approvals Manager
Miss Nicole Curtis	Approvals Specialist
Mrs Isabel Moldon	Observer
Mrs Frances Sarah Sharratt	Observer

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry	
Trial registration: data set	NA	All items from the World Health Organization Trial Registration Data Set	
Protocol version	NA	Date and version identifier	
Funding	9	Sources and types of financial, material, and other support	
Roles and responsibilities: contributorship	11	Names, affiliations, and roles of protocol contributors	

1	Roles and	NA	Name and contact information for the trial sponsor
2	responsibilities:		
3	sponsor contact		
4	information		
5			
6			
7	Roles and	NA	Role of study sponsor and funders, if any, in study design;
8	responsibilities:		collection, management, analysis, and interpretation of data;
9	sponsor and funder		writing of the report; and the decision to submit the report for
10			publication, including whether they will have ultimate authority
11			over any of these activities
12			
13			
14			
15	Roles and	NA	Composition, roles, and responsibilities of the coordinating
16	responsibilities:		centre, steering committee, endpoint adjudication committee,
17	committees		data management team, and other individuals or groups
18			overseeing the trial, if applicable (see Item 21a for data
19			monitoring committee)
20			
21			
22			
23			
24	<b>Introduction</b>		
25			
26	Background and	3-5	Description of research question and justification for
27	rationale		undertaking the trial, including summary of relevant studies
28			(published and unpublished) examining benefits and harms for
29			each intervention
30			
31			
32			
33	Background and	NA	Explanation for choice of comparators
34	rationale: choice of		
35	comparators		
36			
37			
38	Objectives	4-5	Specific objectives or hypotheses
39			
40			
41	Trial design	5-6	Description of trial design including type of trial (eg, parallel
42			group, crossover, factorial, single group), allocation ratio, and
43			framework (eg, superiority, equivalence, non-inferiority,
44			exploratory)
45			
46			
47			
48	<b>Methods:</b>		
49	<b>Participants,</b>		
50	<b>interventions, and</b>		
51	<b>outcomes</b>		
52			
53			
54	Study setting	5-6	Description of study settings (eg, community clinic, academic
55			hospital) and list of countries where data will be collected.
56			Reference to where list of study sites can be obtained
57			
58			
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1	Eligibility criteria	5-6	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
2			
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6	Interventions:	5-6	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
7	description		
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10	Interventions:	NA	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)
11	modifications		
12			
13			
14			
15	Interventions:	NA	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
16	adherence		
17			
18			
19			
20	Interventions:	NA	Relevant concomitant care and interventions that are permitted or prohibited during the trial
21	concomitant care		
22			
23			
24	Outcomes	6	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
25			
26			
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33			
34	Participant timeline	Figure	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
35		1	
36			
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38			
39			
40	Sample size	7	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
41			
42			
43			
44			
45	Recruitment	5-6	Strategies for achieving adequate participant enrolment to reach target sample size
46			
47			
48			

**Methods: Assignment of interventions (for controlled trials)**

54	Allocation: sequence generation	NA	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be
55			
56			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

1			
2			
3			
4	Allocation	NA	Mechanism of implementing the allocation sequence (eg,
5	concealment		central telephone; sequentially numbered, opaque, sealed
6			envelopes), describing any steps to conceal the sequence until
7	mechanism		interventions are assigned
8			
9			
10	Allocation:	NA	Who will generate the allocation sequence, who will enrol
11	implementation		participants, and who will assign participants to interventions
12			
13			
14	Blinding (masking)	NA	Who will be blinded after assignment to interventions (eg, trial
15			participants, care providers, outcome assessors, data analysts),
16			and how
17			
18			
19			
20	Blinding (masking):	NA	If blinded, circumstances under which unblinding is
21	emergency unblinding		permissible, and procedure for revealing a participant's
22			allocated intervention during the trial
23			
24			

