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The IMPACT Study: Intervening with a Manualised Package to ACHieve treatment adherence in people with Tuberculosis: A mixed methods approach, including a pilot randomised controlled trial

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The IMPACT Study: Intervening with a Manualised Package to ACHieve treatment adherence in people with Tuberculosis: A mixed methods approach, including a pilot randomised controlled trial

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Abstract

Introduction

Compared to the rest of the UK and Western Europe, England has high rates of the infectious disease tuberculosis (TB). TB is curable, although treatment is for at least six months - and longer when disease is drug resistant. If patients miss too many doses (non-adherence), they may transmit infection for longer and the infecting bacteria may develop resistance to the standard drugs used for treatment. Non-adherence may therefore risk both their health and that of others. Within England, certain population groups are thought to be at higher risk of non-adherence, but the factors contributing to this have been insufficiently determined, as have the best interventions to promote adherence. The objective of this study is to develop a manualised package of interventions for use as part of routine care within National Health Services to address the social and cultural factors that lead to poor adherence to treatment for TB disease.

Methods and analysis

This study uses a mixed methods approach, with six study components. These are: (i) scoping reviews of the literature, (ii) qualitative research with patients, carers and healthcare professionals, (iii) development of the intervention, (iv) a pilot randomised controlled trial of the manualised intervention, (v) a process evaluation to examine clinical utility, and (vi) a cost analysis.

Ethics and dissemination

This study received ethics approval on 24th December 2018 from Camberwell St. Giles Ethics Committee, UK (REC reference 18/LO/1818). Findings will be published and disseminated through peer-reviewed publications and conference presentations, published in an end of study report to our funder (the National Institute for Health Research, UK), and presented to key stakeholders.

Trial Registration Number

ISRCTN 95243114

Article Summary: Strengths and limitations of this study

Strengths

- Patient-centred, mixed methods approach, based on a robust understanding of the evidence on social, cultural and personal factors that influence adherence to medication to treat tuberculosis.
- Evidence and experience of adherence captured from a variety of perspectives from across the UK, including patients, their carers, and healthcare workers.
- Generalisable patient population of individuals at risk of non-adherence across low tuberculosis (TB) incidence settings.
- Development of a pragmatic and easy-to-use tool that captures the best evidence on adherence and allows its application in the clinic setting.

Limitations

- The study culminates in a pilot trial of the manualised intervention; a larger subsequent definitive trial is needed to test whether the intervention is efficacious and cost-effective beyond any initial conclusions regarding validity and feasibility derived from the pilot.

Introduction

Against a background of rising tuberculosis (TB) in the 1990s and 2000s, the need for a comprehensive approach to TB control in England was deemed necessary by Public Health England (PHE) and the National Health Service (NHS) England. In January 2015, these bodies jointly launched the 'Collaborative Tuberculosis Strategy for England 2015-2020'[1]. This seeks to reduce TB incidence, decrease health inequalities, and ultimately contribute to international efforts to eliminate TB as a public health problem. Ensuring that people can take all of their medication as prescribed is one of the strategy's priorities, as poor adherence to treatment for TB is a driver of worse patient outcomes[2–9], increases the risk of transmission (due to delayed sputum culture conversion)[10], and can promote the development of drug resistance[3,11–16]. Subsequent National Institute for Health and Care Excellence (NICE) guidance noted the lack of robust TB research in this area[17].

Barriers to optimal adherence to treatment for TB may occur for a number of reasons. These include:

- patient-related factors, including perceptions and beliefs,
- cultural influences and current mental state,
- structural economic factors and social support networks,
- health service factors that include treatment complexity as well as accessibility of those services and the relationships patients develop with service providers[18,19].

Non-adherence is not a single issue and may take various forms e.g. suboptimal implementation (skipping doses), or stopping treatment early (for example, as soon as a patient feels better; this is discontinuation)[20].

Although a series of studies have been undertaken to define the population groups most at risk of non-adherence[19], it is currently difficult, prior to starting medication, to identify who may struggle with taking treatment as prescribed. To date, methods to support treatment address some, but not all, of the important underlying reasons for poor adherence. For example, the World Health Organization's recent focus on digital technologies reflects our attention on individual-level determinants of adherence and reminder/observation-based systems[21]; far less research has addressed the social and structural barriers to staying on TB treatment.

In the UK, the development of an intervention to support adherence to treatment that is sensitive to the individual's cultural background and social circumstances, and can be routinely delivered within the NHS, is critical. To this purpose, a mixed-methods, patient-centred, approach to the study of the modifiable factors that influence patients' adherence to treatment for TB is required.

Methods and analysis

Research question

Can a manualised intervention be developed to address the social, cultural, and structural barriers that lead to non-adherence to treatment in NHS patients with active TB?

Aim

To develop, pilot, and evaluate process and interim outcomes for an effective manualised intervention that improves the likelihood of treatment completion among NHS patients at risk of poor adherence due to social, cultural, and structural factors.

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 (the Perceptions and Practicalities (PAPA) approach [18]) 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 with multiple components that can identify (a) NHS patients most at risk of non-adherence, (b) the salient modifiable barriers, and (c) the tailored support mechanisms required to meet individual patient 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).

Study design

This study uses a mixed methods approach. There are 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 the different elements are described separately below, the research activities for each will overlap, and some will run concurrently. The full programme of work and relationships between subsections is shown in Figure 1.

i. Scoping Review

To underpin the development of the manualised intervention, the first study sub-section will undertake literature reviews to answer the following research questions:

- i) What personal, social, cultural, health systems-related and structural factors affect individuals' ability to adhere to treatment for TB?
- ii) What kinds of intervention have been developed to address the multiple levels (personal, social, cultural, systems 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?

These questions will be answered through the three following reviews:

1) A scoping review of qualitative studies that examine the personal, social, cultural, health systems-related and structural factors affecting adherence to treatment for TB from the perspectives of adult patients, care givers, or health care providers, as well as studies that evaluate interventions to support adherence to treatment for TB.

1
2
3
4 **2) A critical review of quantitative studies** examining the personal, social, cultural, health systems-
5 related and structural factors affecting adherence to treatment for TB.
6

7
8 **3) A critical review of quantitative studies that have examined the effectiveness of interventions**
9 **to improve adherence in people taking treatment for TB**, building on existing systematic reviews,
10 including the provision and delivery of information and/or education; enablers and/or incentives;
11 social support; case management approaches.
12

13
14 Together, these three reviews will enable us to conduct a critical interpretive synthesis of findings
15 from qualitative and quantitative studies examining the assumptions and mechanisms of effect
16 underlying interventions to improve adherence to treatment for TB.
17

18 19 **ii. Formative Research**

20 21 **Formative research methods, recruitment and eligibility**

22
23 In line with findings from the scoping review, we will develop topic guides for qualitative interviews
24 exploring current models of TB service delivery in the study sites, providers' views on the barriers
25 and facilitators for treatment adherence, and TB patients' and their family members' experiences of
26 starting and staying on treatment. The thematic analysis of these interviews will complement
27 insights gained from the scoping reviews which will allow us to refine a conceptual framework of
28 adherence building on the Perceptions and Practicalities Approach (PAPA) [18]. Approximately 60
29 participants will be enrolled.
30
31

32
33 Adults (aged 18 and over) who are currently taking or recently completed treatment will be
34 identified by the local TB service at four UK sites (Edinburgh, London [Central London & East London]
35 and Southampton) and asked to take part in the study. The services have been chosen for their
36 patient diversity, geographic spread and as reflecting the national TB picture. The patient group will
37 be enriched with people who have been poorly adherent to treatment, although we will also include
38 patients who report full adherence so that we can capture what may have enabled them to take
39 treatment as prescribed. With patient consent, family members and/or carers will also be
40 approached and asked to participate.
41

42
43 Health and social care workers from both primary and secondary care settings will be directly
44 approached by researchers and invited to be interviewed. All those approached will be aged 18 or
45 over and involved in TB management and care.
46

47 48 **Data collection methods**

49
50 Three different methods of data collection will be used to undertake the formative research.

51 52 **1) In-depth interviews – patients and family members/carers**

53
54 These will be conducted as individual interviews with approximately 30 participants, using a topic
55 guide. The areas to be explored are: self-perception; personal beliefs and practices related to
56 medicine-taking; health literacy and health-seeking behaviour; social support; cultural norms around
57 health-seeking behaviour; financial and other structural barriers.
58
59
60

2) Cognitive assessments - patients

To ensure that the validated questionnaires (i.e. Beliefs about Medicines Questionnaires[22] and the Brief Illness Perception Questionnaire[23]), are accessible and acceptable to patients, we will also conduct cognitive interviews with 10 patients. We will then have confidence to use them in the later pilot study to assess patient perceptions and practicalities affecting adherence to anti-TB therapy. These will explore self-perception; personal beliefs; and practices related to medicine-taking.

