Intervening with a Manualised Package to AChieve treatment adherence in people with Tuberculosis
The IMPACT study

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ISRCTN95243114

PROTOCOL VERSIONS

Version stage	Version no	Version date	Protocol updated & finalised by	Detail the reason(s) for the protocol update
Current	3.0	21/08/2018	Marc Lipman Marcia Darvell	NIHR feedback
Previous	2.0	17/05/2018	Marc Lipman	JRO and investigator comments
Previous	1.1	18/04/2018	Colin Campbell Elisha Pickett	JRO and investigator comments
Previous	1.0	2018-01-31	Marc Lipman	Initial version

DECLARATIONS

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

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

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:  Date 21/08/2018

Print Name (in full): Marc Lipman

Position: Consultant physician and Reader

On behalf of the Study Sponsor:

Signature:..... Date...../...../.....

Print Name (in full):.....

Position:.....

STUDY SUMMARY

Identifiers	
IRAS Number	231542
REC Reference No	REC
Sponsor Reference No	17/0726
Other research reference number(s) (if applicable)	16/88/06 (National Institute for Health Research- NIHR)
Full (Scientific) title	Intervening with a Manualised Package to AChieve treatment adherence in people with Tuberculosis: the IMPACT study.
Health condition(s) or problem(s) studied	Adherence to tuberculosis treatment in vulnerable populations
Study Type i.e. Cohort etc.	Scoping review, qualitative work, pilot cluster randomised controlled trial, process evaluation.
Target sample size	Formative Research: • Interviews with patients (6-8 per site), Interviews with patient's family members/ carers (1-2 per site). Total 30 • Interviews with patients (cognitive assessment) (2-4 per site). Total 10 • Interviews with providers (4-6 per site). Total 20 Pilot Stage: • 80 patients on treatment for tuberculosis. Process Evaluation: • 20 interviews with patients 20 interviews with healthcare providers
STUDY TIMELINES	
Study Duration/length	36 months
Expected Start Date	1/01/2018
End of Study definition and anticipated date	31/12/2020
Key Study milestones	Ethical submission and staff recruitment, scoping review and intervention development, pilot study, process evaluation.
FUNDING & OTHER	
Funding	NIHR Health Technology Assessment
Other support	N/A
STORAGE OF SAMPLES (if applicable)	
Human tissue samples	N/A
Data collected / Storage	All records will have a unique identifier. All data will be handled according to current General Data Protection

	Regulations and Caldecott principles, including anonymisation prior to analysis and publication, as well as storage in password protected files and on secure (NHS) computers within the UCL Respiratory Department. Need-to-know access only will be provided.
KEY STUDY CONTACTS	
Chief Investigator	Dr Marc Lipman Consultant Physician & Reader University College London Centre for Respiratory Medicine, The Grove Centre, Royal Free Hospital, Rowland Hill Street, London, NW3 2AG Email: marclipman@nhs.net Tel: 020 7317 7560

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI's role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The CI is responsible for the submission of annual reports, as required. The CI will notify REC of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties- this includes the CI of any breaches or incidents related to the study.

KEY WORDS

Adherence
Manualised
Treatment
Tuberculosis

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRCT	Cluster Randomised Controlled Trial
CRO	Contract Research Organisation
DOT	Directly observed therapy
DMC	Data Monitoring Committee
GAfREC	Governance Arrangement for NHS Research Ethics
GDPR	General Data Protection Regulations
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
MD	Medical Device
MDR	Multidrug Resistant
ISRCTN	International Standard Randomised Controlled Studies Number
PAPA	Perceptions and Practicalities Approach
PI	Principal Investigator
PHE	Public Health England
PIS	Participant Information Sheet
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
QA	Quality Assurance
TMF	Trial Master File
QMU	Queen Margaret University, Edinburgh
QMUL	Queen Mary University of London
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TB	Tuberculosis
UCL	University College London
UK	United Kingdom
VOT	Video Observed Therapy

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1 INTRODUCTION AND RATIONALE

Compared to the rest of the UK and Western Europe, England has a major problem with the infectious disease tuberculosis (TB). The large amount of TB in the country has led Public Health England (PHE) and NHS England to develop a national TB control plan[1]. Treatment lasts a long time (at least six months, and even more in people with drug resistant TB). Finding ways to make sure that people are able to take all of their medication as prescribed is one of the plan's priorities. If people miss doses (described as being 'non-adherent or poorly adherent to treatment), their TB can develop resistance to the usual drugs, risking both their health and that of others.

Poor adherence to treatment can occur for a number of reasons. These include someone not knowing much about their disease condition and why they need to take their treatment, side effects from the drugs, or people choosing to stop their treatment as soon as they feel better, rather than taking the entire course. Wider psychological, social, cultural and economic issues, including stigma due to having TB, lack of support from family members or friends, homelessness, drug and alcohol misuse and barriers to good access to NHS services also play a part. Poor adherence to treatment for TB is a key driver of negative patient outcomes and impedes population-level control through increased transmission and development of drug resistance. In the UK, treatment completion and adherence among TB patients is variable.

Patients with multi-drug resistant (MDR) TB, whether acquired through poor treatment adherence or as a primary infection, have particularly poor treatment completion (around 60%, compared to over 85% in people with drug sensitive TB). Vulnerable migrants similarly have a higher risk of poor treatment completion[2]. Although patients without drug resistant TB and no social risk factors are more likely to adhere to their treatment, if they do become non adherent, they can also contribute to ongoing transmission and are at risk of developing drug resistance. Unfortunately, current methods of treatment support are not particularly helpful in identifying these individuals; and do not try to explore the important underlying reasons for non-adherence which may themselves need to be addressed.

The need to ensure that patients adhere to treatment - and finding ways to support them in doing so has been highlighted in the PHE/NHS England collaborative TB strategy[3]. Subsequent NICE guidance noted the lack of robust research in this area[4].

2 RESEARCH QUESTION, AIM AND OBJECTIVES

2.1 Research Question

Can a manualised package of interventions be developed to help overcome the social and cultural factors that lead to poor adherence to treatment in patients with active tuberculosis?

2.2 Aim

To develop, pilot, and evaluate process and interim outcomes for a manualised intervention package that improves adherence to treatment for TB among NHS patients at risk of poor adherence due to social and cultural factors.

2.3 Objectives

1) Synthesise current knowledge on (a) determinants of adherence to treatment for TB, and (b) interventions that can support adherence, with particular emphasis on social and cultural

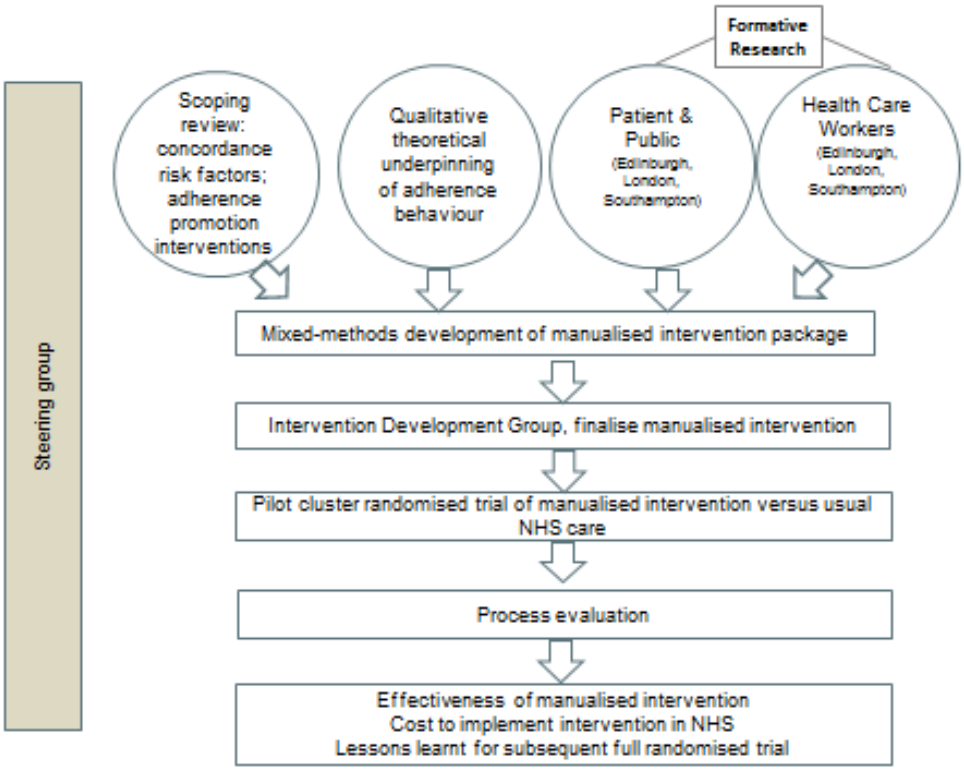
barriers. (Scoping Review and Conceptual Framework)
2) Apply a conceptual framework of adherence endorsed by NICE Guidelines and the Perceptions and Practicalities (PAPA) approach (see Appendix 1: PAPA Framework) to elucidate and address the personal, socio-cultural, and health systems context, mechanisms, and pathways of poor adherence among NHS patients with TB. (Formative Research)
3) Develop a manualised intervention package with multiple components that can identify (a) NHS patients most at risk of non-adherence, (b) the salient modifiable barriers; and (c) tailor support mechanisms to meet individual needs by matching appropriate interventions to specific barriers, as recommended by NICE. (Development of Intervention)
4) Pilot the intervention package in people at risk of poor adherence to define how the components work in combination and separately. (Pilot Study)
5) Evaluate the process of implementation of this intervention through describing the challenges and facilitators in delivering the package as intended (fidelity, reach) and assessing the impact of the intervention through evaluation of adherence indicators. (Process Evaluation)
6) Use the findings of the pilot to assess the costs of delivering the manualised intervention in an NHS setting, and to guide development of a proposal for a full randomised controlled trial (RCT). (Cost Analysis and Future Work)

3 STUDY DESIGN

This section is presented in six sub-sections, reflecting the six objectives: i) Scoping Review and Conceptual Framework; ii) Formative Research; iii) Development of Intervention; iv) Pilot Study; v) Process Evaluation; vi) Cost Analysis and Future Work.

Although these components are described separately below, the research activities for each will overlap, and some will run concurrently (Appendix 2: Gantt chart). This study uses a mixed methods approach, with different methods employed in each of the study components. For example, behavioural science methods will be used to understand the determinants of acceptability and adherence in the pilot study, the scoping review will inform the development of the manual and a cluster randomized design will be used to pilot the intervention. The full programme of work and relationships between subsections is shown in Figure 1.

Figure 1- Components of the IMPACT study



3.1 Scoping Review and Conceptual Framework (i)

Scoping Review The scoping review of relevant literature on 'adherence to TB treatment' will inform a conceptual framework for the project methods and approach. The review will investigate the following research questions:

i) What personal, social, cultural, health systems-related, and structural factors affect individuals' ability to adhere to TB treatment?
ii) What kinds of intervention have been developed to address the multiple levels (personal, social, cultural, system and structural) at which barriers to adherence may operate?
iii) What is the evidence for the successful impact of interventions to address barriers to adherence to treatment for TB?