**Methods: Data collection, management, and analysis**

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26			
27			
28			
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32	Data collection plan	8-9	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and
35			a description of study instruments (eg, questionnaires,
36			laboratory tests) along with their reliability and validity, if
37			known. Reference to where data collection forms can be found,
38			if not in the protocol
39			
40			
41			
42			
43	Data collection plan:	8-9	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for
45			participants who discontinue or deviate from intervention
46			protocols
47			
48			
49			
50	Data management	8-9	Plans for data entry, coding, security, and storage, including
51			any related processes to promote data quality (eg, double data
52			entry; range checks for data values). Reference to where details
53			of data management procedures can be found, if not in the
54			protocol
55			
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1	Statistics: outcomes	7	Statistical methods for analysing primary and secondary
2			outcomes. Reference to where other details of the statistical
3			analysis plan can be found, if not in the protocol
4			
5			
6	Statistics: additional	7	Methods for any additional analyses (eg, subgroup and adjusted
7	analyses		analyses)
8			
9			
10	Statistics: analysis	NA	Definition of analysis population relating to protocol non-
11	population and		adherence (eg, as randomised analysis), and any statistical
12	missing data		methods to handle missing data (eg, multiple imputation)
13			
14			
15	<b>Methods: Monitoring</b>		
16			
17	Data monitoring:	NA	Composition of data monitoring committee (DMC); summary
18	formal committee		of its role and reporting structure; statement of whether it is
19			independent from the sponsor and competing interests; and
20			reference to where further details about its charter can be found,
21			if not in the protocol. Alternatively, an explanation of why a
22			DMC is not needed
23			
24			
25			
26			
27	Data monitoring:	<a href="#">NA</a>	Description of any interim analyses and stopping guidelines,
28	interim analysis		including who will have access to these interim results and
29			make the final decision to terminate the trial
30			
31			
32			
33	Harms	NA	Plans for collecting, assessing, reporting, and managing
34			solicited and spontaneously reported adverse events and other
35			unintended effects of trial interventions or trial conduct
36			
37			
38	Auditing	<a href="#">NA</a>	Frequency and procedures for auditing trial conduct, if any, and
39			whether the process will be independent from investigators and
40			the sponsor
41			
42			
43	<b>Ethics and</b>		
44	<b>dissemination</b>		
45			
46			
47	Research ethics	<a href="#">9</a>	Plans for seeking research ethics committee / institutional
48	approval		review board (REC / IRB) approval
49			
50			
51	Protocol amendments	<a href="#">NA</a>	Plans for communicating important protocol modifications (eg,
52			changes to eligibility criteria, outcomes, analyses) to relevant
53			parties (eg, investigators, REC / IRBs, trial participants, trial
54			registries, journals, regulators)
55			
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1	Consent or assent	<a href="#">NA</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
2			
3			
4			
5	Consent or assent: ancillary studies	<a href="#">NA</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
6			
7			
8			
9			
10	Confidentiality	<a href="#">8-9</a>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
11			
12			
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15	Declaration of interests	<a href="#">11</a>	Financial and other competing interests for principal investigators for the overall trial and each study site
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18			
19	Data access	<a href="#">8-9</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
20			
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24	Ancillary and post trial care	<a href="#">NA</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
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28	Dissemination policy: trial results	<a href="#">9</a>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
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37	Dissemination policy: authorship	<a href="#">NA</a>	Authorship eligibility guidelines and any intended use of professional writers
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41	Dissemination policy: reproducible research	<a href="#">NA</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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44	<b>Appendices</b>		
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46			
47	Informed consent materials	<a href="#">NA</a>	Model consent form and other related documentation given to participants and authorised surrogates
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51	Biological specimens	<a href="#">NA</a>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable
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# BMJ Open

## A feasibility study evaluating the uptake, effectiveness and acceptability of routine screening of pregnant migrants for latent tuberculosis infection in antenatal care: a research protocol

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Manuscripts



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3 **A feasibility study evaluating the uptake, effectiveness and acceptability of routine**  
4 **screening of pregnant migrants for latent tuberculosis infection in antenatal care: a**  
5 **research protocol**  
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## Abstract

### Introduction

Globally, Tuberculosis (TB) is a leading cause of death in women of reproductive age and there is high risk of reactivation of latent tuberculosis infection (LTBI) in pregnancy. The uptake of routine screening of migrants for LTBI in the UK in primary care is low. Antenatal care is a novel setting which could improve uptake and can lend insight into the feasibility and acceptability of offering opt-out screening for LTBI.

### Methods and analysis

This is an observational feasibility study with a nested qualitative component. The setting will be the antenatal clinics in three hospitals in East London, UK. Inclusion criteria are pregnant migrant women aged 16-35 years attending antenatal clinics who are from countries with a TB incidence of greater than 150/100,000 including sub-Saharan Africa, and who have been in the UK for less than 5 years. Participants will be offered LTBI screening with an opt-out interferon gamma release assay (IGRA) blood test, and be invited to complete a questionnaire. Both participants and healthcare providers will be invited to participate in semi-structured interviews or focus groups to evaluate understanding, feasibility and acceptability of routine opt-out LTBI screening. The primary analysis will focus on estimating the uptake of the screening programme along with the corresponding 95% confidence interval. Secondary analysis will focus on estimating the test positivity. Qualitative analysis will evaluate the acceptability of offering routine opt-out LTBI screening to participants and healthcare providers.

## Ethics and dissemination

The study has received the following approvals: Health Research Authority (IRAS 247388) and National Health Service Ethics Committee (19/LO/0557). The results will be made available locally to antenatal clinics and primary care physicians, nationally to NHS England and Public Health England and internationally through conferences and journals.

**Trial Registration Number:** NCT04098341, pre-results.

## Article Summary

### Strengths and limitations of this study:

- The study uses a novel approach of tackling a complex problem of low uptake of latent tuberculosis infection (LTBI) screening in migrants by using an opt-out method and a novel setting: antenatal care
- The study creates new education and training tools for healthcare professionals working in antenatal care
- Our findings will provide a greater understanding of the acceptability of LTBI screening amongst pregnant migrant women and healthcare professionals.
- As this is an observational study, we are unable to demonstrate causality from our results.
- Not being able to interview women who decline LTBI screening may reduce the validity of our findings.