3) Semi-structured Interviews – healthcare providers

These will be undertaken with health care providers responsible for multiple aspects of TB care (doctors, nurses, social workers, directly observed therapy [DOT] providers, managers and administrators). They will focus on providers' perceptions of factors affecting patient understanding of TB and its treatment; service delivery models including staffing; organisation of care; communication. We will interview four to six providers at each site, aiming for a total of 20 interviews.

iii. Development of the manualised intervention

Intervention development process

The data collected from the scoping reviews and formative research will be presented to, and synthesised by, an Intervention Development Group (IDG). A manualised intervention will be developed to identify (a) NHS patients most at risk of non-adherence, (b) their salient modifiable barriers, and (c) the tailored support mechanisms that meet individual patient needs by matching appropriate interventions to these specific barriers.

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 constitution of the IDG 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.

Intervention contents

The manualised intervention is likely to consist of a screening and assessment tool, in addition to a package of measures that can be tailored to the needs of individual patients from different population groups.

As patterns of adherence may be irregular over time, it is intended that the manualised intervention will be administered to all patients at each patient review. The tool thus needs to be quick and easy to administer. It may be electronically linked to patient records, enabling a comprehensive picture of the risk of possible non-adherence to be developed for each patient, as well as within a clinic population. The various delivery options for the intervention (such as using paper or an app) will be considered during its development stage.

The menu of supportive measures may, for example, include:

- Informational intervention: e.g. providing a convincing story setting out the rationale and on-going 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 their treatment regimens to alternatives[24].
- Practicalities and Capability based interventions: video observed therapy [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. housing, drug and alcohol services, and social care; providing peer-support.

iv. Piloting the intervention

Study design, recruitment and eligibility

Once the intervention is developed, proof-of-concept is required within the real world. This will be undertaken using a cluster randomised pilot study that compares the manualised intervention to the usual standard of care in four London clinics treating TB. Two clinics will be randomly allocated to the intervention and two to standard of care. Participants starting treatment for TB will be enrolled. These are likely to include people at greater risk of poor adherence such as migrants newly arrived in the UK, people whose first language is not English, 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.

Patients included in the pilot study will be aged 18 or over and will be started on treatment for TB, irrespective of site of disease. We will exclude patients who are unable to provide informed consent, those already on treatment and those who are not expected to live for the duration of the study (a minimum of six months from starting treatment).

The purpose of the pilot study is not formal hypothesis testing. Given this, a target sample size of 80 patients enrolled (20 per site) was identified for the pilot study as providing useful information that can help determine whether the intervention will be deliverable within a clinical setting. It will also guide the development of a possible larger definitive study using the intervention. The four TB clinics of interest (in East and North London) each treat in excess of 60 relevant patients per annum.

Based on usage of DOT within the clinic populations seen at the treatment sites (i.e. individuals currently identified as needing adherence support), we estimate that around 33% of patients will be at risk of 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 of the 80 patients recruited will be identified as requiring adherence support. This sample size allows us to measure consent to enrolment for 80 individuals, data completeness for adherence and treatment outcomes for 80 individuals, data on acceptability and feasibility of the intervention package for around 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).

Outcomes of the pilot

The primary outcome of the study will be level of adherence, measured as the proportion of prescribed doses taken and assessed at six months from the start of treatment. In addition to this

primary outcome, a number of secondary outcomes will also be measured, as follows:

- 1) Proportion consenting to the study.
- 2) Completeness of data for measures of adherence and treatment completion.
- 3) Proportion of patients withdrawing during the study and the reasons why.
- 4) Proportion of patients identified as needing adherence support in the intervention arm.
- 5) Proportion of patients offered adherence support and accepting it in the intervention arm.
- 6) Documentation of which adherence-promoting activities have been implemented among patients both in the standard of care and intervention arm, and when.
- 7) Detailed treatment implementation information: e.g. proportion of patients completing treatment, proportion of patients still on treatment after nine months or at study completion (whichever is the earlier).
- 8) Patterns of adherence (implementation and discontinuation).
- 9) Impact of manualised intervention on maintaining adherence over the duration of treatment.
- 10) Process variables – adherence-related perceptions and practicalities.

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, and compared with pill counts. Patients within the study will be asked 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 DOT or VOT methods being used, a record of missed doses will be kept.

At each appointment, participants will also be asked to provide a 5ml sample of urine to check for adherence to the prescribed anti-TB medication; and they will be asked directly whether they have managed to take all their medicines and if they have missed any doses [25].

Administration of the manualised intervention

The patient's case manager (usually the TB clinic nurse), plus a study research nurse, will apply the intervention in partnership 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. These will be continued throughout the course of treatment, or stopped if no longer deemed to be relevant or required on reassessment.

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 on-going treatment after six months, they will be seen as clinically indicated. At each review, adherence assessments will be performed in addition to an assessment of perceptions and practicalities, the completion of the BMQ and the EQ-5D-5L Quality of Life questionnaire[22,26]. The manualised intervention will be applied if the patient is attending a clinic that has been randomised to the intervention arm.

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 nine months from starting anti-TB therapy.

Analysis and interpretation

Where possible, univariable analyses such as Fisher's exact test will be undertaken to compare each outcome measure listed earlier between study arms (intervention and control). An assessment of the balance in baseline characteristics between the study arms will also be conducted. If randomisation has failed to evenly distribute key baseline characteristics (e.g. age, sex, ethnicity, or other factors identified as important during the scoping reviews), then multivariable logistic regression analyses adjusting for these factors will also be undertaken, subject to constraints on the degree of adjustment, which depend on the prevalence of the outcome and sample size. Inter-site variability in outcomes will be measured. The need to adjust for clustering by clinical care provider will be assessed; clustering by site alone cannot be formally adjusted for due to the modest number of sites in the pilot study.

The analysis of the first three of our secondary outcomes will address the feasibility of a definitive trial following a similar design to the pilot. Analysis of secondary outcomes four to six addresses the intervention, and complements the process evaluation (see below). 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. They can also offer an alert in the unlikely event that the intervention is harmful.

v. Process evaluation

Evaluation method

We will evaluate the implementation process by analysing the challenges and facilitators in delivering the package. The impact of the intervention will be assessed by evaluation of adherence indicators. We will 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 RCT.

The process evaluation will consist of a description of the process of intervention implementation. It will assess how 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.

Process measures, recruitment and eligibility

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 at all four London sites. We will interview 20 patients (five at each study site i.e. 10 from each arm); and, if possible, 20 health care workers (five at each site). The patients will be selected within each site using purposeful sampling of clinic lists of every fourth patient with active TB.

Key outputs will include a qualitative evaluation of delivery, the development of a narrative description of the process of intervention implementation and maintenance and a quantitative

1
2
3 assessment of adherence-related perceptions and practicalities within intervention and control
4 groups.
5

6 We will invite participation in the process evaluation from patients enrolled in the pilot study or staff
7 members treating patients at one of the four London sites also involved in delivering the pilot study.
8 They will be included if they are aged 18 or over and able to provide informed consent.
9

10 11 **vi. Cost Analysis and Future Work**

12
13 In order to generate realistic estimates of the cost of the intervention, cost data from the NHS
14 perspective will be collected during the pilot study using NICE guideline implementation tools.
15

16
17 After the pilot study and process evaluation have been completed, a final intervention package will
18 be designed for use in a definitive RCT of the manualised package of interventions. The design of this
19 final package will be based on the results of the process evaluation and the experience gained during
20 the piloting of the intervention, modifying the definitive trial design and/or data collection
21 accordingly.
22

23 24 **Patient and public engagement**

25 As documented above, patient representatives will sit on the IDG for the study. In addition, TB Alert,
26 the UK's only national TB charity, has membership of the IDG. The role of the IDG, which will meet
27 regularly throughout the study, is described in section iii. At the end of the study, the IDG will be
28 involved in commenting on the findings and contributing to the dissemination plan.
29

30 31 **Ethics and dissemination**

32 This study received ethics approval on 24th December 2018 from Camberwell St Giles Ethics
33 Committee (REC reference 18/LO/1818). Findings will be published and disseminated through peer-
34 reviewed publications and conference presentations, published in an end of study report to our
35 funder (the National Institute for Health Research, UK), and presented to key stakeholders.
36