To address these three questions, researchers at QMU (Queen Margaret University, Edinburgh) and UCL will conduct three separate reviews that will enable the following outputs:

1. A narrative synthesis of findings from *qualitative* studies examining the personal, social, cultural, health systems-related and structural factors affecting adherence to treatment for TB (led by QMU, Edinburgh)
2. A critical review of *quantitative* studies examining the personal, social, cultural, health systems-related and structural factors affecting adherence to treatment for TB (led by University College London, UCL)
3. A critical review of studies that have examined the effectiveness of interventions to improve

adherence in people taking treatment for TB (led by UCL).

Together, these three reviews will enable us to conduct a critical interpretive synthesis of findings from qualitative and quantitative studies examining the assumptions and mechanisms of effect underlying interventions to improve adherence to treatment for TB (QMU and UCL).

3.1.1 Scoping Review of qualitative studies examining the personal, social, cultural, health systems-related, and structural factors affecting adherence to treatment for TB.

We adopt a recent definition of a scoping review as "a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge" [(5)]. We will follow six stages in conducting the scoping review[(6)]:

1) Clarify and link the purpose and research question (s).
2) Identify relevant studies, using the following inclusion and exclusion criteria

   Inclusion criteria:
   i) studies that examine reasons for adherence and non-adherence to treatment for TB from the perspectives of children, adult patients, care givers, or health care providers AND studies that evaluate interventions to support adherence to treatment for TB
   ii) studies from any discipline or theoretical tradition that uses qualitative methods, including papers that used both qualitative and quantitative methods and reported qualitative findings

   Exclusion criteria:
   i) studies that exclusively use quantitative methods to examine reasons for adherence/non-adherence to TB treatment AND/OR studies that evaluate uptake of interventions to support adherence to TB treatment
   ii) studies published in languages other than English

3) Use an iterative team approach (QMU team) to select studies, refine the search strategy, and review articles for inclusion.
4) Extract and chart data based on a collectively agreed data-charting form that includes variables relevant to the research question(s). Charting will be iterative; the first 5-10 studies included will be done independently by two researchers (from QMU) to check consistency in the approach.
5) Analyse the studies in three stages including: a descriptive bibliometric summary, a qualitative analysis of the key themes emerging from the studies as pertinent to the research question(s), and a critical interpretive synthesis[(7)].
6) Report results and implications of scoping review for development of the manualized intervention; and consult with the Intervention Development Group to incorporate any further issues or suggestions.

3.1.2 Critical review of quantitative studies to synthesise evidence on the personal, social, cultural, health systems-related and structural factors affecting adherence to treatment for TB.

Inclusion criteria:

i) empirical studies employing prospective, longitudinal, cross-sectional or retrospective designs
ii) studies reporting information on individuals with active TB
iii) when studies present treatment completion rates, a definition for completion has been provided

Exclusion criteria:

i) studies that exclusively use qualitative methods to examine reasons for adherence/non-adherence to treatment for TB
ii) studies published in languages other than English

Exposure: The primary exposures of interest are the risk factors that may influence adherence. Thus, studies reporting on patient demographics, knowledge and attitudes, characteristics of TB disease, social characteristics of patients and comorbidities will be included in the review. As will studies looking at health systems and environmental factors.

Outcome: Studies will be included in the review if the primary outcome is adherence. Adherence will be determined by for example self-reporting through attendance at follow-up appointments, collecting prescriptions from clinics, pill counts and pharmacy reports, electronic devices (such as Medication Event Monitoring System caps), urine inspection, testing for drug levels and directly observed therapy attendance or video-observed therapy sessions.

Selection process: For the initial screening stage, two reviewers will select articles by screening the title and abstract to assess whether they fulfil the study eligibility criteria. Two reviewers will conduct abstract selection and critical appraisal of the full-text articles. Reasons for rejection of articles during both the initial screening and at the full-text screening process will be noted and any discrepancies discussed.

Data extraction: Data extraction will be systematized using a pre-defined standardised template.

3.1.3 Critical review of studies that have examined the effectiveness of interventions to improve adherence in people taking treatment for TB

We will build on existing systematic reviews of interventions, including studies that assess the effectiveness of a strategy or intervention aimed at improving adherence, such as the provision and delivery of information and/or education; enablers and/or incentives; social support; case management approaches; and studies of modifiable determinants of treatment adherence.

The comparator will either be usual care or an alternative intervention.

Population: Adults, young people and children who have or are suspected to have TB, regardless of drug sensitivity.

Outcome: Treatment adherence. Adherence will be determined by for example self-reporting through attendance at follow-up appointments, collecting prescriptions from clinics, pill counts and pharmacy reports, electronic devices (such as Medication Event Monitoring System caps), urine inspection, testing for drug levels and directly observed therapy attendance or video-observed therapy sessions.

Selection process: For the initial screening stage, two reviewers will select articles by screening the title and abstract to assess whether they fulfil the study eligibility criteria. Two reviewers will conduct abstract selection and critical appraisal of the full-text articles. Reasons for rejection of articles during both the initial screening and at the full-text screening process will be noted and any discrepancies discussed.

Data extraction: Data extraction will be systematized using a pre-defined standardised template.

Applicability: Are the findings relevant to patients treated within the NHS?

For the two critical reviews, a random sample of 10% of references will be screened independently by two reviewers at UCL, and differences resolved by consensus. Screening will occur of titles initially, followed by abstracts and then full texts. The degree of concordance will be assessed and, if above 95%, the remaining references will be screened by one reviewer alone. Levels of concordance will be assessed and differences resolved by consensus and the involvement of other members of the research team, all of which will be fully documented.

3.1.4 Search Strategies

Development of search strategies for the three reviews will be created with advice from expert Information and Library Support from QMU and UCL. The initial strategy will be developed in MEDLINE (Ovid Interface), and then adapted for other databases.

Scoping review for qualitative literature: MEDLINE, EMBAS, ECINAHL, PsychInfo, Assia, Web of Science, Scopus, Open Grey, Google Scholar and, Cochrane databases. Our draft search strategy will combine MeSH and free text terms (including term explosion) for the following: tuberculosis AND (adherence OR compliance OR concordance) AND treatment AND (qualitative OR ethnograph* OR anthropolog* OR sociol* OR phenomenol* OR narrative)

Critical review for quantitative literature: CINAHL, MEDLINE, PsycINFO, Assia, Web of Science, Scopus, Open Grey, Cochrane databases and Google Scholar. We will use combined MeSH and free text terms (including term explosion) for the following search strategy: tuberculosis, patient acceptance of health care, adherence, non-adherence, concordance, directly observed therapy

Critical review of interventions to support adherence: MEDLINE, EMBAS, ECINAHL, PsychInfo, Assia, Web of Science, Scopus, Open Grey, Google Scholar and, Cochrane databases. Our draft search strategy will combine MeSH and free text terms (including term explosion) for TB; interventions (education, information dissemination, social support, incentives, case management, enablers, directly observed therapy (DOT), video observed therapy (VOT), reminders, e-health, m-health);and treatment outcomes/adherence.

A filter for human studies will be applied. No filters for study type will be applied for TB studies. We will remove editorials, news items and letters. Searches will be performed only for English Language articles.

3.1.5 Database Development

Reference databases will be created in EndNote or equivalent, where records will also be manually and electronically de-duplicated. Screening and extraction will occur in a Microsoft Access database to ensure that all retrieved references are fully tracked.

3.1.6 Quality assessment

Studies will be quality assessed and data extracted into pre-designed databases by the respective reviewers (QMU, UCL) and using the appropriate tools in the NICE methods manual for each study design. Differences between the reviewers will be resolved by consensus.

Scoping reviews do not conventionally undertake quality assessments[8,9]; however, we will develop a matrix following guidelines for quality assessment of qualitative research papers and apply this to selected studies in order to exclude studies that do not meet an acceptable standard for methodological criteria. This will use the PRISMA 2 guidance[10].

For the review of quantitative studies and the effectiveness of interventions to support adherence, assessment of risk of bias of individual studies and outcomes will be conducted by two reviewers independently and will subsequently be discussed with a third researcher for arbitration if needed. Cross-study assessment of strength of evidence for particular risk factors affecting adherence will use the AMSTAR 2 critical appraisal tool[11]. Specifically, differential outcome measurement in exposed and unexposed cohort populations, incomplete follow-up, failure to control for confounding, difference in measurement of exposure, and selection of exposed and unexposed in cohort studies from different populations will be examined. We will test each outcome for risks of bias, inconsistency, indirectness, imprecision, publication bias and any additional domains deemed appropriate. We will prioritise direct objective measures of adherence, which are less prone to reporting bias.

3.1.7 Synthesis and development of conceptual framework

Outputs from the scoping review of qualitative studies will include a descriptive bibliometric summary, and a qualitative analysis of the key themes emerging from the studies that are relevant to the research question(s). The review of quantitative studies will report adherence measures during treatment for TB for the interventions identified within the search. Interventions that have demonstrated efficacy will be presented within evidence tables. These will be arranged and divided according to different treatment durations and regimens. Inconsistency on identified risk factors across instruments of assessment, and for different time periods (initiation phase of treatment and/or continuation phase and/or throughout treatment) will be reported separately. Sub-analyses to assess whether treatment regimens are predictors of non-adherence will be performed. A narrative synthesis of the studies will be compiled, including a consideration of the socio-economic context in which included interventions were implemented and where other critical factors were present, such as drug resistance profiles of the study population.

The findings from the three reviews will be used to build on the NICE-approved PAPA-based approach (see Appendix 1: PAPA Framework) to improving adherence support by:

- Identifying potentially modifiable determinants of adherence-related motivation and ability which have not been identified from the PAPA theoretical model which is baed on research on adherence across a range of conditions that includes other infectious diseases

- Identifying personal, social, cultural, health systems-related, and structural factors that interact with individual-level determinants (motivation and ability) to influence adherence directly or indirectly.

These steps will allow us to map the relationships, pathways, and mechanisms of effect between these factors and adherence outcomes for TB patients on treatment, including when specific interventions to support adherence are employed.

We will present the outputs of these reviews and the initial emergent framework development in an accessible and visual format. This, together with the findings from the formative work, will be provided to the patient and professionals from the Manualised Intervention Development Group to elicit comment and discuss the application of the framework to support the study methodology and the main output of this work programme (see Section 3.3).

As described above, a further output from the review of both qualitative and quantitative studies will include a critical interpretive synthesis[7] examining the theoretical assumptions and proposed mechanisms of effect underlying interventions adopted to support individuals' adherence to treatment in high, low, and middle-income care settings. This method provides critical interrogation of the ways in which the literature has constructed the problematics of 'poor adherence', the nature of assumptions on which it draws, and what has influenced the choice of proposed strategies.

3.2 Formative Research (ii)

Building on the conceptual framework developed in the first phase, the formative research will use qualitative methods to elicit TB patients' experiences of starting and staying on treatment, and health providers' views on the barriers and facilitators for TB treatment adherence. We will also interview, with patient consent, carers and family members involved with patients who are receiving or have received treatment for TB.

3.2.1 Patients and Carers/Family members

Adults who are currently taking or recently completed treatment will be identified by the local TB service and asked to take part in the study. The patient group will be enriched with people who have been poorly-adherent to treatment, though we will also include patients who report full adherence, so that we can capture what led them to take treatment as prescribed. With patient consent, family members and/or carers will also be approached and asked to take part. The participants will receive travel costs and refreshments during the interviews. These will be in line with INVOLVE guidance. The eligibility criteria for participants are described in Section 4.2.