## Introduction

### Context

Tuberculosis (TB) remains a significant global health problem affecting an estimated 10 million people worldwide in 2019 leading to 1.4 million deaths (1). TB is one of the leading causes of death in women of reproductive age (15-45 years) (2). In 2018, an estimated 3.2 million women globally were infected with TB and almost half a million women died from TB (3). Indirect maternal deaths account for 28% of total maternal deaths, of which 15-35% are due to TB (2).

The World Health Organisation defines LTBI as a 'state of persistent immune response stimulation by *Mycobacterium Tuberculosis* antigens without evidence of clinically manifested active TB' (1). A quarter of the world's population is estimated to have latent TB infection (LTBI) (4). Individuals with LTBI have no signs and symptoms of active TB but remain at risk of developing active TB in their lifetime. LTBI acts as a reservoir for active TB and TB elimination requires strategies for LTBI control (5). The risk of reactivation of LTBI is higher in pregnancy (6). This risk may be due to T-cell suppression and reduced interferon-gamma production (7).

In low TB incidence countries, TB transmission is limited and most active cases of TB occur due to reactivation of LTBI imported from high incidence settings (8). Uptake of LTBI screening in primary care is low (9, 10). Antenatal care is a new setting for LTBI screening and understanding the factors affecting the feasibility and acceptability of LTBI screening in this setting are first steps towards developing effective interventions to improving LTBI screening uptake.

## Current knowledge

In women of childbearing age (16-45years), TB is one of three leading causes of death globally (4). Diagnosis of TB in pregnancy is often delayed as pregnancy can mask some of the clinical manifestations of TB (11, 12). TB in pregnancy is associated with poor perinatal, foetal and maternal outcomes (13, 14).

The UK has one of the highest TB incidence rates in Western Europe. The incidence of TB among those born outside the UK is 14 times higher at 39.0 per 100,000 population and accounting for 74% of all new cases of TB in England in 2019 (15). Public Health England's TB migrant health guide strategy recommends migrant screening for LTBI in high incidence areas in England such as the London Boroughs of Tower Hamlets, Newham and Waltham Forrest (16, 17).

The London Borough of Newham was spearheading a large-scale LTBI screening programme in anticipation of the national programme. A total of 20,905 LTBI tests were reported between July 2014 and June 2017 across England with nearly half of the tests taking place in Newham (9, 10). Between April 2015 and June 2016, 5,622 eligible migrants in England were offered an LTBI test, 2,904 (51%) of whom attended for the test (9).

Effective screening for LTBI is key to reducing TB incidence in the UK. There is good evidence that screening and treatment of LTBI is a cost-effective intervention that significantly reduces the risk of developing active disease and the risk of onward transmission (18, 19). The national LTBI migrant screening programme has been

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3 rolled out but there is insufficient evidence on the best setting for uptake of LTBI  
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5 screening.  
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10 There is limited qualitative research about the acceptability to women of LTBI  
11 screening in pregnancy. Reasons for low uptake may be due to stigma of having active  
12 TB or fear of a positive test result affecting their immigration status. An opt-out  
13 approach to LTBI screening may normalise the process and has the potential to  
14 reduce barriers such as stigma, as well as practical barriers (20).  
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24 Provider knowledge and understanding of the risks of TB, screening and treatment  
25 can be a major predictor of successful management of TB (21). Data from a local LTBI  
26 screening programme has highlighted that offer of screening varies amongst GP  
27 practices indicating that health care provider knowledge and attitude may influence  
28 offer of screening (22).  
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38 Evaluating the impact of healthcare provider training to improve TB management has  
39 mainly been performed in low-income countries and there are only a few rigorous TB  
40 training evaluation studies available (21). E-learning modules use pre- and post-  
41 training tests to evaluate acquired knowledge. A GP E-learning module has been  
42 developed by the national TB charity "TB Alert" to enhance knowledge of GPs  
43 responsible for screening and treatment of LTBI but the effectiveness of the module  
44 has not been formally evaluated.  
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56 **Rationale for LTBI screening in antenatal care**  
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3 Pregnancy can predispose to reactivation of LTBI and diagnosis can be delayed due  
4 to reduced awareness among healthcare providers and reluctance to investigate non-  
5 specific TB symptoms by chest radiography (23). Risks of LTBI reactivation and delays  
6 in diagnosis of TB can be mitigated by screening an at-risk pregnant migrant  
7 population for LTBI. A simple clinical algorithm recommended by the WHO based on  
8 absence of current cough, fever, weight loss, and night sweats can help to exclude  
9 active TB disease. Moreover, healthcare professionals will have a higher index of  
10 suspicion for active TB in IGRA positive pregnant migrant women presenting with  
11 symptoms suggestive of TB, thus preventing a delay in diagnosis (24).  
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26 Pregnant migrants may not be accessing routine health care and often do not have a  
27 GP. Antenatal care may therefore be a key opportunity to assess the woman's health  
28 and screen for TB. Antenatal care provides an opportunity for health promotion such  
29 as advocating GP registration and is a time when parents may be particularly receptive  
30 to public health information and promotion.  
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40 Routine opt-out testing has proven effective for other diseases (HIV / Hepatitis B, C)  
41 (25). Factors affecting successful uptake of screening programmes include how the  
42 test is offered, by whom, to whom, and in what setting (26). Pregnant women screened  
43 for HIV during pregnancy perceived routine opt-out HIV testing as beneficial for both  
44 women and their unborn babies (26). Globally, some countries offer routine screening  
45 for TB in pregnancy mainly through symptom screen and sputum examination (19).  
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3 LTBI screening for migrants from high TB incidence countries in antenatal care has  
4 shown high uptake in the U.S. but feasibility of LTBI screening in antenatal clinics in  
5 the UK has not been evaluated (27).  
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## 11 12 **Research hypothesis and aims**