37 38 **Conclusion**

39
40 Our study will develop and pilot a manualised intervention to improve adherence to treatment for
41 TB in the UK using a mixed methods, patient-centred and provider-informed approach. This will
42 enable us to begin to understand what motivates patients' treatment behaviour, whilst ensuring
43 deliverability within the NHS. Our work is based on a robust understanding of the evidence on social,
44 cultural and personal factors that influence adherence, and the interventions that are most effective
45 in addressing these. The study reflects the geographic spread of TB in the UK and captures not only
46 patient and expert clinical and academic experience, but also that of family and carers to develop
47 the intervention. A key feature of the study is the co-production of a pragmatic and easy-to-use tool
48 that utilises the best evidence on adherence, and allows its application in the clinic setting in a
49 dynamic and iterative way.
50

51
52 Although the final pilot study may be limited to a relatively small sample size, it is hoped that its
53 broad patient-centred perspective will make a useful contribution to our understanding of, and
54 ability to deal effectively with, the risks of non-adherence to TB treatment in a population that can
55 find this challenging. As many of the factors influencing adherence are likely to be generalisable to
56 patients with other conditions in both high and low resource settings, this study also has the
57 potential to inform adherence interventions in other disease areas.
58
59
60

Authors' contributions

ML, IA, RH, KK and HRS conceived of the work. HRS, IA, AC, RH, KK, MM, AS, NV and ML designed the work. HRS, CNJC, MD, RH, KK, drafted the manuscript. All authors critically revised the manuscript and gave final approval of the version of the protocol manuscript to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part are appropriately investigated and resolved.

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Competing interests statement

IA, MD, HK, KK, ML, MM, EP, AS, FW have no competing interests to declare.

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CNJC reports personal fees from Public Health England, outside the submitted work.

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Figure legends

Figure 1- The IMPACT study

The six mixed-methods elements of the IMPACT [Intervening with a Manualised Package to Achieve treatment adherence in people with Tuberculosis] study and the relationships between them. The study is guided by a steering group, which has oversight over the entire process and culminates in a pilot study with associated evaluatory elements.

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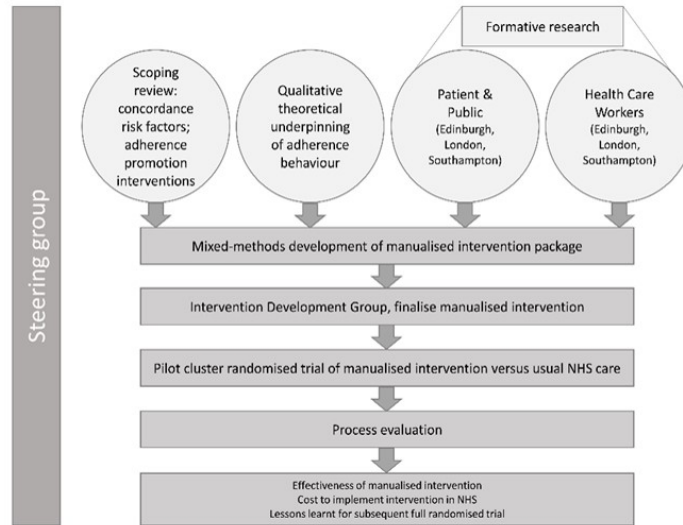


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The IMPACT Study: Intervening with a Manualised Package to ACHieve treatment adherence in people with Tuberculosis: A mixed methods approach, including a pilot randomised controlled trial

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1 The IMPACT Study: Intervening with a Manualised Package to ACHieve 2 treatment adherence in people with Tuberculosis: A mixed methods 3 approach, including a pilot randomised controlled trial

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Abstract**Introduction**

Compared to the rest of the UK and Western Europe, England has high rates of the infectious disease tuberculosis (TB). TB is curable, although treatment is for at least six months - and longer when disease is drug resistant. If patients miss too many doses (non-adherence), they may transmit infection for longer and the infecting bacteria may develop resistance to the standard drugs used for treatment. Non-adherence may therefore risk both their health and that of others. Within England, certain population groups are thought to be at higher risk of non-adherence, but the factors contributing to this have been insufficiently determined, as have the best interventions to promote adherence. The objective of this study is to develop a manualised package of interventions for use as part of routine care within National Health Services to address the social and cultural factors that lead to poor adherence to treatment for TB disease.

50

Methods and analysis

This study uses a mixed methods approach, with six study components. These are: (i) scoping reviews of the literature, (ii) qualitative research with patients, carers and healthcare professionals, (iii) development of the intervention, (iv) a pilot randomised controlled trial of the manualised intervention, (v) a process evaluation to examine clinical utility, and (vi) a cost analysis.

56

Ethics and dissemination

This study received ethics approval on 24th December 2018 from Camberwell St. Giles Ethics Committee, UK (REC reference 18/LO/1818). Findings will be published and disseminated through peer-reviewed publications and conference presentations, published in an end of study report to our funder (the National Institute for Health Research, UK), and presented to key stakeholders.

62

Trial Registration Number

ISRCTN 95243114

65

66 **Article Summary: Strengths and limitations of this study**

67 **Strengths**

- 68 • Patient-centred, mixed methods approach, based on a robust understanding of the evidence
69 on social, cultural and personal factors that influence adherence to medication to treat
70 tuberculosis.
- 71 • Evidence and experience of adherence captured from a variety of perspectives from across
72 the UK, including patients, their carers, and healthcare workers.
- 73 • Generalisable patient population of individuals at risk of non-adherence across low
74 tuberculosis (TB) incidence settings.
- 75 • Development of a pragmatic and easy-to-use tool that captures the best evidence on
76 adherence and allows its application in the clinic setting.

77

78 **Limitations**

- 79 • The study culminates in a pilot trial of the manualised intervention; a larger subsequent
80 definitive trial is needed to test whether the intervention is efficacious and cost-effective
81 beyond any initial conclusions regarding validity and feasibility derived from the pilot.

82

83

84 Introduction

85
86 Against a background of rising tuberculosis (TB) in the 1990s and 2000s, the need for a
87 comprehensive approach to TB control in England was deemed necessary by Public Health England
88 (PHE) and the National Health Service (NHS) England. In January 2015, these bodies jointly launched
89 the 'Collaborative Tuberculosis Strategy for England 2015-2020'[1]. This seeks to reduce TB
90 incidence, decrease health inequalities, and ultimately contribute to international efforts to
91 eliminate TB as a public health problem. Ensuring that people can take all of their medication as
92 prescribed is one of the strategy's priorities, as poor adherence to treatment for TB is a driver of
93 worse patient outcomes[2–9], increases the risk of transmission (due to delayed sputum culture
94 conversion)[10], and can promote the development of drug resistance[3,11–16]. Subsequent
95 National Institute for Health and Care Excellence (NICE) guidance noted the lack of robust TB
96 research in this area[17].

97
98 Barriers to optimal adherence to treatment for TB may occur for a number of reasons. These
99 include:

- 100 • patient-related factors, including perceptions and beliefs,
- 101 • cultural influences and current mental state,
- 102 • structural economic factors and social support networks,
- 103 • health service factors that include treatment complexity as well as accessibility of those
104 services and the relationships patients develop with service providers[18,19].

105
106 Non-adherence is not a single issue and may take various forms e.g. suboptimal implementation
107 (skipping doses), or stopping treatment early (for example, as soon as a patient feels better; this is
108 discontinuation)[20].

109
110 Although a series of studies have been undertaken to define the population groups most at risk of
111 non-adherence[19], it is currently difficult, prior to starting medication, to identify who may struggle
112 with taking treatment as prescribed. To date, methods to support treatment address some, but not
113 all, of the important underlying reasons for poor adherence. For example, the World Health
114 Organization's recent focus on digital technologies reflects our attention on individual-level
115 determinants of adherence and reminder/observation-based systems[21]; far less research has
116 addressed the social and structural barriers to staying on TB treatment.

117
118 In the UK, the development of an intervention to support adherence to treatment that is sensitive to
119 the individual's cultural background and social circumstances, and can be routinely delivered within
120 the NHS, is critical. To this purpose, a mixed-methods, patient-centred, approach to the study of the
121 (modifiable factors that influence patients' adherence to treatment for TB is required.

122 Methods and analysis

123 Research question

124
125 Can a manualised package of intervention be developed to help overcome the social and cultural
126 factors that lead to poor adherence to treatment in NHS patients in the United Kingdom with active
127 TB?
128

129 Aim

130
131 To develop, pilot, and evaluate process and interim outcomes for an effective manualised
132 intervention that improves the likelihood of adherence to treatment among NHS patients at risk of
133 poor adherence due to social, cultural, and structural factors.