3.2.2 Health and Social Care Providers

Health and social care workers from both primary and secondary care settings will be directly approached by researchers and invited to take part in the formative work. The TB nurse is often the patient's case manager and hence can develop strong bonds with their patients. We will therefore ensure we include TB nurses at each study site. The providers will receive travel costs and refreshments during the interviews. The eligibility criteria for participants are described in Section 4.2.

3.2.3 Formative Research Methods

Three different methods of data collection will be used (Table 1):

1) **In-depth interviews** with patients and where possible, their caregivers, i.e. family or other significant members of their social networks who provide care or support
2) **Cognitive assessments** with a purposive selection of patients representing key vulnerable populations
3) **Semi-structured interviews** with health providers responsible for TB care (doctors, nurses, social workers, DOT providers, managers and administrators)

The purposive sampling approach will allow us to capture the social and demographic population groups who are more likely to be non-adherent. Based on previous experience plus the scoping review, a qualitative sampling framework covering important socio-demographic characteristics (such as age, sex, ethnicity, socio-economic status) relevant to access and adherence to treatment for TB will be used to ensure our sample represents the range of patient experiences.

3.2.4 In-depth Interviews

Using a Topic Guide (see Appendix 3: Patient Interview Topic Guide), interviews will be conducted with patients. They will focus on issues of systemic barriers to accessing health care, experience of illness and treatment-seeking trajectory, social support, and any relevant cultural factors influencing TB treatment literacy and medicine-taking. Where possible, and with patient consent, a family member or other social contact close to the index case will be invited to be interviewed separately.

The issues discussed within the interview may result in the participants talking about personal subjects. We will endeavour to ensure that this information remains confidential, and only used to develop an understanding of their experience of healthcare, tuberculosis and treatment. We will inform them of this when they are first approached about the study. However, we will also let them know that we have a duty of care to safeguard adults and children, which includes acting appropriately if we are given information that suggests that an adult or child is at risk of harm.

Given the in-depth nature and length of interviews, we estimate that 6-8 patient interviews per site, plus an additional 1-2 family members or carers per site (estimated total therefore 30 interviews across participating sites), is both feasible and adequate.

3.2.5 Cognitive Assessments

This will be performed by purposively sampling for risk of non-adherence to achieve a cohort of patients (n=10) who report non-adherence or for whom clinical information indicates a high risk of this. We will conduct in-depth interviews as part of the process described in Section 3.2.4, using the Patient Interview Topic Guide (Appendix 3).

To ensure that the validated questionnaires used in the pilot study [which assess patient perceptions and practicalities affecting adherence to medication for TB (Beliefs about Medicines Questionnaire [BMQ-Specific for TB, and BMQ-General], and the Brief Illness Perception Questionnaire (Appendix 4 and Appendix 5)] are accessible and acceptable to patients, we will conduct brief cognitive interviews with 10 patients. This comprises a short interview where questionnaires are presented to patients who are then asked to 'think aloud' as they complete them. For example we will explore the ease of completion of the questionnaires: identifying any difficulties in understanding or answering the questions, as well as whether they miss key patient-relevant issues.

This standard process for piloting questionnaires which assess patients' views and perspectives allows us to make small adjustments to improve the acceptability of the questionnaires without compromising the validity and reliability of the measures.

3.2.6 Semi-structured Interviews

These will be performed with health care providers, and will focus on their own perception of their patients' understanding of TB and its treatment. By asking providers to recall specific examples, and encouraging reflexivity, the interviews will enable comprehensive mapping of patient pathways to identify systems-related enablers and barriers during the diagnostic and treatment trajectory that may impact upon adherence. We will interview 4-6 providers at each site, aiming for a total of 20.

Table 1– Populations, methods, sampling and recruitment of patients and providers taking part in manualised intervention formative research

Method/population	Sampling strategy/sample	Recruitment/site	Areas of inquiry
In-depth interviews with patients/carers/family members	Purposive selection of patients, on treatment or recently completed, enriched from ethnic or societal groups at risk of low adherence. Carers/relatives of patients Sample: 6-8 patients & 1-2 family members /carers per site (total - 30)	Edinburgh London Barts London Royal Free Southampton	Self-perception; personal beliefs and practices related to medicine-taking. Health literacy and health-seeking behaviour; social support; cultural norms around health-seeking behaviour; financial and other structural barriers
Cognitive assessment (interview and questionnaire review) with patients	Purposive selection of patients, on treatment or recently completed with poor adherence, Sample: 2-4 per site (total - 10)	Edinburgh London Barts London Royal Free Southampton	Self-perception; personal beliefs and practices related to medicine-taking
Semi-structured interviews with providers	Purposive selection. Sample: 4-6 per site (total - 20)	Edinburgh London Barts London Royal Free Southampton	Providers' perceptions of factors affecting patient understanding of TB and treatment; service delivery model including staffing, organisation of care and communication

3.2.7 Data analysis

Interviews will be recorded (with participant's permission) and transcribed verbatim. Interviews are expected to last 45-60 minutes. Where appropriate, translations services (face-to-face, and by telephone if appropriate) will be used to support people whose first language is not English.

The research elements exploring social and cultural factors influencing adherence as well as providers' perceptions will be conducted by Dr. Kielmann and team at the Institute for Global Health and Development, Queen Margaret University. Interview transcriptions will be subjected to a thematic analysis[12] to identify the key concepts and themes, in line with the information obtained from the scoping review. It will adopt a phenomenological approach that privileges subjective, lived experience of illness and a grounded theory approach to the data analysis. Data on health systems issues gained through mapping of patient pathways will be structured so as to lend itself to visual display, for example, through flow-charts and decision-making trees.

Personal factors that may be relevant to adherence, and so could input into the development of the manualised intervention, will be identified through cognitive assessments performed by Professor Horne and team at the Centre for Behavioural Medicine, University College London. Methods will use framework analysis following the PAPA approach. This is to identify additional themes relating to perceptions and practicalities driving adherence/nonadherence that are not adequately represented in the validated questions in section 3.2.5 (and Appendices 4 & 5). Cognitive assessments will also sense-check any changes we make to the questionnaires. We do not expect this to be an issue, given their successful use as in vulnerable populations with infection[13].

The data generated through qualitative data collection methods comprises textual and visual data (e.g. diagrams or maps). Assigning unique identifier codes to all data files, with the coding manual available to relevant co-investigators (Dr Kielmann at the QMU and Professor Horne at UCL), will ensure anonymity of all data sources. All hard copies of the data will be kept in a central, secure, and locked location. All data files will be appropriately labelled, with a documented list of relevant abbreviations, inclusive of the site of data collection (Edinburgh, London, Southampton), the type of data (Map; Field Notes; In-depth Interviews, with type of informant; etc.), date data collected, person responsible for data (initials of original data collector and data transcribed, as relevant). Data files will be organised into relevant sub-folders and folders. All data files will be password protected. All data files will be backed-up in a secure data location.

Audio data will be transcribed by professional transcribers, following an agreed protocol for all transcriptions, to ensure uniformity across sites and across transcribers. All transcriptions will be stored as Word or Excel files, both easily uploaded to software for qualitative data analysis (e.g. NVivo or ATLAS.ti). Textual data in the form of documents and field notes will be stored as Word of PDF documents, again easily uploaded for analysis in software for qualitative data analysis (e.g. NVivo or ATLAS.ti). Visual data collected manually on patient pathways and the organisation of care, will be captured electronically via REDCap. All data systems and data handling procedures for capturing, transferring, analysing and storing the study data will be developed and tested to verify their ability to preserve participant confidentiality. The Chief Investigator will have overall responsibility for data transfer and storage.

Data analysis will be performed at QMU and UCL. Anonymised and/or aggregated results will be received by the research teams, with anonymised information being transformed as required to produce the manualised intervention (see Appendix 6: Management and Data Flow Charts)

The patient interviews and patient pathway mapping data will enrich and substantiate findings from the scoping review, identify context- and population-specific enablers and barriers in vulnerable groups. This data will enable us to apply the draft conceptual framework and tailor its application to the specific population, taking into account the context, processes, and mechanisms of effect that help to elucidate reasons for poor adherence, and can suggest pragmatic, feasible and sustainable interventions to support adherence within an NHS context.

3.3 Development of Manualised Intervention (iii)

The development of the manualised intervention will utilise the evidence from literature obtained through the scoping and critical reviews plus the formative research applied within the conceptual framework. The resulting intervention will contain both social and clinical elements. The results of the formative research, and its synthesis within a dynamic conceptual framework regarding understanding poor adherence to treatment for TB in vulnerable groups, will help identify the optimal parameters for a prototype manualised intervention that can be presented to a panel: the Intervention Development Group (IDG).

3.3.1 Intervention Development Group

The panel will be convened in Year 2 of the study, at the end of the formative research and before the pilot study commences. The IDG will include:

- patients (in particular the homeless, ethnic minorities, migrants new to the UK, and patients with drug resistant TB)
- family members/significant others of affected persons
- members of the public
- health care professionals (from both primary and secondary care)
- other professionals who work with patients/communities affected by TB.

The group will be supported by TB Alert and Find&Treat (as described in Section 8, Patient and Public involvement), as well as by North Central and North East London TB services (clinical support and expertise), the TB Nurses Network (clinical nursing support and expertise) and UCLPartners TB Clinical Research Network (to ensure generalisability to diverse patient populations and stakeholders). It will contain representatives from Edinburgh and Southampton. This will enable a co-production approach to ensure that the intervention is pragmatic, can be delivered within the context of existing care pathways and is of benefit to service users and those who are likely to access the intervention.

The IDG will meet to develop the manual based on information from the review, and formative research, as well as materials developed for promoting informed choice addressing perceptual and practical barriers to adherence developed for use in other diseases[14,15].

Members of the group will be remunerated for their time, and travel costs. They will also receive support and payment for any further time spent preparing for the meeting.

A further meeting will take place for the IDG to agree and feedback on the final output from the first meeting. The IDG will also have the opportunity to review the manualised intervention in practice during the cluster randomized trial pilot. This will be to determine whether the intervention performs as expected and would be suitable for a larger definitive study.

3.3.2 Manual contents

The manualised intervention will consist of a screening tool and a package of measures that can be tailored to the needs of individual patients from different population groups. In line with the conceptual framework and information derived from the scoping and critical reviews plus formative work, it will distinguish three areas that may lead to poor adherence, namely personal (including psychological) factors, the impact of the social and cultural environment, and health systems level barriers and failures.

To be adopted successfully into existing care pathways, our intervention must:

- Be succinct, as it is intended to be delivered by nurses and health workers as part of routine care.
- Contain a brief 'practice guide' (e.g. one side of A4) to help the health practitioner tailor support to meet the patient's needs.
- Be supplemented by a health care professional training manual and materials to facilitate a stepped-care approach whereby more intensive interventions (e.g. VOT, text reminders) can be targeted to those patients who require them.
- Contain a narrative that enables the intervention to be contextualised appropriately for the patient. For example, the first use of the intervention will be prior to the person starting anti-TB treatment. The next time may be after two weeks of therapy – by which point the adverse effects of anti-TB medication may have become in themselves a barrier to adherence.
- Be translated into the commonest languages spoken by TB patients (based on the experience of the PREDICT study, and the National Knowledge Service for TB where TB information and study material has been translated into multiple languages).