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15 We hypothesise that offering routine opt-out LTBI screening to an at-risk pregnant  
16 migrant population in antenatal care will be feasible and acceptable to pregnant  
17 migrant women and healthcare providers.  
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24 To test our hypothesis, we will assess the uptake, feasibility and acceptability of  
25 screening an at-risk pregnant migrant population for LTBI at routine antenatal booking  
26 visits in secondary care, using opt-out IGRA testing. The results from this feasibility  
27 study will allow us to develop a definitive large-scale cluster randomised controlled  
28 trial (RCT) evaluating the effectiveness of a LTBI screening in antenatal care, the  
29 effectiveness of interventions used to maximise migrant screening for LTBI in  
30 pregnancy and to increase uptake of LTBI treatment postpartum.  
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## 43 **Methods and analysis**

### 44 **Study protocol**

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46 This is a prospective observational feasibility study with nested qualitative research  
47 which will take place in antenatal booking clinics of three hospitals in East London  
48 (The Royal London Hospital, Newham University Hospital and Whipps Cross  
49 University Hospital). The study started on 29<sup>th</sup> April 2019 and the first participant was  
50 recruited on 3<sup>rd</sup> July 2019. The study is due to finish on 31<sup>st</sup> May 2022.  
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Educational and training tools will be developed before the study begins. Healthcare providers involved in antenatal care will be asked to complete an E-learning module on active TB/LTBI, which has been developed by the study team, along with the national TB charity (TB Alert) and the Royal College of Midwives.

Study participants will enter the cohort when they attend the antenatal clinic for their booking appointment, after they meet inclusion criteria (Table 1). Midwives will counsel and offer LTBI screening as an opt-out IGRA (Interferon gamma release assay) blood test alongside other routine investigations for blood borne viruses at the initial booking appointment. The study will assume valid implied consent for participation if women undertake an IGRA test at the time it is offered by the midwife on an opt-out basis. Participants will be given a Participant Information Sheet by the midwife at this appointment detailing the study. Routine blood tests, including IGRA, will be taken by phlebotomists based in antenatal care.

**Table 1: Inclusion and exclusion criteria**

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>- Pregnant migrant women aged 16-35 years</li> <li>AND</li> <li>- from high TB incidence countries (incidence of TB of &gt;150/100,000 including sub-Saharan Africa)</li> <li>AND</li> <li>- who have been in the UK for less than 5 years</li> </ul>	<ul style="list-style-type: none"> <li>- Previous history of TB or LTBI</li> <li>- Individuals who are unable to consent</li> <li>- Evidence of current active TB (based of history, examination, blood tests, chest X-ray findings or other radiological findings)</li> </ul>

At the time of offer of LTBI screening, we will record routine clinical data of all eligible pregnant migrant women including those who do not accept screening. Data on age,

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3 ethnicity, year of entry to the UK, pre-existing medical conditions and antenatal history  
4 which is routinely recorded in the medical notes will be collected.  
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10 All eligible pregnant migrant women will be screened for active TB by their midwives  
11 using a standardised symptom assessment questionnaire that includes the WHO  
12 recommended TB symptoms screen during their initial booking appointment. Study  
13 participants with a positive IGRA blood test will then undergo screening for active TB  
14 using the WHO recommended TB symptoms screen at 20 weeks, 30-34 weeks,  
15 delivery and post-partum. Data on symptoms of active TB will be collected at each  
16 time point (see Figure 1).  
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28 Participants will leave the study 6 weeks post-delivery or at the time of miscarriage if  
29 they have had a miscarriage.  
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35 Study participants with a positive IGRA blood test will be referred to the local TB clinic  
36 (if screened at The Royal London Hospital or Whipps Cross University Hospital) or to  
37 their GP (if screened in Newham University Hospital). TB clinics or GPs will review  
38 these individuals and initiate LTBI treatment according to local protocols.  
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47 All eligible pregnant women will be asked to complete a short questionnaire on  
48 acceptability of LTBI screening, knowledge about TB/LTBI, and barriers to screening.  
49 At the end of pregnancy, women will be asked to complete the same questionnaire to  
50 compare the perception and knowledge of active TB/LTBI before and after the  
51 screening intervention. Trained research personnel will obtain written informed  
52 consent from the participant for the questionnaire.  
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5 We have used the SPIRIT reporting guidelines for this paper (28).  
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## 9 10 Outcomes