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 (the Perceptions and Practicalities (PAPA) approach [18] 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 (a series of systematic actions applied on the basis of a patient's needs assessment) with multiple components that can identify (a) NHS patients most at risk of non-adherence, (b) the salient modifiable barriers, and (c) the tailored support mechanisms required to meet individual patient needs by matching appropriate interventions to specific barriers, as recommended by NICE. (Development of Intervention)
A manualised intervention was considered to be a suitable approach to managing adherence in TB, as it will enable a set of measures to be applied consistently within different NHS settings that will aid both clinicians and patients throughout the treatment journey. The content of the intervention will use existing support measures, employed in a systematic and structured way, and may also include any new interventions that are developed in response to the formative research. Pilot the intervention package in people at risk of poor adherence to define how the components work in combination and separately. (Pilot Study)
- 4) 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)
- 5) 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).

Study design

This study uses a mixed methods approach. There are 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 the different elements are described separately below, the research activities for each will overlap, and some will run concurrently. The full programme of work and relationships between subsections is shown in Figure 1.

i. Scoping Review

To underpin the development of the manualised intervention, the first study sub-section will undertake literature reviews to answer the following research questions:

- i) What personal, social, cultural, health systems-related and structural factors affect individuals' ability to adhere to treatment for TB?
- ii) What kinds of intervention have been developed to address the multiple levels (personal, social, cultural, systems 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?

These questions will be answered through the three following reviews:

1
2
3 185
4 186 **1) A scoping review of qualitative studies** that examine the personal, social, cultural, health
5 187 systems-related and structural factors affecting adherence to treatment for TB from the
6 188 perspectives of adult patients, care givers, or health care providers, as well as studies that evaluate
7 189 interventions to support adherence to treatment for TB. Data from all settings will be considered,
8 190 but with a particular focus on low incidence, high income, settings.

9 191
10 192 **2) A critical review of quantitative studies** examining the personal, social, cultural, health systems-
11 193 related and structural factors affecting adherence to treatment for TB. This review focuses on low
12 194 incidence, high income, settings and observational study designs. Given the scoping nature of the
13 195 review, findings will be descriptively analysed and not be stratified or disaggregated e.g. by site of
14 196 disease. All relative and absolute measures of effect will be extracted.

15 197
16 198 **3) A critical review of quantitative studies that have examined the effectiveness of interventions**
17 199 **to improve adherence in people taking treatment for TB**, building on existing systematic reviews,
18 200 including the provision and delivery of information and/or education; enablers and/or incentives;
19 201 social support; case management approaches. Given the more limited literature, both observational
20 202 studies and clinical trials will be included, from all settings. Findings will be descriptively analysed.

21 203
22 204 Together, these three reviews will enable us to conduct a critical interpretive synthesis of findings
23 205 from qualitative and quantitative studies examining the assumptions and mechanisms of effect
24 206 underlying interventions to improve adherence to treatment for TB.

25 207 26 208 **ii. Formative Research**

27 209 28 210 **Formative research methods, recruitment and eligibility**

29 211
30 212 In line with findings from the scoping review, we will develop topic guides for qualitative interviews
31 213 exploring current models of TB service delivery in the study sites, providers' views on the barriers
32 214 and facilitators for treatment adherence, and TB patients' and their family members' experiences of
33 215 starting and staying on treatment. The thematic analysis of these interviews will complement
34 216 insights gained from the scoping reviews which will allow us to refine a conceptual framework of
35 217 adherence building on the Perceptions and Practicalities Approach (PAPA) [18]. Approximately 60
36 218 participants will be enrolled.

37 219
38 220 Adults (aged 18 and over) who are currently taking or recently completed treatment will be
39 221 identified by the local TB service at four UK sites (Edinburgh, London [Central London & East London]
40 222 and Southampton) and asked to take part in the study. The services have been chosen for their
41 223 patient diversity, geographic spread and as reflecting the national TB picture. The patient group will
42 224 be enriched with people who have been poorly adherent to treatment, although we will also include
43 225 patients who report full adherence so that we can capture what may have enabled them to take
44 226 treatment as prescribed. With patient consent, family members and/or carers will also be
45 227 approached and asked to participate.

46 228
47 229 Health and social care workers from both primary and secondary care settings will be directly
48 230 approached by researchers and invited to be interviewed. All those approached will be aged 18 or
49 231 over and involved in TB management and care.

50 232 51 233 **Data collection methods**

52 234
53 235 Three different methods of data collection will be used to undertake the formative research.

236

1) In-depth interviews – patients and family members/carers

These will be conducted as individual interviews with approximately 30 participants, using a topic guide. The areas to be explored are: 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.

242

2) Testing of BMQ and BIPQ Questionnaires with patients for their suitability

To ensure that the validated questionnaires (i.e. Beliefs about Medicines Questionnaires[22] and the Brief Illness Perception Questionnaire[23], are accessible and acceptable to patients, we will also conduct cognitive interviews with 10 patients. We will then have confidence to use them in the later pilot study to assess patient perceptions and practicalities affecting adherence to anti-TB therapy. These will explore self-perception; personal beliefs; and practices related to medicine-taking.

249

3) Semi-structured Interviews – healthcare providers

These will be undertaken with health care providers responsible for multiple aspects of TB care (doctors, nurses, social workers, directly observed therapy [DOT] providers, managers and administrators). They will focus on providers' perceptions of factors affecting patient understanding of TB and its treatment; service delivery models including staffing; organisation of care; communication. We will interview four to six providers at each site, aiming for a total of 20 interviews.

257

We will use a framework approach [24] to facilitate initial analysis of the interview transcripts. Short patient case studies will be created for each patient interview. Data on health systems issues gained through mapping patient pathways and provider interviews will be organised using a deductive approach, with appropriate visual pathways.

262

iii. Development of the manualised intervention

264

Intervention development process

The data collected from the scoping reviews and formative research will be presented to, and synthesised by, an Intervention Development Group (IDG). A manualised intervention will be developed to identify (a) NHS patients most at risk of non-adherence, (b) their salient modifiable barriers, and (c) the tailored support mechanisms that meet individual patient needs by matching appropriate interventions to these specific barriers.

271

The IDG will include:

273

- patients (in particular the homeless, ethnic minorities, migrants new to the UK, and patients with drug resistant TB)

274

- family members/significant others of affected persons

275

- members of the public

276

- health care professionals (from both primary and secondary care)

277

- other professionals who work with patients/communities affected by TB

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The constitution of the IDG 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.

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Intervention contents

The manualised intervention is likely to consist of a screening and assessment tool, in addition to a package of measures that can be tailored to the needs of individual patients from different

1
2
3 287 population groups.

4 288

5 289 As patterns of adherence may be irregular over time, it is intended that the manualised intervention
6 290 will be administered to all patients at each patient review. The tool thus needs to be quick and easy
7 291 to administer. It may be electronically linked to patient records, enabling a comprehensive picture of
8 292 the risk of possible non-adherence to be developed for each patient, as well as within a clinic
9 293 population. The various delivery options for the intervention (such as using paper or an app) will be
10 294 considered during its development stage.

11 295

12 296 The menu of supportive measures may, for example, include:

13 297

- 14 297 • Informational intervention: e.g. providing a convincing story setting out the rationale and
15 298 on-going need for medication, addressing concerns about potential adverse effects and
16 299 consequences of treatment and what to do if such events occur e.g. the participant will be
17 300 informed that it is possible to change their treatment regimens to alternatives[25].
- 18 301 • Practicalities and Capability based interventions: video observed therapy [VOT], DOT,
19 302 reminders including text messaging, automated methods for monitoring and feedback
20 303 including electronic dosette boxes, use of a medication app, incentives e.g. financial and
21 304 food vouchers, mitigation and management of drug toxicity due to treatments.
- 22 305 • Social and system interventions: offering flexibility in appointments; enhanced guidance on
23 306 'navigating' clinic pathways; signposting patients to relevant services, e.g. housing, drug and
24 307 alcohol services, and social care; providing peer-support.