As patterns of adherence may be irregular over time, it is intended that the manualised intervention will be administered at each patient review to all patients. Hence the screening tool needs to be quick and easy to administer. It may be electronically linked to patient records – so enabling a comprehensive picture of risk of possible poor-adherence to be developed for each patient, as well as within a clinic population. While it is intended that the manualised intervention can be administered using a hard copy printed form, it is possible that an electronic app may offer both greater flexibility, and be more acceptable to some patients. The various delivery options for the intervention will be considered during its development stage.

The menu of supportive measures is likely to include:

- Informational intervention: For example, by preventing and addressing doubts about the personal need for continued treatment (especially in the absence of symptoms) through offering a convincing story setting out the rationale and ongoing need for medication, addressing concerns about potential adverse effects and consequences of treatment and what to do if such events occur e.g. the participant will be informed that it is possible to change treatment to alternatives[16].
- Practicalities and Capability based interventions: VOT, DOT, reminders including text messaging, automated methods for monitoring and feedback including electronic dosette boxes, use of a medication app, incentives e.g. financial and food vouchers, mitigation and management of drug toxicity due to treatments.
- Social and system interventions: offering flexibility in appointments; enhanced guidance on 'navigating' clinic pathways; signposting patients to relevant services, e.g. homelessness, drug and alcohol services, and social care; providing peer-support.

3.4 Piloting the intervention (iv)

Once the intervention is developed, proof-of-concept is required within the real world. This pilot study will use a Cluster Randomised Controlled Trial (CRCT) design comparing the manualised intervention to the usual standard of care in four clinics treating TB. It will enable a process evaluation to be performed using a structure, process and outcome evaluation model. The study also mimics the likely design of the subsequent definitive trial, on a smaller scale, and therefore informs the feasibility of that trial.

3.4.1 Setting and Population

The setting of the pilot study will be hospital and community sites where TB patients are currently supported to complete treatment**.** We will work with four large TB clinics in East and North London, two sites from within Barts Health NHS Trust (Mile End and Newham clinics) and two from the Royal Free London NHS Foundation Trust (Edgware and Hampstead clinics) each of which treat in excess of 60 TB patients per annum. The clinics manage a broad mix of patients representative of the national demographic picture of contemporary TB. This includes established and newly arrived migrants, the homeless, those with mental and physical co-morbidities, people who misuse drugs or alcohol, and the immunosuppressed (through associated illness, including HIV, or medication). The clinics are also regional referral centres for MDR TB. Within each Trust we shall allocate one clinic to the intervention and one to standard of care, ensuring balance between study arms. Piloting the intervention in this way in four sites, each of which has its own TB nursing, and administrative team, yet are within two large Trusts, strikes a balance between performing a much larger and more expensive pilot at several financially distinct, and potentially geographically remote sites, and having minimal cross-contamination when running the pilot.

In particular, we will recruit migrants newly arrived in the UK, people whose first language is not English, women who are pregnant, people with a mental health disorder, people taking immunosuppressive therapy or known to have immunodeficiency, those with a previous history of treatment for TB, or poor-adherence with anti-TB medication, and people with a current or previous history of drug or alcohol misuse will be included (see Section 4.3 for eligibility criteria)

3.4.2 Outcome Measures

Primary outcome

1) Adherence and treatment completion rates:
    a) Adherence (percentage of prescribed doses taken) assessed at six months from the start of treatment.

Secondary outcomes

1) Percent consenting to the study
2) Completeness of data for measures of adherence and treatment completion
3) Proportion of patients identified as needing adherence support in intervention arm
4) Proportion of patients offered adherence support and accepting it in the intervention arm
5) Adherence and treatment completion proportions:
    a) proportion of patients completing treatment
    b) proportion of patients still on treatment after 9 months or at study completion (whichever is the earlier)
    c) Patients lost to follow up
6) Patterns of adherence
7) Process variables – adherence-related perceptions and practicalities (assessed using validated questionnaires – with adaptations if necessary – see above).
8) Impact of manualised intervention on adherence for the duration of treatment.

3.4.3 Measures of treatment completion and adherence

Our primary measure of adherence will be pill counts performed by the research nurse or clinical team. Other measures will also be used (see below)

3.4.3.1 Pill counts

An issue with any study of adherence is that methods which check for levels of adherence may, in themselves, promote or discourage it. For example the use of an electronic medication measuring device such as a MEMs cap, that records each time a pill bottle is opened and is part of the pill container, is different to a standard bottle top and will alert patients that their adherence is being checked. One way round this is to give patients recording devices and not tell them that this has been done. We feel that this solution is both ethically and programmatically difficult to implement, and so have chosen to use simple measures of adherence within the study.

We will ask the patients within the study to bring their medication to each appointment, so that it can be counted and compared to expected levels based on what has been prescribed. In the case of Directly Observed or Video Observed Therapy methods being used, a record of missed doses will be kept. Rules will be developed to manage patients who do not bring their medication with them when they are reviewed. Examples of this would include a phone call or text to the patient on the day of the clinic appointment, if they have previously forgotten to bring their medication with them; and a review of their daily activities to identify issues that may prevent them from taking their medication when for example they are at work or in social settings, including the clinic.

Pill counts will be the Primary Outcome Measurement for the study, triangulated with other adherence measures outlined below.

3.4.3.2 Urine Tests

In the study urine samples will be collected from patients in accordance with the patient consent form and patient information sheet. Samples will be processed and disposed of in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter. No samples will be stored as part of this study.

We will ask participants to donate a 5ml sample of urine to check for adherence to prescribed medication for tuberculosis. These samples will be collected when the patient attends their clinic appointments and will be additional samples to those required as part of routine clinical care.

Urine testing for detecting isoniazid metabolites will utilise a commercially available assay (IsoScreen, GFC Diagnostics Ltd, Oxfordshire (UK), if the patient is taking Isoniazid – see **APPENDIX 7: IsoScreen Urine Testing).**

3.4.3.3 Patient Reported

Patient-reported drug administration, timely clinic attendance as planned, urine tests for anti-TB drug metabolites and - if the patient is receiving either DOT or VOT- objective evidence of taking medication[17]. These will be validated against the other adherence measures and the quality of each assessed.

3.4.4 Study Arms

Manualised intervention
The patient's case manager (usually the clinic TB nurse) plus study research nurse will apply the manual in partnership and consultation with the patient to identify whether personal, socio-cultural and/or systems risk factors are present that suggest likely poor adherence with treatment. If these

are identified, then the relevant measures outlined in the manualised intervention that may mitigate these will be reviewed and implemented with the agreement of the participant. This process will be aided by the use of narrative aids (developed during the production of the manualised intervention) that will help both the patient and clinical team to put into context the particular risk factor for non-adherence, how it affects the patient and why it is important to manage this. The agreed measures, which may include an incentive or enabler, social support or referral to another service to manage a specific issue, will be sustained throughout the course of treatment.

Standard care for TB

The national adoption of approaches such as cohort review[18] to TB management means that all patients have case managers, and at the start of treatment are assessed for a set of risk factors felt to be associated with likely poor-adherence. These focus generally on areas such as homelessness, drug and alcohol misuse, previous incarceration and mental health issues rather than other psycho-social factors such as what having TB means to the person, or whether they feel that they really need to take treatment. If a risk factor is identified then the patient will be offered the relevant support available in the clinic. All patients will be followed throughout their treatment by their case manager; and if concerns regarding adherence are identified, further support measures will be implemented in line with clinic practice. Although a process evaluation will be performed during the pilot study (see below), the researchers will not intervene to provide advice or to suggest a change in practice in either arm, should they identify a problem. The exception to this would be if the Study Steering Committee had concerns about study conduct or outcome and wished to stop the trial.

Study schedule of visits

Study subjects will be seen at weeks 0, 2, 4, 8, 12, 16, 20 and 24 (earliest date of treatment completion). Should they require ongoing treatment after 6 months they will be seen as clinically indicated. At each review, adherence assessments will be performed (see above) in addition to an assessment of perceptions and practicalities, the completion of the BMQ (Beliefs about Medicines Questionnaire)[19], the Brief Illness Perception Questionnaire (BIPQ)[20] and the EQ5D Quality of Life questionnaire (APPENDIX 5: Beliefs about Medicines Questionnaire (BMQ-Specific and BMQ-General), APPENDIX 6: The Brief Illness Perception Questionnaire, APPENDIX 8: EQ5D-L). The manualised intervention will be applied if the patient is attending a clinic that has been randomised to the intervention arm.

Adherence-related perceptions and practicalities and the distribution of adherence barriers between intervention and control groups over time, will be captured. This will also allow us to assess the feasibility of applying quantitative measures of adherence-related perceptions and practicalities as a process variable in the full trial.

3.4.5 Follow up

Most patients who do not have clinically important drug resistant disease receive six months of treatment. To allow for treatment interruptions, patients within the pilot study will be followed to either treatment completion or for a total of 9 months from starting anti-TB therapy. Although patients with extensive or drug resistant disease (who can require therapy for anything between nine and 20 months) may not have all of their treatment captured within the pilot, (depending on time of entry into the study) the maximal time of 18 months that a participant could be within the study enables us to obtain good data on the majority of patients with complex TB. The maximal duration of time that a participant remains within the study depends on their planned treatment duration (minimum 6 months), and when during the pilot study that they are recruited. The shortest possible follow up will be 6 months.

3.4.6 Analysis and interpretation

For each outcome measure listed earlier, the percentage overall and by study arm (intervention and control) will be presented. Fisher's exact test to test the difference between arms for each outcome will be used. It should be noted that these tests do not provide great certainty as the clustering by site cannot be formally acknowledged using such a modest number of sites in the pilot study. Variability between sites in outcomes will be measured.

The analysis of the first two of our secondary outcomes will address the feasibility of a definitive trial following a similar design to the pilot. Analysis of the third and fourth outcomes addresses the intervention, and complements the process evaluation. Analysis of the primary outcome and final secondary outcomes around treatment adherence and completion provides initial information, given the modest sample size, concerning the effectiveness of the intervention, and may assist the sample size calculation for the definitive trial. It can offer also an alert in the unlikely event that the intervention is clearly harmful.

3.5 Process evaluation (v)

The process evaluation will consist of a description of the process of intervention implementation. It will assess how the well the manualised intervention achieves its intended aim compared to standard care.

We will consider:

1) The fidelity of the intervention as delivered in comparison to how it was designed and envisaged
2) The reach of the intervention (the proportion of the target group receiving it)
3) The barriers to facilitating implementation of the intervention and how these can be addressed
4) The pre-existing factors that facilitated implementation.

3.5.1 Process measures

Process measures for each element of the package will be developed once the manual development has been completed, and used to assess success. They will include acceptability, uptake and change in practice. We will work with patients and staff separately, and at all four London sites. We will interview 20 patients (5 at each study site, hence 10 from each arm); and if possible 20 health care workers (5 at each site). The patients will be selected within each site using purposeful sampling of clinic lists of every fourth patient with active TB. Reasonable expenses incurred by participants will be reimbursed. These include transportation and refreshments to reflect the additional estimated 1 hour involved in taking part in the process evaluation.

Key outputs:

1) **Qualitative evaluation of intervention delivery** will entail review of routine data sources including clinic lists, TB treatment register as well as project instruments, in particular the adherence risk assessment tools and records of intensified adherence support delivery.
2) **Development of narrative description of process of intervention implementation and maintenance**, through qualitative research methods. This will focus on understanding the key obstacles and facilitators to delivery of the package. Interviews will be conducted with staff members involved in patient reception, care, and follow-up. Semi-structured observation will be used to document staff communication and care practices at each stage of patients' trajectories within the clinics. Further patient interviews will be conducted towards the end of treatment to understand their perceptions of the information, care, support, and

communication received.