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12 Our primary outcomes are (i) the uptake of screening for LTBI in antenatal care  
13 assessed by the proportion of eligible migrant women offered a test who accepted  
14 LTBI screening, and (ii) the offer of IGRA blood test screening by healthcare providers  
15 assessed by the proportion of migrant women eligible for screening who were offered  
16 an IGRA test.  
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26 Secondary outcomes are: rates of LTBI and active TB identified in pregnant migrant  
27 women during the study period, time to diagnosis, understanding and acceptability of  
28 LTBI screening and acceptability of interventions to increase screening uptake,  
29 perceived facilitators and barriers influencing uptake of LTBI screening and treatment  
30 uptake post-partum, increase in knowledge and awareness about active TB/ LTBI  
31 amongst pregnant migrant women and healthcare providers and estimation of some  
32 of the parameters required for evaluation of cost-effectiveness of LTBI screening in  
33 antenatal care compared to primary care.  
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47 Process outcomes of the study are the numbers of eligible participants and screening  
48 acceptance rate, proportion of eligible pregnant migrant women who were offered  
49 LTBI screening, views and experiences of participants on study recruitment methods,  
50 data collection methods, and retention in the study and level of NHS support required  
51 for the proposed definitive cluster RCT.  
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## Patient and Public Involvement

Healthwatch Newham conducted a survey to evaluate patient experiences of the LTBI screening programme in Newham, to identify the key factors that influence the uptake of screening, and to understand why patients decline screening. The results of this survey have influenced the design of this study, and migrants with LTBI has provided useful information about how LTBI screening could be better conducted. Evaluation of patient experiences demonstrated that migrants would like to be offered a LTBI test directly by their GP or nurse and that the test should be part of a general check-up. Our intervention has been designed to provide this by incorporating the offer of an Interferon-gamma release-assay (IGRA test) into routine antenatal care check-ups by midwives. The concept and the study design has been developed in close collaboration with TB Alert (UK TB charity), with the support of the East London Katherine Twining network PPI group (Katie's Team) and the Centre for Maternal and Child Health Research at City, University of London's service user panel and former TB/ LTBI patients. PPI members felt that testing for LTBI as an opt-out approach is an acceptable intervention for pregnant migrant women.

## Sample size

A sample of 200 pregnant migrant women offered testing allows this study to estimate the screening uptake rate (key primary outcome for the feasibility study) with adequate precision across a range of possible values of the rate. If the uptake rate is 50% (at which precision is lowest) then this can be estimated within 6% either side, i.e., a 95% confidence interval of 44-56%. If, however the rate is as high as 80% (or equivalently as low as 20%) then the rate can be estimated within 5%.

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3 These precision calculations are based on the standard Normal approximation and  
4 formula for a 95% confidence interval for a proportion p based on a sample size n: p  
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6  $\pm 1.96 \times \sqrt{p \times (1-p) / n}$ .  
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## 10 11 12 Statistical analysis

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15 The primary analysis will focus on estimating the uptake of the screening programme  
16 along with the corresponding 95% confidence interval. Secondary analysis will focus  
17 on estimating the test positivity. Associations between uptake and potential  
18 explanatory variables will be assessed using the Chi squared test, and the strength of  
19 association will be presented as an odds ratio with 95% confidence interval.  
20 Identification of which characteristics are associated after adjusting for others will be  
21 performed using multiple logistic regression, and adjusted odds ratios will be  
22 presented.  
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## 36 37 38 Nested qualitative research

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40 Study participants will be invited to participate in semi-structured interviews or focus  
41 groups to explore acceptability of LTBI screening in antenatal care, understanding of  
42 LTBI amongst eligible pregnant women and health care providers, potential use of  
43 educational resources in each of these groups and potential barriers/facilitators to  
44 LTBI screening and treatment uptake.  
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53 A theoretical framework derived from the literature, survey and demographic data will  
54 be used to select a purposive sample to explore a range of relevant opinions and  
55 experiences. This will include interviewing women who have taken up screening as  
56 well as those who have not, or where this is not practicable, those within communities  
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3 that might be offered screening. Sample size is guided by data saturation: for thematic  
4 analysis of semi-structured interviews this is likely to occur between 10 and 40  
5 participants and for focus groups 24-32 participants. Trained research personnel will  
6 obtain written informed consent from the participant for the semi-structured interviews  
7 and focus groups.  
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17 Study participants will be invited to take part in two interviews. The first will take place  
18 early in the study (see Figure 1) and will explore participants' understanding of LTBI,  
19 along with perceived acceptability of the study and intervention, participants'  
20 perceptions of their own risk of TB, their understanding of the prevention of TB and  
21 their views on the opt-out screening. The interview will also explore factors that  
22 influence participants' decision to be screened and suggestions for what might  
23 motivate them or other women to be screened, and their perspectives on the study  
24 data collection methods. Furthermore, participants' views and attitudes to LTBI  
25 treatment during or immediately after pregnancy will be assessed.  
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40 A second follow-up interview will take place towards the end of the study (see Figure  
41 1) with those participants who test IGRA positive to discuss their response to receiving  
42 a positive screening result, feelings around future treatment and explore what factors  
43 might encourage/ discourage women from taking up treatment post-partum. Themes  
44 and concepts identified from the first set of interviews will inform the topics raised in  
45 the second interviews. This iterative approach will allow follow-up interviews to build  
46 on and explore further the participant experience, and to incorporate issues raised by  
47 other participants.  
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3 Women who decline participation in LTBI screening will be asked by recruiting  
4 midwives whether they consent for an independent researcher to contact them for an  
5 interview to explore their views. If few 'declining' women consent, up to three  
6 community-based focus groups will be conducted with migrant women of childbearing  
7 ages, and if appropriate men, in relevant populations to explore their awareness and  
8 their views about screening.  
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19 Semi-structured interviews will also be conducted with 6-8 healthcare providers,  
20 including those who are involved in delivering the intervention, those who have  
21 expertise in managing pregnant women and local GPs to whom pregnant women may  
22 seek advice about screening and treatment for LTBI.  
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30 Two further focus groups with midwives, physicians and nurses, each involving around  
31 8-12 participants will add a different perspective to that of the women. Their views and  
32 experiences on approaches to screening for TB/ LTBI in antenatal care, along with  
33 perceived barriers/ facilitators to LTBI screening and treatment, from a service or  
34 community perspective, will be explored.  
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44 Interview and focus group data will be analysed thematically, using constant  
45 comparison techniques, to identify, interpret and report patterns (themes) representing  
46 beliefs and experiences that participants share (or differ on) in relation to the research  
47 questions. The interviews and focus groups will also assess the views and  
48 experiences of participants and healthcare providers on study recruitment methods,  
49 data collection methods, facilitators and barriers to involvement, and compliance to  
50 study procedures.  
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## Data management