25 308

26 309 **iv. Piloting the intervention**

27 310

28 311 **Study design, recruitment and eligibility**

29 312 Once the intervention is developed, proof-of-concept is required within the real world. This will be
30 313 undertaken using a cluster randomised pilot study that compares the manualised intervention to the
31 314 usual standard of care in four London clinics treating TB. Two clinics will be randomly allocated to
32 315 the intervention and two to standard of care. In the latter, the amount of support provided to
33 316 patients is based on perceived need, as identified by a nurse-led review and a needs assessment.
34 317 Most patients will have supported self-administered therapy, whilst others will be offered DOT
35 318 and/or VOT if this is felt to be appropriate.

36 319

37 320 All consecutive patients aged 18 or over who are about to start treatment for TB, irrespective of site
38 321 of disease, will be approached to take part in the study. We will exclude individuals who are unable
39 322 to provide informed consent, those already on treatment and those who are not expected to live for
40 323 the duration of the study (a minimum of six months from starting treatment). Within the pilot study,
41 324 it is essential to capture the entire treatment period for each patient, in order to assess the
42 325 effectiveness of the intervention. . Due to the nature of the TB patient population in the UK, patients
43 326 are likely to include people at greater risk of poor adherence such as migrants newly arrived in the
44 327 UK, people whose first language is not English, people with a mental health disorder, people taking
45 328 immunosuppressive therapy or known to have immunodeficiency, those with a previous history of
46 329 treatment for TB, or poor-adherence with anti-TB medication, and people with a current or previous
47 330 history of drug or alcohol misuse.

48 331

49 332 The purpose of the pilot study is not formal hypothesis testing. Given this, a target sample size of 80
50 333 patients enrolled (20 per site) was identified for the pilot study as providing useful information that
51 334 can help determine whether the intervention will be deliverable within a clinical setting. It will also
52 335 guide the development of a possible larger definitive study using the intervention. The four TB clinics
53 336 of interest (in East and North London) each treat in excess of 60 relevant patients per annum.

54 337

1
2
3 338 Based on usage of DOT within the clinic populations seen at the treatment sites (i.e. individuals
4 339 currently identified as needing adherence support), we estimate that around 33% of patients will be
5 340 at risk of non-adherence. Taking this as a minimum (as the manualised intervention is likely to be
6 341 more sensitive than current risk assessments), we would expect that at least 26 of the 80 patients
7 342 recruited will be identified as requiring adherence support. This sample size allows us to measure
8 343 consent to enrolment for 80 individuals, data completeness for adherence and treatment outcomes
9 344 for 80 individuals, data on acceptability and feasibility of the intervention package for around 40
10 345 individuals, and data on acceptability and feasibility of adherence support for at least 26 individuals
11 346 (13 receiving the manualised intervention and 13 standard care).
12 347

13
14 348 **Outcomes of the pilot** The primary outcome of the study will be level of adherence, measured as
15 349 the proportion of prescribed doses taken and assessed at six months from the start of treatment. In
16 350 addition to this primary outcome, a number of secondary outcomes will also be measured, as
17 351 follows:
18 352

- 19 353 1) Proportion consenting to the study.
- 20 354 2) Completeness of data for measures of adherence.
- 21 355 3) Proportion of patients withdrawing during the study and the reasons why.
- 22 356 4) Proportion of patients identified as needing adherence support in the intervention arm.
- 23 357 5) Proportion of patients offered adherence support and accepting it in the intervention arm.
- 24 358 6) Documentation of which adherence-promoting activities have been implemented among
25 359 patients both in the standard of care and intervention arm, and when.
- 26 360 7) Detailed treatment implementation information: e.g. proportion of patients completing
27 361 treatment, proportion of patients still on treatment after nine months or at study
28 362 completion (whichever is the earlier).
- 29 363 8) Patterns of adherence (implementation and discontinuation).
- 30 364 9) Impact of manualised intervention on maintaining adherence over the duration of
31 365 treatment.
- 32 366 10) Process variables – adherence-related perceptions and practicalities.

33 367 34 368 **Measures of adherence**

35 369 Our primary measure of adherence will be data obtained from medication monitoring boxes [26].
36 370 The boxes will not be set up act as a reminder system. Other measures will also be used and
37 371 compared with this. These will include pill counts (the remaining medication in the box at the end of
38 372 each month), and also patient-reported adherence, where we will ask patients to estimate how
39 373 many doses they have missed in the last month. In the case of DOT or VOT methods being used, a
40 374 record of missed doses will be kept.
41 375

42 376 **Administration of the manualised intervention**

43 377 The patient's case manager (usually the TB clinic nurse), plus a study research nurse, will apply the
44 378 intervention in partnership with the patient to identify whether personal, socio-cultural and/or
45 379 systems risk factors are present that suggest likely poor adherence with treatment. If these are
46 380 identified, then the relevant measures outlined in the manualised intervention that may mitigate
47 381 these will be reviewed and implemented with the agreement of the participant. These will be
48 382 continued throughout the course of treatment, or stopped if no longer deemed to be relevant or
49 383 required on reassessment.
50 384

51 385 **Study schedule of visits**

52 386 Study subjects will be seen at weeks 0, 2, 4, 8, 12, 16, 20 and 24 (earliest date of treatment
53 387 completion). Should they require on-going treatment after six months, they will be seen as clinically
54 388 indicated. At each review, adherence assessments will be performed in addition to an assessment of
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3 389 perceptions and practicalities, the completion of the BMQ and the EQ-5D-5L Quality of Life
4 390 questionnaires [22,27] and the GAD-7 [28] and PHQ-9[29] to assess anxiety and depression. The
5 391 manualised intervention will be applied if the patient is attending a clinic that has been randomised
6 392 to the intervention arm. All data will be collected by the research nurse, using standardised forms.
7 393

8 394 **Follow Up**

9 395 Most patients who do not have clinically important drug resistant disease receive six months of
10 396 treatment. To allow for treatment interruptions, patients within the pilot study will be followed to
11 397 either treatment completion or for a total of nine months from starting anti-TB therapy.
12 398

13 399 **Analysis and interpretation**

14 400 Where possible, univariable analyses will be undertaken to compare each outcome measure listed
15 401 between study arms (intervention and control). For the primary outcome (adherence) the mean
16 402 percentage value will be reported by arm (intervention and control) and histograms used to describe
17 403 the distribution of values by study arm. Binary secondary outcomes will be reported by the
18 404 proportion of individuals achieving this within each arm. The need to adjust for clustering by site and
19 405 clinical care provider will be assessed using the cluster summary method (a t-test to compare the
20 406 cluster means or proportions [as appropriate, two values per arm] between arms). An assessment of
21 407 the balance in baseline characteristics between the study arms will also be conducted. If
22 408 randomisation has failed to evenly distribute key characteristics (e.g. age, sex, ethnicity, or other
23 409 factors identified as important during the scoping reviews), then the cluster means or proportions
24 410 will be adjusted for these differences before applying the t-test. This two-stage approach to analysis
25 411 is described by Hayes and Moulton [30]. We recognise that adherence data may be highly skewed
26 412 and thus require compensatory analytical approaches.

27 413 The analysis of the first three of our secondary outcomes will address the feasibility of a definitive
28 414 trial following a similar design to the pilot. Analysis of secondary outcomes four to six addresses the
29 415 intervention, and complements the process evaluation (see below). Analysis of the primary outcome
30 416 and final secondary outcomes around treatment adherence and completion provides initial
31 417 information - given the modest sample size - concerning the effectiveness of the intervention, and
32 418 may assist the sample size calculation for the definitive trial. They can also offer an alert in the
33 419 unlikely event that the intervention is harmful.
34 420

35 421 **Power calculation**

36 422 Although we are undertaking a pilot study and thus the numbers enrolled are small, Table 1
37 423 indicates the power of our primary analysis to detect a range of absolute increases in adherence (10-
38 424 30%) from a variety of baseline values (50-90%).
39 425
40 426

Table 1- Power calculation for the pilot study

Given a sample size of 80 individuals (40 per arm), across a range of baseline levels of adherence and absolute increases in that level, the pilot study has the following power.

Baseline adherence	Absolute increase	Power
70	30	0.98
60	30	0.88
50	30	0.82
80	20	0.86
70	20	0.61
60	20	0.49
90	10	0.54
80	10	0.24
70	10	0.18

v. Process evaluation

Evaluation method

We will evaluate the implementation process by analysing the challenges and facilitators in delivering the package. The impact of the intervention will be assessed by evaluation of adherence indicators. We will 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 RCT.

The process evaluation will consist of a description of the process of intervention implementation. It will assess how 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.

Process measures, recruitment and eligibility

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 at all four London sites. We will interview 20 patients (five at each study site i.e. 10 from each arm); and, if possible, 20 health care workers (five at each site). The patients will be selected within each site using purposeful sampling of clinic lists of every patient with active TB, to enable us to reflect the demographic spread of patients.