3) **Quantitative assessment of adherence-related perceptions (using the Necessity Concerns Framework) and practicalities within intervention and control groups** [13]

3.6 Cost Analysis and Future Work (vi)

This will be performed in collaboration with Health Economists at the UCL Institute of Global Health. We will collect cost data from an NHS perspective using NICE guideline implementation tools to generate realistic estimates of the cost of the intervention. These data will be summarised into a format that commissioners can use as the basis for subsequent decisions on investments to improve TB adherence. In particular, this will draw on existing studies such as National Institute for Health Research (NIHR) RP-PG-0407-10340: Improving the management and control of tuberculosis among hard to reach groups (TB REACH), which includes a comparison of DOT and VOT, and other cost analysis as part of NIHR and Department of Health funded work.

After the pilot study and process evaluation have been completed, a final intervention package will be designed for use in a definitive RCT of the manualised package of interventions. The design of this final package will be based on the results of process evaluation and the experience gained during the piloting of the intervention, modifying the definitive trial design and/or data collection accordingly.

4. ELIGIBILITY CRITERIA

The study will recruit participants during the Formative Stage (iii) and Pilot Study (iv).

4.1 Recruitment to Formative Study (ii) and Pilot Study (iv)

4.1.1 Formative Study (ii)

It is planned to enroll approximately 60 participants into the Formative Research Study, this will include a mixture of both patients with a current or previous history of TB, their family members and carers, and Healthcare workers involved in the management of TB cases (i.e. TB nurse or case manager; Table 1).

4.1.2 Pilot study

It is planned to enroll 80 participants starting treatment for TB into the Pilot Study. We aim, in particular, to recruit people at greater risk of poor adherence (such as those affected by wider psychological, social, cultural and economic issues).

Patients attending the four TB clinics taking part in the study will be informed about the study via advertising material within the clinics. Those who are diagnosed subsequently with active TB (approximately 1 in 4 of new referrals) and are eligible for the study will be approached with further information, and asked if they would like to take part. To ensure that the study participants are truly representative of the clinic population, a record of those patients who do not wish to take part will be kept in the screening log. This will contain routinely collected data such as age and sex. It will not enable patients to be identified through deductive disclosure.

4.2 Eligibility criteria - Formative Study (iii)

4.2.1 Subjects with TB, their family members and carers

Inclusion criteria:

(i) Age ≥ 18 years
(ii) Able to provide Informed Consent
(iii) People who are suspected to have or have previously had TB. Family members/carers of consented participants will also be approached and consented (where possible)

Exclusion criteria:

(i) Unable to give informed consent

4.2.2 Health providers

Inclusion criteria

(i) Age ≥18 years
(i) Able to provide informed consent
(ii) Healthcare professionals who are involved in TB management and care

Exclusion criteria

(i) Unable to sign informed consent

4.3 Eligibility Criteria - Pilot Study (iv)

Inclusion criteria

(i) Age ≥18 years
(ii) Able to provide informed consent
(iii) Being started on treatment for TB affecting any part of the body.

Exclusion criteria

(i) Patients already on treatment for TB at the point they attend the TB services in the study
(ii) If the patient is not expected to live for the duration of the study (that is a minimum of six months from starting treatment)

4.4 Eligibility Criteria - Evaluation Study (v)

Inclusion criteria

(i) Age ≥18 years
(ii) Able to provide informed consent
(iii) Started on treatment for TB at one of the four London sites OR a staff member treating patients at one of the four London sites

Exclusion criteria

(i) Unable to sign informed consent

4.5 Randomisation procedures

Randomisation occurs at the clinic level prior to the pilot trial. Within each of the two selected NHS trusts one clinic will be allocated at random to the intervention and one to standard of care. This

allocation will be conducted through random computerized permutation using Stata 15 software.

4.6 Unblinding

The study will not require unblinding procedures.

5. CONSENT

5.1 Informed Consent

A member of the patient's clinical care team (independent of the research team) will first approach the patient about the study. If the participant indicates that they are happy to consider taking part then an appropriately trained member of the research team, as designated on the delegation log, will go through the written information sheet with the patient which will explain the research and the level of participation/commitment required. The researcher will discuss the consent process and provide the opportunity for the participant to ask any questions. Once the potential participant has confirmed that they have enough information about the study they will be given adequate time to decide whether or not they wish to participate.

Participants who decide that they wish to take part in the study will then provide written informed consent by signing and dating the study consent form, which will be witnessed and dated by a member of the research team with delegated responsibility to do so. Written informed consent will always be obtained prior to study specific procedures/investigations.

The original signed consent form will be retained in the clinical notes, with a copy in the Investigator Site File and a copy provided to the participant. The participant will specifically consent to their GP being informed of their participation in the study. The right to refuse to participate without giving reasons will be respected.

5.2 Withdrawal procedure

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study if s/he judges this to be in the patient's best interests. Unnecessary withdrawal of patients should however be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

There are two withdrawal options:

1) Withdrawing completely (i.e. withdrawal from both the study and provision of follow-up data)
2) Withdrawing partially (i.e. withdrawal from full study procedures but continuing to provide partial follow-up data by attending clinic and completing questionnaires).

Consent will be sought from participants choosing option 1 to retain data collected up to the point of withdrawal. Participants will be asked if they would be happy for the reason for the decision to withdraw to be recorded.

6. SCHEDULE

6.1 Start and duration

Study will commence January 2018. Total duration is 36 months. The different components will run as required to achieve completion by 31 December 2020 (see Appendix 2: GANTT Chart).

7. STATISTICAL METHODS

7.1 Recruitment to pilot study and sample size

Eligible participants will be approached at all four sites and the nature of the pilot study will be explained. Over a 9 month period, we will recruit 80 consenting subjects (20 at each site). Depending on where they receive their treatment they will be offered either the manualised intervention or standard care when starting treatment for TB.

Patients attending the four TB clinics taking part in the study will be informed about the study via advertising material within the clinics. Those who are diagnosed subsequently with active TB (approximately 1 in 4 of new referrals) and are eligible for the study will be approached with further information, and asked if they would like to take part. To ensure that the study participants are truly representative of the clinic population, a record will be kept of those patients who do not wish to take part. This will contain routinely collected data.

Using as a stringent measure of complexity in UK patients the requirement for Directly Observed anti-TB Therapy within the clinic populations seen at the two sites, we estimate that around 33% of patients will have a risk factor for non-adherence. Taking this as a minimum (as the manualised intervention is likely to be more sensitive than current risk assessments), we would expect that at least 26 patients will be identified as requiring adherence support. This sample size allows us to measure consent for more than 100 individuals, data completeness for adherence and treatment outcomes for 80 individuals, data on acceptability and feasibility of the intervention package for 40 individuals, and data on acceptability and feasibility of adherence support for at least 26 individuals (13 receiving the manualised intervention and 13 standard care).

We will use the first 80 participants to determine feasibility and define measures that may improve participation and recruitment. It is not planned to recruit more patients to the pilot study as this may bring with it extra costs. We will not rely on this phase of the trial for hypothesis testing - as at this point the results obtained will be unpowered. The effect size will not be looked at formally and no explicit conclusions will be drawn.

8. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients and the public will be actively involved in the following:

- Design of the research
- Management of the research (eg steering / advisory group)
- Developing participant information resources

- Contributing to the reporting of the research
- Dissemination of research findings

This study was prepared in conjunction with TB Alert and Find&Treat. TB Alert is the UK's national TB charity, whose focus is on making sure people with TB are promptly diagnosed and supported appropriately during treatment. Find&Treat work alongside the NHS and third sector services as a specialist TB outreach team. They support vulnerable communities including the homeless, drug or alcohol misusers, disadvantaged migrants and ex-prisoners. Working collaboratively, we have ensured that our proposal focuses on the needs of people who may find it difficult to adhere to TB treatment for a range of social and other factors. Also, a charity representative and a former patient who is a member of the TB Action Group (patient advocate group facilitated by TB Alert) contributed to the qualitative study design and provided input into the planned development of the manualised intervention, as well as the pilot study.

There will be full PPI involvement during the development of the intervention, including issues around the approach to participants, production of the ethics application and supporting material such as information sheets and posters. There will be PPI stakeholder representatives on the Study Steering Committee, drawn from TB Alert and former TB patients. The PPI representatives will contribute to the final report, ensuring that this represents the views of the forum and records their involvement in the project. Finally, we will work with our PPI Study Steering Committee members and stakeholder charities to ensure that there is effective translation and dissemination of the evidence generated from the study into formats accessible to the community.

9. FUNDING AND SUPPLY OF EQUIPMENT

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

The National Institute of Health Research is funding this trial via the Health Technology Assessment Programme. Grant funds will be used to support the design, conduct, analysis and reporting of this trial.

The research costs for the study (HTA Project: 16/88/06) have been supported by National Institute for Health Research – an amount of £763,745.00 was awarded on the 31st October 2017.

10. DATA HANDLING AND MANAGEMENT

10.1 Data Protection and Confidentiality

All data will be handled in accordance with the General Data Protection Regulations (GDPR).

All participants will be given a unique study numbers. Case Report Forms (CRFs) used will not bear the participant name or contain any identifiable data.

The interviews will be recorded and transcribed. Qualitative data recordings (staff and patient interviews) will be transcribed and translated; observation notes will be extracted from the forms.

All data will be anonymised through the use of culturally appropriate pseudonyms, and through removal of any personal or familial references not immediately relevant to the interview content.

Staff will be bound by existing confidentiality agreements through their employment at UCL. The study will be fully compliant with Caldicott principles and the General Data Protection Regulations. Any published output will not allow identification of any participant through deductive disclosure.

The study information at UCL (traceable only with codes) will be stored in a locked offices of the clinical or research teams, stored in password protected files (electronic) or locked filing cabinet (paper). Only members of clinical research team will have access. Data will be collected and stored according to current General Data Protection Regulations. All study documents, including data collection forms, will be stored in a secure location. Data flow for the formative research and pilot cluster randomised trial are shown in Appendix 6.

Personal data relating to participants will be stored under a unique patient identifier and would therefore uphold confidentiality. Those on the participant direct care team and Principal Investigator will have access to the participant personal data. So too will members of the research team who have direct contact with the people taking part in the study. This will occur once consent has been obtained.

In compliance with the requirement of the funders and conditions stipulated by UCL, anonymised data sets will be retained for at least 5 years.

11. PEER AND REGULATORY REVIEW

11.1 Ethics and Research Governance

The study will be reviewed by an Independent Research Ethics Committee and the Health Research Authority. All study data will be held in accordance with NHS data protection principles including the use of secure password protected systems. UCL will be the nominated sponsor.

The study will be reviewed by an Independent Research Ethics Committee (NHS Research Ethics Committee). Study amendments, will be submitted by the CI to the sponsor. Trial related essential documents will be assessed by the sponsor and submitted in writing to the appropriate REC, Regulatory Authority and Trust Research & Development (R&D) for approval prior to implementation.

Before the site can enroll patients into the trial, the investigator at site or designee must apply for NHS permission from their Trust Research & Development (R&D) Department.

The CI will supply the Sponsor with a final report of the clinical trial, which will then be submitted to the MHRA and REC within one year of the end of the trial.