All study data will be managed according to the Clinical Effectiveness Group (CEG) data management policy. Data will be entered directly onto a purpose-built database where possible (paper CRFs will be used as a backup if required).

Source data will be taken from the women's antenatal records and entered directly onto a database. Questionnaire data will be generated directly and then entered into the database.

The Investigator will ensure that patient anonymity is protected and maintained. They will also ensure that patient identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

The study will collect personal data and information about the participants either directly or from their clinical team. Routine clinical data will be entered onto a secure computer database, either by the research team or directly via a secure internet connection. The data will be pseudoanonymised. Any data processed by those outside the research team (research registrar, nurse or project coordinator) will be anonymised. All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.



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6 Transcripts from interviews and focus groups will be archived securely and audio-  
7  
8 records destroyed securely following study closure in accordance with City, University  
9  
10 of London's data management and retention policy. As all transcripts are de-identified  
11  
12 at transcription stage to ensure confidentiality, and personal data will be securely  
13  
14 destroyed one year after study closure, no personal data will be included in archived  
15  
16 records.  
17  
18  
19  
20  
21

## 22 Ethics and Dissemination:

23  
24 The study has received approval from The Health Research Authority (IRAS 247388)  
25  
26 and London- City & East Research Ethics Committee (19/LO/0557). The study has  
27  
28 been registered with clinicaltrials.gov (NCT04098341, pre-results). The results will be  
29  
30 made available locally to antenatal clinics and primary care physicians, nationally to  
31  
32 NHS England and Public Health England and internationally through conferences  
33  
34 and journals.  
35  
36  
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## 40 Discussion

41  
42 Systematic national implementation of the LTBI screening programme is essential to  
43  
44 achieving the aims of the collaborative strategy and support the WHO goal of TB  
45  
46 elimination. The uptake of LTBI screening amongst migrants is low. This study seeks  
47  
48 to provide patient-centred, migrant-inclusive evidence of the uptake, feasibility and  
49  
50 acceptability of routine opt-out LTBI screening amongst pregnant migrants in antenatal  
51  
52 care. It also seeks to understand potential facilitators and barriers from a healthcare  
53  
54 provider perspective. We will assess whether this site of screening results in higher  
55  
56 rates of LTBI screening uptake. The results of this study will inform the design of a  
57  
58  
59  
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1  
2  
3 cluster RCT trial evaluating the effectiveness of acceptable interventions to maximise  
4 migrant screening for LTBI in pregnancy, and to increase uptake of LTBI treatment  
5  
6  
7  
8 postpartum.  
9

## 10 11 12 **Funding**

13  
14  
15 This study has been funded by National Institute of Health Research (NIHR) Research  
16  
17 for patient benefit programme (Funding reference: PB-PG-0317-20039).  
18  
19

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23  
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25  
26 Institute of Health Research (Funding reference: PB-PG-0317-20039), Health  
27  
28 Research Authority (IRAS 247388) and London- City & East Research Ethics  
29  
30 Committee (reference: 19/LO/0557).  
31  
32  
33  
34  
35

## 36 37 38 **Authors' contributions**

39 HK, ST, CMcC, AC, ZD, PJW, CG and IA designed the study and secured funding.  
40  
41 AR trained healthcare providers and recruited participants for the study. AR wrote  
42  
43 the first draft of the manuscript. All other authors reviewed drafts of this manuscript  
44  
45 and commented upon them.  
46  
47  
48