Key outputs will include a qualitative evaluation of delivery, the development of a narrative description of the process of intervention implementation and maintenance and a quantitative assessment of adherence-related perceptions and practicalities within intervention and control groups.

We will invite participation in the process evaluation from patients enrolled in the pilot study or staff

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3 478 members treating patients at one of the four London sites also involved in delivering the pilot study.
4 479 They will be included if they are aged 18 or over and able to provide informed consent. This will
5 480 include probing anticipated versus real-life delivery of the intervention.
6 481

8 482 **vi. Cost Analysis and Future Work**

9 483
10 484 In order to generate realistic estimates of the cost of the intervention, cost data from the NHS
11 485 perspective will be collected during the pilot study using a cost data collection tool used by health
12 486 economists (The Client Service Receipt Inventory, CSRI), modified for TB [31].
13 487

14 488 After the pilot study and process evaluation have been completed, a final intervention package will
15 489 be designed for use in a definitive RCT of the manualised package of interventions. The design of this
16 490 final package will be based on the results of the process evaluation and the experience gained during
17 491 the piloting of the intervention, modifying the definitive trial design and/or data collection
18 492 accordingly.
19 493

21 494 **Patient and public engagement**

22 495 As documented above, patient representatives will sit on the IDG for the study. In addition, TB Alert,
23 496 the UK's only national TB charity, has membership of the IDG. The role of the IDG, which will meet
24 497 regularly throughout the study, is described in section iii. At the end of the study, the IDG will be
25 498 involved in commenting on the findings and contributing to the dissemination plan.
26 499

29 500 **Ethics and dissemination**

30 501 This study received ethics approval on 24th December 2018 from Camberwell St Giles Ethics
31 502 Committee (REC reference 18/LO/1818). Findings will be published and disseminated through peer-
32 503 reviewed publications and conference presentations, published in an end of study report to our
33 504 funder (the National Institute for Health Research, UK), and presented to key stakeholders.
34 505

36 506 **Conclusion**

37 507
38 508 Our study will develop and pilot a manualised intervention to improve adherence to treatment for
39 509 TB in the UK using a mixed methods, patient-centred and provider-informed approach. This will
40 510 enable us to begin to understand what motivates patients' treatment behaviour, whilst ensuring
41 511 deliverability within the NHS. Our work is based on a robust understanding of the evidence on social,
42 512 cultural and personal factors that influence adherence, and the interventions that are most effective
43 513 in addressing these. The study reflects the geographic spread of TB in the UK and captures not only
44 514 patient and expert clinical and academic experience, but also that of family and carers to develop
45 515 the intervention. A key feature of the study is the co-production of a pragmatic and easy-to-use tool
46 516 that utilises the best evidence on adherence, and allows its application in the clinic setting in a
47 517 dynamic and iterative way.
48 518

49 519 Although the final pilot study may be limited to a relatively small sample size, it is hoped that its
50 520 broad patient-centred perspective will make a useful contribution to our understanding of, and
51 521 ability to deal effectively with, the risks of non-adherence to TB treatment in a population that can
52 522 find this challenging. As many of the factors influencing adherence are likely to be generalisable to
53 523 patients with other conditions in both high and low resource settings, this study also has the
54 524 potential to inform adherence interventions in other disease areas.
55 525
56 526

527 **Authors' contributions**

528 ML, IA, RH, KK and HRS conceived of the work. HRS, IA, AC, RH, KK, MM, AS, NV, FW, HK, EP and ML
529 designed the work. HRS, CNJC, MD, RH, KK, drafted the manuscript. All authors critically revised the
530 manuscript and gave final approval of the version of the protocol manuscript to be published. All
531 authors agree to be accountable for all aspects of the work in ensuring that questions related to the
532 accuracy or integrity of any part are appropriately investigated and resolved.

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537
538 The views expressed are those of the author(s) and not necessarily those of the National Health
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540
541 This is an abridged version of the full study protocol, which can be accessed at
542 <https://www.fundingawards.nihr.ac.uk/award/16/88/06>

544 **Competing interests statement**

545 IA, MD, HK, KK, ML, MM, EP, AS, FW have no competing interests to declare.

546
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553 engagement and patient support programmes to healthcare policy makers, providers and industry.

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559
560 CNJC reports personal fees from Public Health England, outside the submitted work.

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3 649 **Figure legends**
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6 651 **Figure 1- The IMPACT study**

7 652 The six mixed-methods elements of the IMPACT [Intervening with a Manualised Package to Achieve
8 653 treatment adherence in people with Tuberculosis] study and the relationships between them. The
9 654 study is guided by a steering group, which has oversight over the entire process and culminates in a
10 655 pilot study with associated evaluatory elements.
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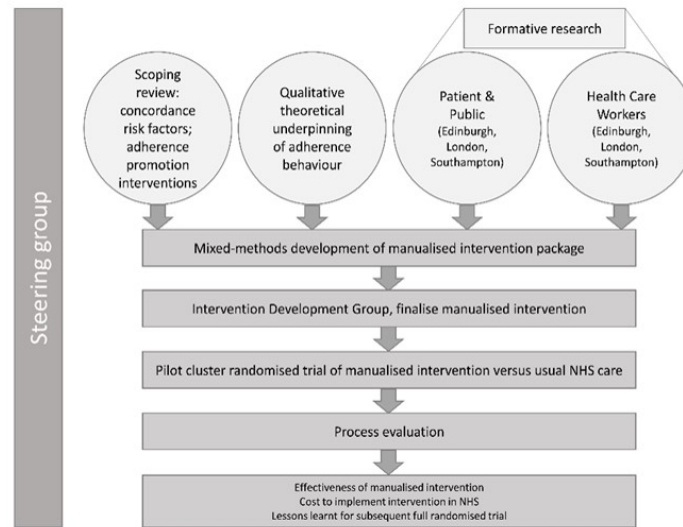


Figure 1- The IMPACT study

The six mixed-methods elements of the IMPACT [Intervening with a Manualised Package to Achieve treatment adherence in people with Tuberculosis] study and the relationships between them. The study is guided by a steering group, which has oversight over the entire process and culminates in a pilot study with associated evaluatory elements.

159x92mm (150 x 150 DPI)

BMJ Open

The IMPACT Study: Intervening with a Manualised Package to ACHieve treatment adherence in people with Tuberculosis. A protocol paper for a mixed methods study, including a pilot randomised controlled trial

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1 The IMPACT Study: Intervening with a Manualised Package to ACHieve 2 treatment adherence in people with Tuberculosis. A protocol paper for a 3 mixed methods study, including a pilot randomised controlled trial

4
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38 **Abstract**

39 **Introduction**

40 Compared to the rest of the UK and Western Europe, England has high rates of the infectious
41 disease tuberculosis (TB). TB is curable, although treatment is for at least six months - and longer
42 when disease is drug resistant. If patients miss too many doses (non-adherence), they may transmit
43 infection for longer and the infecting bacteria may develop resistance to the standard drugs used for
44 treatment. Non-adherence may therefore risk both their health and that of others. Within England,
45 certain population groups are thought to be at higher risk of non-adherence, but the factors
46 contributing to this have been insufficiently determined, as have the best interventions to promote
47 adherence. The objective of this study is to develop a manualised package of interventions for use as
48 part of routine care within National Health Services to address the social and cultural factors that
49 lead to poor adherence to treatment for TB disease.

50

51 **Methods and analysis**

52 This study uses a mixed methods approach, with six study components. These are: (i) scoping
53 reviews of the literature, (ii) qualitative research with patients, carers and healthcare professionals,
54 (iii) development of the intervention, (iv) a pilot randomised controlled trial of the manualised
55 intervention, (v) a process evaluation to examine clinical utility, and (vi) a cost analysis.

56

57 **Ethics and dissemination**

58 This study received ethics approval on 24th December 2018 from Camberwell St. Giles Ethics
59 Committee, UK (REC reference 18/LO/1818). Findings will be published and disseminated through
60 peer-reviewed publications and conference presentations, published in an end of study report to our
61 funder (the National Institute for Health Research, UK), and presented to key stakeholders.