11.2 Internal Review

The study has been peer reviewed in accordance with the requirements outlined by UCL and was reviewed externally as part of the NIHR peer review mechanism. The Sponsor has accepted these reviews as adequate evidence of peer review.

12. RECORDING AND REPORTING OF EVENTS AND INCIDENTS

12.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity or • consists of a congenital anomaly or birth defect

*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.

12.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

12.2.1 Severity

The generic categories below are given for use as a guide.

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

12.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events)
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition)
Not related	There is no evidence of any causal relationship
Not Assessable	Unable to assess on information available

12.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the procedure listed in the Investigator Brochure, SPC, manual of Operation (amend as appropriate) **or clearly defined in this protocol**
Unexpected	An adverse event which is not consistent with the information about the procedure listed in the manual of operation (or other – amend as appropriate)* **or clearly defined in this protocol**

* this includes listed events that are more frequently reported or more severe than previously reported

12.3 Recording adverse events

Choose most appropriate sentence(s):
All adverse events will be recorded in the medical records in the first instance.

12.4 Procedures for recording and reporting Serious Adverse Events

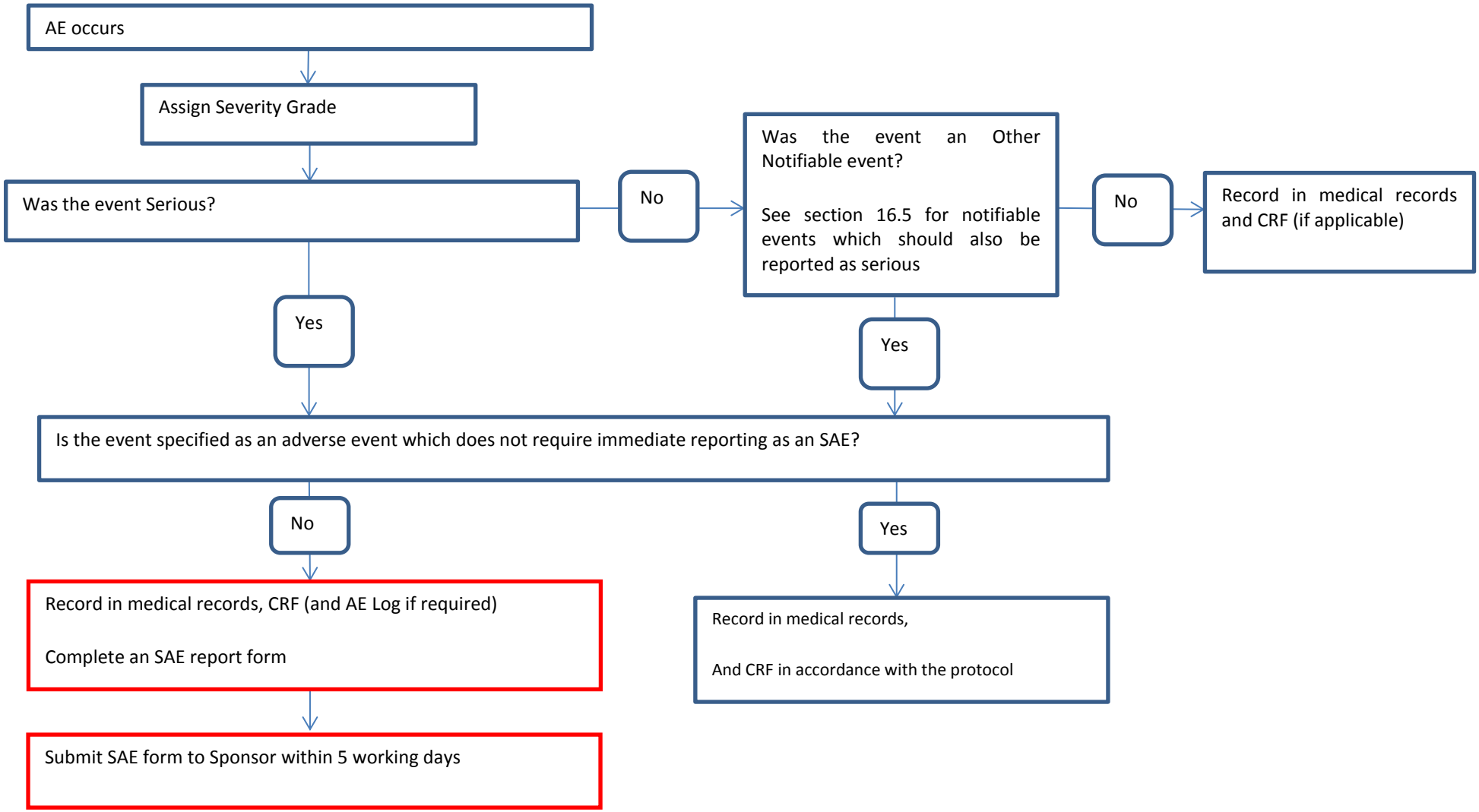
All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log (the sponsors AE log is used to collate SAEs and AEs so that the CI can review all in one place for trend analysis. If this data will be collated on a database throughout the study, from which a line listing of the SAEs can be extracted for review, an AE log will not be required).

All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed forms for unexpected SAES must be sent within 5 working days of becoming aware of the event to the Sponsor
Email forms to Research-incidents@ucl.ac.uk (if sponsored by UCL)

Figure 2- flow chart for SAE reporting



12.4.1 Serious Adverse Events that do not require reporting

All SAE will be reported.

12.5 Reporting Urgent Safety Measures

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

12.6 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree:

1) the safety or physical or mental integrity of the participants of the study; or
2) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

12.7 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

1) It is an accident or other incident which results in injury or ill health.
2) It is contrary to specified or expected standard of patient care or service.
3) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
4) It puts the Trust in an adverse position with potential loss of reputation.
5) It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

1) It is an accident or other incident which results in injury or ill health.
2) It is contrary to specified or expected standard of patient care or service.
3) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
4) It puts the Trust in an adverse position with potential loss of reputation.
5) It puts Trust property or assets in an adverse position or at risk of loss or damage.

13. MONITORING AND AUDITING

The CI will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The CI will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

14. INTELLECTUAL PROPERTY

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL with the understanding that they may use know-know gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCL IPR.

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

15. ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The CI confirms that he/she will archive the study master file at Royal Free Hospital for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The PI at each participating site agrees to archive his/her respective site's study documents for at least 5 years and in line with all relevant legal and statutory requirements.

16. PUBLICATION AND DISSEMINATION POLICY

A comprehensive report will be prepared. This will include recommendations regarding the manualised intervention and any subsequent evaluation required. The report will summarise findings particularly relevant to UK TB control policy. In addition to a formal report to the HTA, the research will be disseminated through peer reviewed publications, conference presentations and engagement with policy makers, patients and the public (via local clinical networks, community-based programmes working with at-risk for TB populations and voluntary sector agencies).

It is expected that there will be at least three research publications arising from this work: these

include the results of the scoping review, the manualised intervention and the formative research that went into its development, and the pilot study and process evaluation. We also plan to publish the study protocol.

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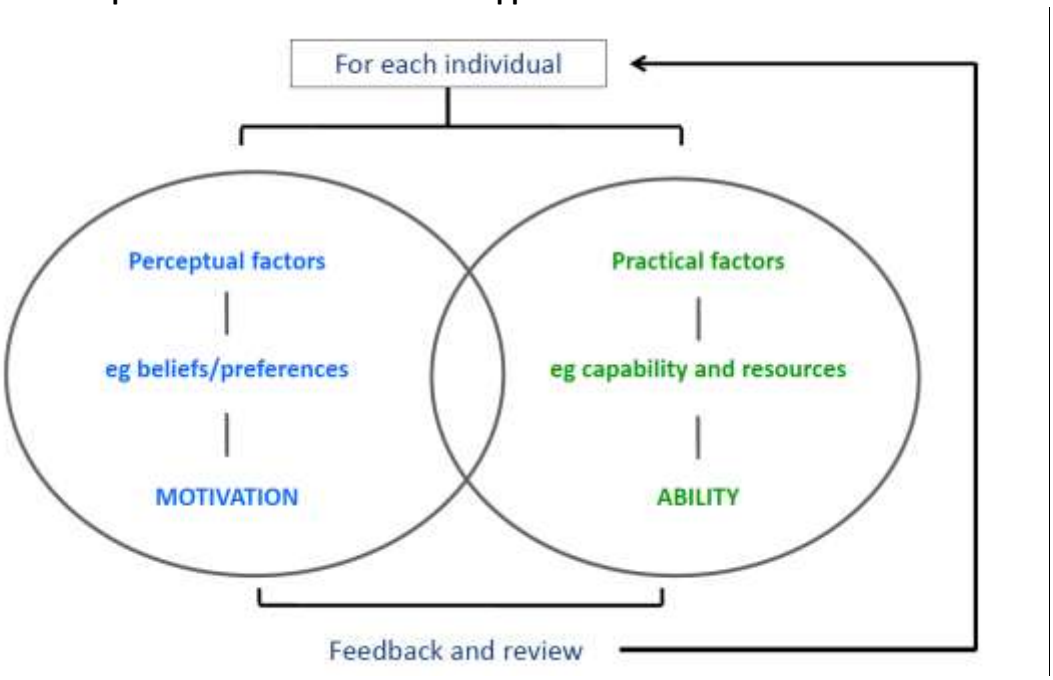
18. APPENDICES

3.1 APPENDIX 1: PAPA Framework

Applying NICE medicines adherence guidelines: the Perceptions and Practicalities Approach
The PAPA is based on the recognition that non-adherence is best understood as a variable behaviour, rather than a trait characteristic. Adherence varies not just between individuals but within the same individual over time and across treatment: in other words, most of us are non-adherent some of the time. Adherence/non-adherence is determined by the unique interaction of each individual with the illness and treatment. Poor adherence can arise for many reasons, though these may be grouped under two broad classifications: "can't" and "don't want to". Non-adherence may be both intentional and unintentional in the same individual. Unintentional non-adherence occurs when the patient wants to take the medicine but is prevented from doing so by barriers beyond their control, such as poor recall or comprehension of instructions, difficulties in administering the treatment, simply forgetting or because they cannot afford it. Conversely non-adherence may be intentional when the patient decides not to follow the treatment recommendations. Adherence/non-adherence is a product of motivation and ability.
The NICE Medicines Adherence Guidelines recommend that support be tailored to meet the needs of the individual by addressing both the perceptions e.g. personal beliefs about the illness, treatment, and self-efficacy and practicalities e.g. capability, resources and opportunity influencing the motivation and ability to start and continue with treatment[21]. This can be summarised as a `Perceptions and Practicalities Approach (Figure 1).

Figure 1 Perception and Practicalities model applied to adherence to treatment for TB.