## 49 50 51 **Conflict of Interest**

52 PJW acknowledges funding from the MRC Centre for Global Infectious Disease  
53  
54 Analysis (grant number MR/R015600/1); this award is jointly funded by the MRC and  
55  
56 Foreign, Commonwealth and Development Office (FCDO) under the MRC/FCDO  
57  
58 Concordat agreement and is also part of the European and Developing Countries  
59  
60

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Figure 1. Timeline of study project (Assessment and follow-up of migrant women)

**Word count: 3909**

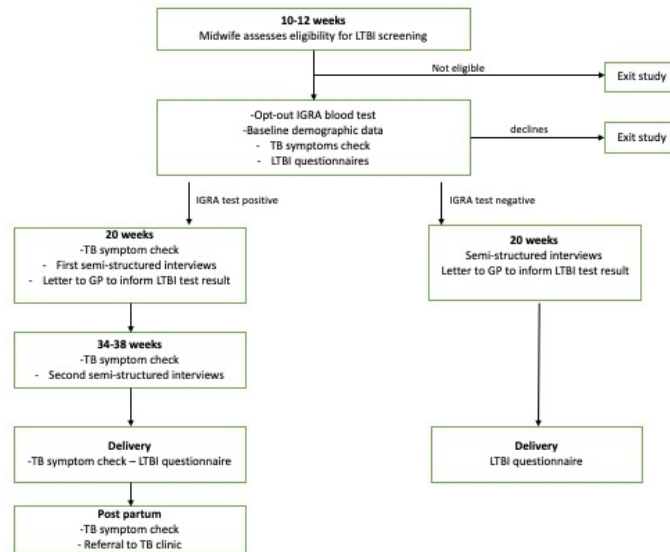


Figure 1. Timeline of study project (Assessment and follow-up of migrant women)

338x190mm (54 x 54 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry	
Trial registration: data set	NA	All items from the World Health Organization Trial Registration Data Set	
Protocol version	NA	Date and version identifier	
Funding	9	Sources and types of financial, material, and other support	
Roles and responsibilities: contributorship	11	Names, affiliations, and roles of protocol contributors	

1	Roles and	NA	Name and contact information for the trial sponsor
2	responsibilities:		
3	sponsor contact		
4	information		
5			
6			
7	Roles and	NA	Role of study sponsor and funders, if any, in study design;
8	responsibilities:		collection, management, analysis, and interpretation of data;
9	sponsor and funder		writing of the report; and the decision to submit the report for
10			publication, including whether they will have ultimate authority
11			over any of these activities
12			
13			
14			
15	Roles and	NA	Composition, roles, and responsibilities of the coordinating
16	responsibilities:		centre, steering committee, endpoint adjudication committee,
17	committees		data management team, and other individuals or groups
18			overseeing the trial, if applicable (see Item 21a for data
19			monitoring committee)
20			
21			
22			
23			
24	<b>Introduction</b>		
25			
26	Background and	3-5	Description of research question and justification for
27	rationale		undertaking the trial, including summary of relevant studies
28			(published and unpublished) examining benefits and harms for
29			each intervention
30			
31			
32			
33	Background and	NA	Explanation for choice of comparators
34	rationale: choice of		
35	comparators		
36			
37			
38	Objectives	4-5	Specific objectives or hypotheses
39			
40			
41	Trial design	5-6	Description of trial design including type of trial (eg, parallel
42			group, crossover, factorial, single group), allocation ratio, and
43			framework (eg, superiority, equivalence, non-inferiority,
44			exploratory)
45			
46			
47			
48	<b>Methods:</b>		
49	<b>Participants,</b>		
50	<b>interventions, and</b>		
51	<b>outcomes</b>		
52			
53			
54	Study setting	5-6	Description of study settings (eg, community clinic, academic
55			hospital) and list of countries where data will be collected.
56			Reference to where list of study sites can be obtained
57			
58			
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60			

1	Eligibility criteria	5-6	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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5			
6	Interventions:	5-6	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
7	description		
8			
9			
10	Interventions:	NA	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)
11	modifications		
12			
13			
14			
15	Interventions:	NA	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
16	adherence		
17			
18			
19			
20			
21	Interventions:	NA	Relevant concomitant care and interventions that are permitted or prohibited during the trial
22	concomitant care		
23			
24			
25	Outcomes	6	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
26			
27			
28			
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30			
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33			
34	Participant timeline	Figure	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
35		1	
36			
37			
38			
39			
40	Sample size	7	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
41			
42			
43			
44			
45	Recruitment	5-6	Strategies for achieving adequate participant enrolment to reach target sample size
46			
47			
48			

**Methods: Assignment of interventions (for controlled trials)**

54	Allocation: sequence generation	NA	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be
55			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

1			
2			
3			
4	Allocation	NA	Mechanism of implementing the allocation sequence (eg,
5	concealment		central telephone; sequentially numbered, opaque, sealed
6			envelopes), describing any steps to conceal the sequence until
7	mechanism		interventions are assigned
8			
9			
10	Allocation:	NA	Who will generate the allocation sequence, who will enrol
11	implementation		participants, and who will assign participants to interventions
12			
13			
14	Blinding (masking)	NA	Who will be blinded after assignment to interventions (eg, trial
15			participants, care providers, outcome assessors, data analysts),
16			and how
17			
18			
19	Blinding (masking):	NA	If blinded, circumstances under which unblinding is
20	emergency unblinding		permissible, and procedure for revealing a participant's
21			allocated intervention during the trial
22			
23			
24			