62

63 **Trial Registration Number**

64 ISRCTN registry, ISRCTN95243114, 14th February 2018

65

66 **Secondary identifying numbers**

67 University College London/University College London Hospitals Joint Research Office 17/0726

68 National Institute for Health Research, UK 16/88/06

69

Article Summary: Strengths and limitations of this study

Strengths

- Patient-centred, mixed methods approach, based on a robust understanding of the evidence on social, cultural and personal factors that influence adherence to medication to treat tuberculosis.
- Evidence and experience of adherence captured from a variety of perspectives from across the UK, including patients, their carers, and healthcare workers.
- Generalisable patient population of individuals at risk of non-adherence across low tuberculosis (TB) incidence settings.
- Development of a pragmatic and easy-to-use tool that captures the best evidence on adherence and allows its application in the clinic setting.

Limitations

- The study culminates in a pilot trial of the manualised intervention; a larger subsequent definitive trial is needed to test whether the intervention is efficacious and cost-effective beyond any initial conclusions regarding validity and feasibility derived from the pilot.

88 Introduction

89
90 Against a background of rising tuberculosis (TB) in the 1990s and 2000s, the need for a
91 comprehensive approach to TB control in England was deemed necessary by Public Health England
92 (PHE) and the National Health Service (NHS) England. In January 2015, these bodies jointly launched
93 the 'Collaborative Tuberculosis Strategy for England 2015-2020'[1]. This seeks to reduce TB
94 incidence, decrease health inequalities, and ultimately contribute to international efforts to
95 eliminate TB as a public health problem. Ensuring that people can take all of their medication as
96 prescribed is one of the strategy's priorities, as poor adherence to treatment for TB is a driver of
97 worse patient outcomes[2–9], increases the risk of transmission (due to delayed sputum culture
98 conversion)[10], and can promote the development of drug resistance[3,11–16]. Subsequent
99 National Institute for Health and Care Excellence (NICE) guidance noted the lack of robust TB
100 research in this area[17].

101
102 Barriers to optimal adherence to treatment for TB may occur for a number of reasons. These
103 include:

- 104 • patient-related factors, including perceptions and beliefs,
- 105 • cultural influences and current mental state,
- 106 • structural economic factors and social support networks,
- 107 • health service factors that include treatment complexity as well as accessibility of those
108 services and the relationships patients develop with service providers[18,19].

109
110 Non-adherence is not a single issue and may take various forms e.g. suboptimal implementation
111 (skipping doses), or stopping treatment early (for example, as soon as a patient feels better; this is
112 discontinuation)[20].

113
114 Although a series of studies have been undertaken to define the population groups most at risk of
115 non-adherence[19], it is currently difficult, prior to starting medication, to identify who may struggle
116 with taking treatment as prescribed. To date, methods to support treatment address some, but not
117 all, of the important underlying reasons for poor adherence. For example, the World Health
118 Organization's recent focus on digital technologies reflects our attention on individual-level
119 determinants of adherence and reminder/observation-based systems[21]; far less research has
120 addressed the social and structural barriers to staying on TB treatment.

121
122 In the UK, the development of an intervention to support adherence to treatment that is sensitive to
123 the individual's cultural background and social circumstances, and can be routinely delivered within
124 the NHS, is critical. To this purpose, a mixed-methods, patient-centred, approach to the study of the
125 (modifiable factors that influence patients' adherence to treatment for TB is required.

126 127 Methods and analysis

128 129 Research question

130 Can a manualised package of intervention be developed to help overcome the social and cultural
131 factors that lead to poor adherence to treatment in NHS patients in the United Kingdom with active
132 TB?

133 134 Aim

135 To develop, pilot, and evaluate process and interim outcomes for an effective manualised
136 intervention that improves the likelihood of adherence to treatment among NHS patients at risk of
137 poor adherence due to social, cultural, and structural factors.

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 (the Perceptions and Practicalities (PAPA) approach [18] 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 (a series of systematic actions applied on the basis of a patient's needs assessment) with multiple components that can identify (a) NHS patients most at risk of non-adherence, (b) the salient modifiable barriers, and (c) the tailored support mechanisms required to meet individual patient needs by matching appropriate interventions to specific barriers, as recommended by NICE. (Development of Intervention)
A manualised intervention was considered to be a suitable approach to managing adherence in TB, as it will enable a set of measures to be applied consistently within different NHS settings that will aid both clinicians and patients throughout the treatment journey. The content of the intervention will use existing support measures, employed in a systematic and structured way, and may also include any new interventions that are developed in response to the formative research. It will be compared to normal care.
- 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).

Study design

This study uses a mixed methods approach. There are 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 the different elements are described separately below, the research activities for each will overlap, and some will run concurrently. The full programme of work and relationships between subsections is shown in Figure 1. This paper reflects protocol version 4.0 (26th September 2019)[22].

i. Scoping Review

To underpin the development of the manualised intervention, the first study sub-section will undertake literature reviews to answer the following research questions:

- i) What personal, social, cultural, health systems-related and structural factors affect individuals' ability to adhere to treatment for TB?
- ii) What kinds of intervention have been developed to address the multiple levels (personal, social, cultural, systems 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?

These questions will be answered through the three following reviews:

1
2
3 189 **1) A scoping review of qualitative studies** that examine the personal, social, cultural, health
4 190 systems-related and structural factors affecting adherence to treatment for TB from the
5 191 perspectives of adult patients, care givers, or health care providers, as well as studies that evaluate
6 192 interventions to support adherence to treatment for TB. Data from all settings will be considered,
7 193 but with a particular focus on low incidence, high income, settings.
8 194

9
10 195 **2) A critical review of quantitative studies** examining the personal, social, cultural, health systems-
11 196 related and structural factors affecting adherence to treatment for TB. This review focuses on low
12 197 incidence, high income, settings and observational study designs. Given the scoping nature of the
13 198 review, findings will be descriptively analysed and not be stratified or disaggregated e.g. by site of
14 199 disease. All relative and absolute measures of effect will be extracted.
15 200

16 201 **3) A critical review of quantitative studies that have examined the effectiveness of interventions**
17 202 **to improve adherence in people taking treatment for TB**, building on existing systematic reviews,
18 203 including the provision and delivery of information and/or education; enablers and/or incentives;
19 204 social support; case management approaches. Given the more limited literature, both observational
20 205 studies and clinical trials will be included, from all settings. Findings will be descriptively analysed.
21 206

22
23 207 Together, these three reviews will enable us to conduct a critical interpretive synthesis of findings
24 208 from qualitative and quantitative studies examining the assumptions and mechanisms of effect
25 209 underlying interventions to improve adherence to treatment for TB. Further details on the reviews
26 210 are available in the full protocol[22].
27 211

28 212 **ii. Formative Research**

29 213 **Formative research methods, recruitment and eligibility**

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31 215
32 216 In line with findings from the scoping review, we will develop topic guides for qualitative interviews
33 217 exploring current models of TB service delivery in the study sites, providers' views on the barriers
34 218 and facilitators for treatment adherence, and TB patients' and their family members' experiences of
35 219 starting and staying on treatment. Details about these guides are available within the full
36 220 protocol[22]. The thematic analysis of these interviews will complement insights gained from the
37 221 scoping reviews which will allow us to refine a conceptual framework of adherence building on the
38 222 Perceptions and Practicalities Approach (PAPA) [18]. Approximately 60 participants will be enrolled.
39 223

40 224 Adults (aged 18 and over) who are currently taking or recently completed treatment will be
41 225 identified by the local TB service at four UK sites (Edinburgh, London [Central London & East London]
42 226 and Southampton) and asked to take part in the study. The services have been chosen for their
43 227 patient diversity, geographic spread and as reflecting the national TB picture. The patient group will
44 228 be enriched with people who have been poorly adherent to treatment, although we will also include
45 229 patients who report full adherence so that we can capture what may have enabled them to take
46 230 treatment as prescribed. With patient consent, family members and/or carers will also be
47 231 approached and asked to participate.
48 232

49 233 Health and social care workers from both primary and secondary care settings will be directly
50 234 approached by researchers and invited to be interviewed. All those approached will be aged 18 or
51 235 over and involved in TB management and care.
52 236

53 237 **Data collection methods**

54 238
55 239 Three different methods of data collection will be used to undertake the formative research.
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1) In-depth interviews – patients and family members/carers

These will be conducted as individual interviews with approximately 30 participants, using a topic guide. The areas to be explored are: 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.

2) Testing of BMQ and BIPQ Questionnaires with patients for their suitability

To ensure that the validated questionnaires (i.e. Beliefs about Medicines Questionnaires[23] and the Brief Illness Perception Questionnaire[24], are accessible and acceptable to patients, we will also conduct cognitive interviews with 10 patients. We will then have confidence to use them in the later pilot study to assess patient perceptions and practicalities affecting adherence to anti-TB therapy. These will explore self-perception; personal beliefs; and practices related to medicine-taking.