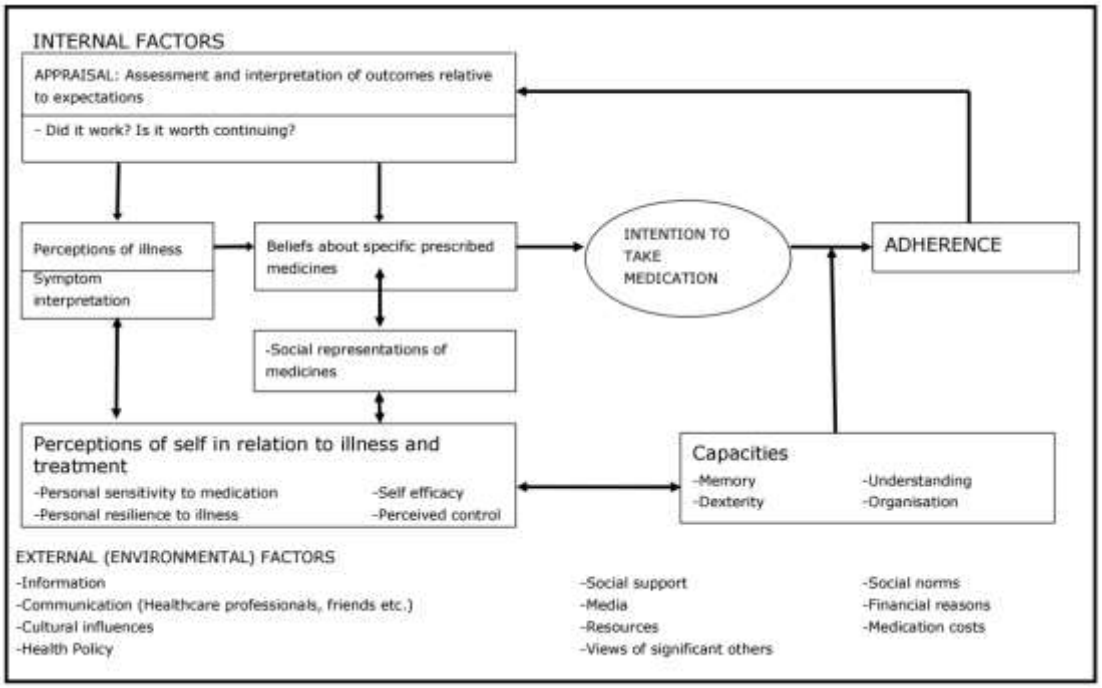
The PAPA explains the limited efficacy of interventions to improve adherence through information provision or 'education'. In order for something to change behaviour, it must be consistent with or change our patients' underlying beliefs.

We have previously used these principles to develop a simple, cost-effective, intervention to support adherence to new medicines prescribed for long-term conditions, delivered by telephone call with a community pharmacist, that resulted in higher adherence and more positive perceptions of treatment (higher

Necessity, lower Concerns) plus fewer medication–related problems (18). This study was the basis for the NHS New Medicines Service.

It is important to recognise that the perceptions and practicalities influencing adherence will be affected by a wide range of external factors including the social and cultural environment and the healthcare system (of which communication with healthcare professionals is a component) - as illustrated in Figure 2.

Figure 2 Perceptions and Practicalities Approach conceptual map of determinants of adherence (taken from Horne *et al* 2005, Reference 8)



18.2 APPENDIX 2: GANTT Chart

Period	**Pre-study**	**Year 1**				**Year 2**				**Year 3**			
Month	**-4**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**
Ethics and staff													
• Ethics approval													
• Staff recruitment			★			★							
Scoping Review and Intervention Development													
• Literature search and data extraction													
• Synthesis and analysis													
• Formative Work													
• Development of manualised intervention							★						
• Intervention Development Group													
Pilot Study													
• Preparation													
• Recruitment										★			
• Follow up & data collection													
• Statistical analysis													★
• Cost analysis													★
Process Evaluation													
Progress report and final report					★				★				★
Publications and dissemination													
Plan definitive study													

18.3 APPENDIX 3: Formative Research Patient Interview Topic Guide

Thank you for agreeing to be interviewed. We are interviewing individuals who are currently or recently have been on TB treatment in order to understand their pathways to care, and the issues they may face while being on treatment. We are conducting interviews with both health providers and patients attending this facility, as well as doing some observations to better understand how patients like yourself experience care in this facility. The questions we will ask you today are focused on your TB care journey, with particular emphasis on how things have been for you since starting on treatment. We value your reflections on your own experience and your thoughts on what, if anything, is needed to improve your care here. As already mentioned in the information sheet and consent form, the interview will take approximately 1 hour of your time. Please do feel free to ask any questions now or during the interview itself.

Patient profile

- Please tell me a little bit about yourself and your situation (probes can include place of origin/residence, length of residence in current location, employment/occupation)
- Do you have any family here? Can you tell me a bit about them?
- How is your health at the moment? How do you feel?
- What kinds of health issues have you faced in the past? How about your family?
- What has been your experience of seeking health care in this city? (probe regarding experience of NHS if from outside the country)
- What have you found positive during with this experience? What have you found negative? (probe on access, transport, ease of finding services)

Pathways to TB treatment and care

- Tell me about when you first started feeling symptoms that led you to seek care? OR
- When were you first screened for TB? Can you recall the experience? (tell me more about it, what were the circumstances?)
- What happened next? How were you diagnosed?
- Did you talk to family or friends about this diagnosis?
- Tell me about when you started coming to this clinic for your treatment (probe for original first impressions, ease of access, general feelings at the time)
- Is there a typical time of day you prefer to visit the clinic? How long does it take you to travel here?
- Do you have to spend money to come to clinic?
- How long are you normally in the clinic? (probe on how much time out of the day is required to receive treatment)
- Are there disadvantages to having to come to the clinic? Advantages?

Treatment adherence issues

Perceptions and practicalities affecting adherence

- What does TB mean to you? (*probe: what did you know about TB before you found out you had the disease? What do you associate the condition with now*?)
- Going back to when you were diagnosed, tell me more about how you were informed. (*probe on who did this, in which facility, how long did they take to explain the diagnosis and treatment?)*
- What do you think about the TB treatment you have been prescribed ?
- How important do you think it is for **you** to follow the prescription?
- How have you felt on this treatment? (*probe on different stages of treatment*)
- Do you have any concerns about the treatment?
- What makes it easy/difficult to stay on treatment? (*probe on social/environmental challenges*)

Social support

- How do you cope with your illness on a daily basis?
- When you are sick, is there anyone in particular who looks after you/supports you?
- If yes – who is this person? How do they support you? (*probe: psychological, social, financial*)
- Are there members of the family or other social contacts who know about your illness? If so, have you been able to talk to them?
- Has there been anyone who helps you stay on track in terms of your treatment?
- If so, how do they help you?
- How often do you see family? What about friends? Has anything changed since you were diagnosed with TB?
- Do you feel that anything has changed for you in terms of your social life since being on TB treatment?
- Do you know other people on treatment? If yes, do you discuss how you feel with them?

[*question to identify social contact interviewee*] Is there a family member or someone who you are close to whom we could interview? We would like to gain their understanding of the issues in supporting you whilst on treatment. We would be very grateful for the opportunity to speak to them.

Structural and health systems issues

- Tell me more about your daily visits for treatment. How many staff members would you say you come in contact with each time? For how long with each?
- Do you ever feel you need more/less time with clinic staff?
- How do you feel you are treated when you come in (probe on whether it is a personable or welcoming experience? (*probe on patient/staff rapport if any*)
- Do you find it easy to get around the clinic?
- Can you give me any examples of a situation that would make it difficult for you to visit the clinic for your treatment (*traffic, work, illness*)? What would you do in this case? (*probe on whether they inform the clinic or if clinic contacts them first*)
- In what ways does the clinic support your treatment currently? What are they doing to help you stay on treatment?
- What could be done to improve your experience of treatment?
- What are your perceptions of the ways staff interact with you or other patients? Do you feel there is strong communication? Do you feel sufficiently supported? (*probe on communication*

content, language issues, staff communication style, is it sufficient, easy to reach out to staff members if necessary)

- Can you recall any instances where you felt that the clinic staff was unavailable to you?
- How important do you think it is to be in regular contact with your treatment team?

Perspectives on Intervention

- Finally, are there any lessons gained from your experience of being on TB treatment that you could share with others who are starting treatment?
- Can you think of anything more that you would have liked to know or would have been helpful to have been explained to you when you were diagnosed?
- What could be improved in the service to support people like you on treatment?
- What could be done differently in this clinic? (*probe: access, opening hours, finding one's way through clinic, communication, care*)

18.4 APPENDIX 4: Beliefs about Medicines Questionnaire (BMQ-Specific and BMQ-General)

The Beliefs about Medicines Questionnaire (BMQ) is an established method for assessing beliefs about medicines. The BMQ comprises two questionnaires which can be used separately or in combination: the BMQ-Specific assessing beliefs about specific medicines prescribed for a particular condition or illness and the BMQ-General Questionnaire assessing background beliefs about pharmaceuticals as a class of treatment .

BMQ-Specific (TB)

Your views About TB MEDICINES

prescribed for you

- We would like to ask you about your personal views about TB Medicines
- These are statements other people have made about their TB Medicines.
- Please show how much you agree or disagree with them by ticking the box.

There are no right or wrong answers

We are interested in your personal views

	Views about TB Medicines	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
N1	**My health, at present, depends on TB Medicines**					
C1	**Having to take TB Medicines worries me**					
N2	**My life would be impossible without TB Medicines**					
C2	**I sometimes worry about the long-term effects of TB Medicines**					
N3	**Without TB Medicines I would be very ill**					
C3	**TB Medicines are a mystery to me**					
N4	**My health in the future will depend on TB Medicines**					
C4	**TB Medicines disrupt my life**					

C5	**I sometimes worry about becoming too dependent on TB Medicines**					
N5	**TB Medicines will cure me of TB**					
C6	**TB Medicines give me unpleasant side effects**					
C7	**Using TB Medicines is embarrassing**					
N6R	**Missing TB Medicines for a day won't matter in the long run**					
C8R	**I am unlikely to get a bad side effect from TB Medicines**					
C9	**Taking TB Medicines has been much worse than expected**					
C10R	**I have received enough information about TB Medicines**					
C11	**I have to take too many pills each day**					
C12	**Having to take TB Medicines makes me stressed**					

BMQ-General

YOUR VIEWS ABOUT
MEDICINES IN GENERAL

- <u>These are statements that other people have made about medicines in general.</u>
- Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right and wrong answers.
We are interested in your personal views

	Views about MEDICINES IN GENERAL	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
BG1	Doctors use too many medicines					
BG2	People who take medicines should stop their treatment for a while every now and again					
BG9	Medicines help many people to live better lives					
BG3	Most medicines are addictive					
BG4	Natural remedies are safer than medicines					
BG11	In most cases the benefits of medicines outweigh the risks					
BG10	In the future medicines will be developed to cure most diseases					
BG6	Most medicines are poisons					
BG5	Medicines do more harm than good					
BG12	Medicines help many people to live longer					
BG7	Doctors place too much trust on medicines					
BG8	If doctors had more time with patients they would prescribe fewer medicines					
PSM1	My body is very sensitive to medicines					
PSM2	My body over-reacts to medicines.					
PSM3	I usually have stronger reactions to medicines than most people					

PSM4	I have had a bad reaction to medicines in the past.					
PSM5	Even very small amounts of medicine can upset my body.					

18.5 APPENDIX 5: The Brief Illness Perception Questionnaire

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?

0	1 2 3 4 5 6 7 8 9	10
no affect at all		severely affects my life

How long do you think your illness will continue?

0	1 2 3 4 5 6 7 8 9	10
a very short time		forever

How much control do you feel you have over your illness?

0	1 2 3 4 5 6 7 8 9	10
absolutely no control		extreme amount of control

How much do you think your treatment can help your illness?