**Methods: Data collection, management, and analysis**

25			
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32	Data collection plan	8-9	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and
35			a description of study instruments (eg, questionnaires,
36			laboratory tests) along with their reliability and validity, if
37			known. Reference to where data collection forms can be found,
38			if not in the protocol
39			
40			
41			
42			
43	Data collection plan:	8-9	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for
45			participants who discontinue or deviate from intervention
46			protocols
47			
48			
49			
50	Data management	8-9	Plans for data entry, coding, security, and storage, including
51			any related processes to promote data quality (eg, double data
52			entry; range checks for data values). Reference to where details
53			of data management procedures can be found, if not in the
54			protocol
55			
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1	Statistics: outcomes	7	Statistical methods for analysing primary and secondary
2			outcomes. Reference to where other details of the statistical
3			analysis plan can be found, if not in the protocol
4			
5			
6	Statistics: additional	7	Methods for any additional analyses (eg, subgroup and adjusted
7	analyses		analyses)
8			
9			
10	Statistics: analysis	NA	Definition of analysis population relating to protocol non-
11	population and		adherence (eg, as randomised analysis), and any statistical
12	missing data		methods to handle missing data (eg, multiple imputation)
13			
14			
15	<b>Methods: Monitoring</b>		
16			
17	Data monitoring:	NA	Composition of data monitoring committee (DMC); summary
18	formal committee		of its role and reporting structure; statement of whether it is
19			independent from the sponsor and competing interests; and
20			reference to where further details about its charter can be found,
21			if not in the protocol. Alternatively, an explanation of why a
22			DMC is not needed
23			
24			
25			
26			
27	Data monitoring:	<a href="#">NA</a>	Description of any interim analyses and stopping guidelines,
28	interim analysis		including who will have access to these interim results and
29			make the final decision to terminate the trial
30			
31			
32			
33	Harms	NA	Plans for collecting, assessing, reporting, and managing
34			solicited and spontaneously reported adverse events and other
35			unintended effects of trial interventions or trial conduct
36			
37			
38	Auditing	<a href="#">NA</a>	Frequency and procedures for auditing trial conduct, if any, and
39			whether the process will be independent from investigators and
40			the sponsor
41			
42			
43	<b>Ethics and</b>		
44	<b>dissemination</b>		
45			
46			
47	Research ethics	<a href="#">9</a>	Plans for seeking research ethics committee / institutional
48	approval		review board (REC / IRB) approval
49			
50			
51	Protocol amendments	<a href="#">NA</a>	Plans for communicating important protocol modifications (eg,
52			changes to eligibility criteria, outcomes, analyses) to relevant
53			parties (eg, investigators, REC / IRBs, trial participants, trial
54			registries, journals, regulators)
55			
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1	Consent or assent	<a href="#">NA</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
2			
3			
4			
5	Consent or assent:	<a href="#">NA</a>	Additional consent provisions for collection and use of
6	ancillary studies		participant data and biological specimens in ancillary studies, if applicable
7			
8			
9			
10	Confidentiality	<a href="#">8-9</a>	How personal information about potential and enrolled
11			participants will be collected, shared, and maintained in order to
12			protect confidentiality before, during, and after the trial
13			
14			
15	Declaration of	<a href="#">11</a>	Financial and other competing interests for principal
16	interests		investigators for the overall trial and each study site
17			
18			
19	Data access	<a href="#">8-9</a>	Statement of who will have access to the final trial dataset, and
20			disclosure of contractual agreements that limit such access for
21			investigators
22			
23			
24	Ancillary and post trial	<a href="#">NA</a>	Provisions, if any, for ancillary and post-trial care, and for
25	care		compensation to those who suffer harm from trial participation
26			
27			
28	Dissemination policy:	<a href="#">9</a>	Plans for investigators and sponsor to communicate trial results
29	trial results		to participants, healthcare professionals, the public, and other
30			relevant groups (eg, via publication, reporting in results
31			databases, or other data sharing arrangements), including any
32			publication restrictions
33			
34			
35			
36	Dissemination policy:	<a href="#">NA</a>	Authorship eligibility guidelines and any intended use of
37	authorship		professional writers
38			
39			
40	Dissemination policy:	<a href="#">NA</a>	Plans, if any, for granting public access to the full protocol,
41	reproducible research		participant-level dataset, and statistical code
42			
43			
44	<b>Appendices</b>		
45			
46	Informed consent	<a href="#">NA</a>	Model consent form and other related documentation given to
47	materials		participants and authorised surrogates
48			
49			
50	Biological specimens	<a href="#">NA</a>	Plans for collection, laboratory evaluation, and storage of
51			biological specimens for genetic or molecular analysis in the
52			current trial and for future use in ancillary studies, if applicable
53			
54			
55			

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