0	1 2 3 4 5 6 7 8 9	10
not at all		extremely helpful

How much do you experience symptoms from your illness?

0	1 2 3 4 5 6 7 8 9	10
no symptoms at all		many severe symptoms

How concerned are you about your illness?

0	1 2 3 4 5 6 7 8 9	10
not at all concerned		extremely concerned

How well do you feel you understand your illness?

0	1 2 3 4 5 6 7 8 9	10
don't understand at all		understand very clearly

How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

0	1 2 3 4 5 6 7 8 9	10

not at all affected emotionally

extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused your illness. The most important causes for me:-

1. _____

2. _____

3. _____

18.6 APPENDIX 6: Data Management and Data Flow Charts

Case Report Forms

Participants at the study sites will be assigned a study number and paper Case Report Forms (CRFs) will be completed at the study sites, anonymised and stored according to General Data Protection Regulations (GDPR) and the University and Trust Information Governance procedures.

Only study number will be entered onto the CRF; patient-identifiable data will be kept separately on the enrolment log and filed in the Site File at the site.

The completed CRFs will be signed off by the Principal Investigator at the site. Trial specific documents held at site will be stored in a secure location and access will be restricted and limited to nominated research staff recorded on the delegation log.

The CRF has been designed to record all study data in a standardised fashion and in the format and order required by the study protocol. This has been reviewed by the sponsor and approved by the Chief Investigator and Statistician

Data will then be entered on to the eCRF for the Pilot and Evaluation phases of the study (a password protected Microsoft Excel database), the anonymised data will then be analysed by the research team.

The excel database will:

- be password protected with user accounts specific for staff trained to use the database as per the delegation log.
- be single data entry with validation checks and source data verification against the data in the database.
- have the ability to add queries to the electronic dataset to assist with follow-up of missing data or other issues.
- record a full audit log of all changes to data
- maintain an audit trail of any change or correction to the case report form or the electronic database. Data will be generated, recorded and reported in compliance with the protocol and with Good Clinical Practice. Free text variables will also be allowed to describe, for example, deviations from protocol.

All stored CRFs will be kept in a secure environment at UCL and in the sites. This will include a locked filing cabinet in a locked room, only accessible by authorised personnel. The key to the participant code list will be kept separately to these documents, in a secure location at the site.

The eCRF will only be accessed by staff authorised to do so on the delegation log, at each site. The

Principal Investigator at each study site will be responsible for data security at each study site and the Chief Investigator will have overall responsibility to ensure that all data is stored and processed in accordance with General Data Protection Regulations and UCL Information Governance. Only anonymised aggregated research outputs (ie analysed data in the form of research papers, reports and statistical analyses) will be shared between study sites.

Security

Data security will be maintained through the use of password protection at computer and database levels for nominated staff only, recorded on the delegation log by the CI.

This database will be held on a secure drive on a NHS server. All data will be stored in accordance with General Data Protection Regulations and the UCL information security policy and trust information governance policies. The drives are backed up regularly, allowing data retrieval in the event of data loss.

Data Archiving

Archiving of data will be authorised by the sponsor following submission of the end study report. The CI is responsible for the secure archiving of all essential trial documents at the coordinating centre and the trial database as per UCL policy. These will be archived for a minimum of 15 years after the end of the study.

The PI or their delegate at the site is responsible for the secure archiving of essential site trial documents as per local trust policy arrangements. Destruction of any essential documents will require authorisation from the sponsor.

Figure 1 Data flow for Formative Research

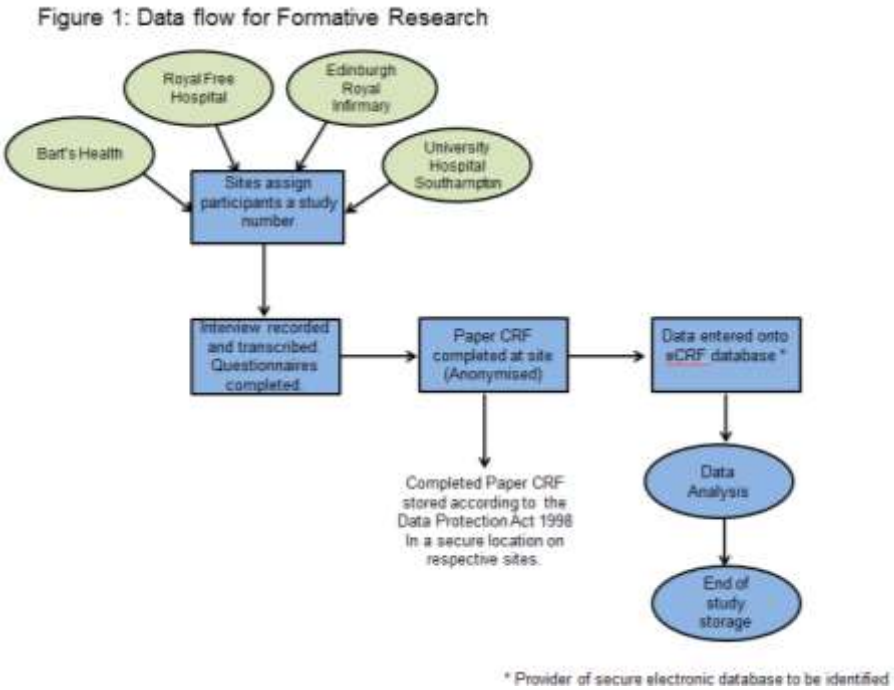
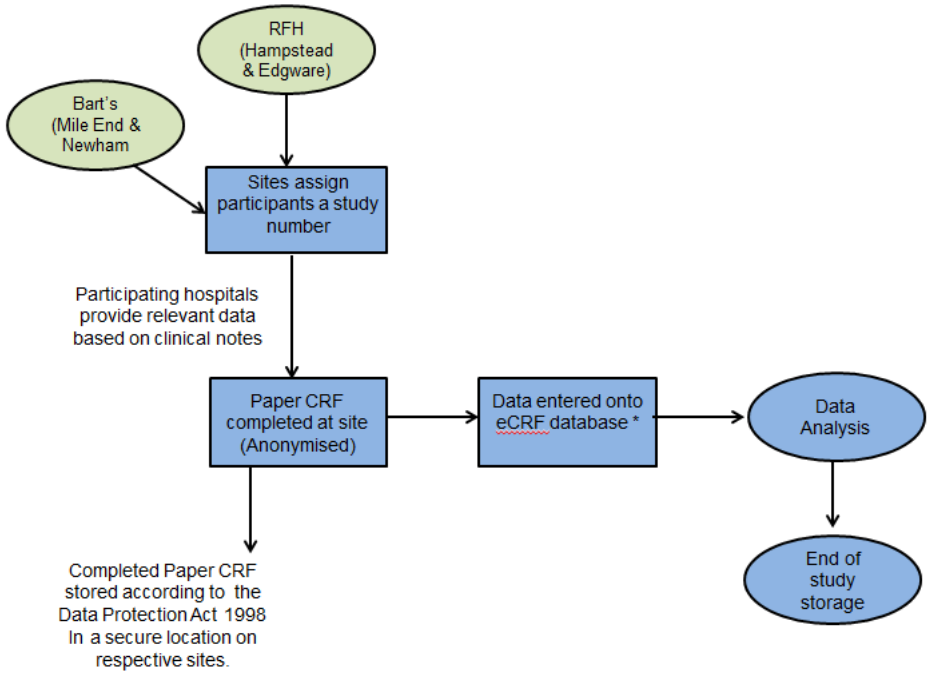


Figure 2 Data flow for Randomised Cluster Control Trial



* Provider of secure electronic database to be identified

18.7 APPENDIX 7 : IsoScreen Urine Testing

What is IsoScreen?
IsoScreen is a urine test to monitor treatment adherence of patients with tuberculosis. It is a 5 minute test that turns blue/black if isoniazid breakdown products are present in urine
IsoScreen is supplied loosely assembled in two parts inside a sealed pouch. The upper syringe is for sample collection. The lower part is where the reaction or test takes place.

How does the test work?

Step by step procedures

1. Unprocessed urine should be collected in a container with a wide neck, such as our urine collecting cup.

2. Draw the urine into the syringe by holding the plunger of the syringe between the thumb and finger while supporting the cap with the other fingers. The plunger should be pulled to the end. There will be a small bubble of air in the syringe.

3. Place the syringe inside the barrel. There is a membrane positioned half-way down the tube. Place the tip of the syringe lightly onto the membrane.

4. Holding the white cap and using the small flanges on the side push down evenly with two

5. thumbs so forcing the syringe down and through the membrane. This is best done with a quick snap action.

6. The 'click' will indicate the cap is now in place and the test activated.

7. IMMEDIATELY push down the plunger, squirting the urine sample into the tube and on top of the chemicals.

8. QUICKLY mix the sample and urine together. This is best done by holding the cap FIRMLY between finger and thumb of one hand and tapping the bottom of the tube repeatedly with the forefinger of the other hand. This will cause a vortex or eddy in the liquid. Alternatively, a vortex mixer can be used. Mix the liquid for 30 seconds.

9. The tablet in the liquid will start to fix and bubble. If the urine sample is from a patient who has taken their isoniazid after about 1 minute the liquid will start to turn blue/black. Leave the test to develop the correct colour for 5 minutes after addition of the sample.

How do I interpret the results?

A dark blue/black indicates treatment adherence, green means the tablet has been taken, but not for about two day and yellow means no treatment has been taken within the last few days.

How long after the last dose of isoniazid will the test remain positive?

Initial tests (Annals of Clinical Biochemistry 2004; 41: 411-413) and an ongoing evaluation shows the test is positive for 24-30 hours after the last dose. If the drug ingestion was longer than this but less than 48 hours the resultant test colour will be green. Any longer than 48 hours the test

colour will remain yellow. However, this will be affected by the acetylator status of the patient.

If I think that a colour is developing should I leave it longer than 5 minutes?

No – leaving the test longer could give spurious results. If isoniazid or its metabolites are present in the urine it will turn dark blue very quickly.

When using the test what is the shortest and longest time I can leave before reading the result?

Normally, a positive sample will change colour within seconds, but it is recommended that the full 5 minutes be left to get a definitive test result.

How do I dispose of the test after use?

It is recommended to place the used test in a 'burn' or 'sharps' bin for disposal.

Can any other substance interfere with the test?

Results suggest there is no other drug or substance that will give the dark blue/purple colour of a positive IsoScreen test.

What is the sensitivity and specificity of the test?

Results suggest that the sensitivity is 97% and specificity is 98%.

Can I use the urine sample as soon as it has been voided?

The test should ideally be used when the urine is at room temperature, but the qualitative nature of the test means a correct result will be obtained with the sample at body temperature.

Will the tests pick up other TB drugs?

Test results show this not to be the case.

What is the test result if I am not sure whether the tests has changed colour?

The test has to be viewed under good lighting conditions, and then if there is any doubt if there has been a colour change then the result is negative. There has to be a visible blue/violet colour change for the result to be positive.

How should I store the tests?

The tests should be stored at room temperature.

What is the shelf-life of the test?

The tests have a shelf-life of at least 12-months after manufacture. The expiry date is printed on the pouch of box.

Where can I go for further information about Isoscreen testing and procedures?

Further information, including a video demonstration can be found at http://www.gfcdiagnostics.com/index.html

Information adapted from www.gfcdiagnostics.com

18.8 APPENDIX 8. EQ5D-5L QoL Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