3) Semi-structured interviews – healthcare providers

These will be undertaken with health care providers responsible for multiple aspects of TB care (doctors, nurses, social workers, directly observed therapy [DOT] providers, managers and administrators). They will focus on providers' perceptions of factors affecting patient understanding of TB and its treatment; service delivery models including staffing; organisation of care; communication. We will interview four to six providers at each site, aiming for a total of 20 interviews.

We will use a framework approach [25] to facilitate initial analysis of the interview transcripts. Short patient case studies will be created for each patient interview. Data on health systems issues gained through mapping patient pathways and provider interviews will be organised using a deductive approach, with appropriate visual pathways.

iii. Development of the manualised intervention

Intervention development process

The data collected from the scoping reviews and formative research will be presented to, and synthesised by, an Intervention Development Group (IDG). A manualised intervention will be developed to identify (a) NHS patients most at risk of non-adherence, (b) their salient modifiable barriers, and (c) the tailored support mechanisms that meet individual patient needs by matching appropriate interventions to these specific barriers.

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 constitution of the IDG 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.

Intervention contents

The manualised intervention is likely to consist of a screening and assessment tool, in addition to a package of measures that can be tailored to the needs of individual patients from different population groups.

As patterns of adherence may be irregular over time, it is intended that the manualised intervention will be administered to all patients at each patient review. The tool thus needs to be quick and easy to administer. It may be electronically linked to patient records, enabling a comprehensive picture of the risk of possible non-adherence to be developed for each patient, as well as within a clinic population. The various delivery options for the intervention (such as using paper or an app) will be considered during its development stage.

The menu of supportive measures may, for example, include:

- Informational intervention: e.g. providing a convincing story setting out the rationale and on-going 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 their treatment regimens to alternatives[26].
- Practicalities and Capability based interventions: video observed therapy [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. housing, drug and alcohol services, and social care; providing peer-support.

iv. Piloting the intervention

Study design, recruitment and eligibility

Once the intervention is developed, proof-of-concept is required within the real world. This will be undertaken using a non-blinded cluster randomised pilot study that compares the manualised intervention to the usual standard of care in four London clinics treating TB. Two clinics will be randomly allocated to the intervention and two to standard of care. In the latter, the amount of support provided to patients is based on perceived need, as identified by a nurse-led review and a needs assessment. Most patients will have supported self-administered therapy, whilst others will be offered DOT and/or VOT if this is felt to be appropriate. We anticipate enrolment to commence in January 2020 (recruitment is pending).

All consecutive patients aged 18 or over who are about to start treatment for TB, irrespective of site of disease, will be approached to take part in the study. We will exclude individuals who are unable to provide informed consent, those already on treatment and those who are not expected to live for the duration of the study (a minimum of six months from starting treatment). Within the pilot study, it is essential to capture the entire treatment period for each patient, in order to assess the effectiveness of the intervention. Due to the nature of the TB patient population in the UK, patients are likely to include people at greater risk of poor adherence such as migrants newly arrived in the UK, people whose first language is not English, 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.

The purpose of the pilot study is not formal hypothesis testing. Given this, a target sample size of 80 patients enrolled (20 per site) was identified for the pilot study as providing useful information that can help determine whether the intervention will be deliverable within a clinical setting. It will also guide the development of a possible larger definitive study using the intervention. The four TB clinics of interest (in East and North London) each treat in excess of 60 relevant patients per annum.

Based on usage of DOT within the clinic populations seen at the treatment sites (i.e. individuals

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3 342 currently identified as needing adherence support), we estimate that around 33% of patients will be
4 343 at risk of non-adherence. Taking this as a minimum (as the manualised intervention is likely to be
5 344 more sensitive than current risk assessments), we would expect that at least 26 of the 80 patients
6 345 recruited will be identified as requiring adherence support. This sample size allows us to measure
7 346 consent to enrolment for 80 individuals, data completeness for adherence and treatment outcomes
8 347 for 80 individuals, data on acceptability and feasibility of the intervention package for around 40
9 348 individuals, and data on acceptability and feasibility of adherence support for at least 26 individuals
10 349 (13 receiving the manualised intervention and 13 standard care).
11 350

12 351 **Outcomes of the pilot**

13 352 The primary outcome of the study will be level of adherence, measured as the proportion of
14 353 prescribed doses taken and assessed at six months from the start of treatment. In addition to this
15 354 primary outcome, a number of secondary outcomes will also be measured, as follows:
16 355

- 17 356 1) Proportion consenting to the study.
- 18 357 2) Completeness of data for measures of adherence.
- 19 358 3) Proportion of patients withdrawing during the study and the reasons why.
- 20 359 4) Proportion of patients identified as needing adherence support in the intervention arm.
- 21 360 5) Proportion of patients offered adherence support and accepting it in the intervention arm.
- 22 361 6) Documentation of which adherence-promoting activities have been implemented among
23 362 patients both in the standard of care and intervention arm, and when.
- 24 363 7) Detailed treatment implementation information: e.g. proportion of patients completing
25 364 treatment, proportion of patients still on treatment after nine months or at study
26 365 completion (whichever is the earlier).
- 27 366 8) Patterns of adherence (implementation and discontinuation).
- 28 367 9) Impact of manualised intervention on maintaining adherence over the duration of
29 368 treatment.
- 30 369 10) Process variables – adherence-related perceptions and practicalities.

31 370 **Measures of adherence**

32 371 Our primary measure of adherence will be data obtained from medication monitoring boxes [27].
33 372 The boxes will not be set up act as a reminder system. Other measures will also be used and
34 373 compared with this. These will include pill counts (the remaining medication in the box at the end of
35 374 each month), and also patient-reported adherence, where we will ask patients to estimate how
36 375 many doses they have missed in the last month. In the case of DOT or VOT methods being used, a
37 376 record of missed doses will be kept.
38 377
39 378

40 379 **Administration of the manualised intervention**

41 380 The patient's case manager (usually the TB clinic nurse), plus a study research nurse, will apply the
42 381 intervention in partnership with the patient to identify whether personal, socio-cultural and/or
43 382 systems risk factors are present that suggest likely poor adherence with treatment. If these are
44 383 identified, then the relevant measures outlined in the manualised intervention that may mitigate
45 384 these will be reviewed and implemented with the agreement of the participant. These will be
46 385 continued throughout the course of treatment, or stopped if no longer deemed to be relevant or
47 386 required on reassessment.
48 387

49 388 **Study schedule of visits**

50 389 Study subjects will be seen at weeks 0, 2, 4, 8, 12, 16, 20 and 24 (earliest date of treatment
51 390 completion). Should they require on-going treatment after six months, they will be seen as clinically
52 391 indicated. At each review, adherence assessments will be performed in addition to an assessment of
53 392 perceptions and practicalities, the completion of the BMQ and the EQ-5D-5L Quality of Life
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3 393 questionnaires [23,28] and the GAD-7 [29] and PHQ-9[30] to assess anxiety and depression. The
4 394 manualised intervention will be applied if the patient is attending a clinic that has been randomised
5 395 to the intervention arm. All data will be collected by the research nurse, using standardised forms.
6 396

7 397 **Follow Up**

8 398 Most patients who do not have clinically important drug resistant disease receive six months of
9 399 treatment. To allow for treatment interruptions, patients within the pilot study will be followed to
10 400 either treatment completion or for a total of nine months from starting anti-TB therapy.
11 401

12 402 **Analysis and interpretation**

13 403 Where possible, univariable analyses will be undertaken to compare each outcome measure listed
14 404 between study arms (intervention and control). For the primary outcome (adherence) the mean
15 405 percentage value will be reported by arm (intervention and control) and histograms used to describe
16 406 the distribution of values by study arm. Binary secondary outcomes will be reported by the
17 407 proportion of individuals achieving the outcome within each arm. The need to adjust for clustering
18 408 by site and clinical care provider will be assessed using the cluster summary method (a t-test to
19 409 compare the cluster means or proportions [as appropriate, two values per arm] between arms). An
20 410 assessment of the balance in baseline characteristics between the study arms will also be conducted.
21 411 If randomisation has failed to evenly distribute key characteristics (e.g. age, sex, ethnicity, or other
22 412 factors identified as important during the scoping reviews), then the cluster means or proportions
23 413 will be adjusted for these differences before applying the t-test. This two-stage approach to analysis
24 414 is described by Hayes and Moulton [31]. We recognise that adherence data may be highly skewed
25 415 and thus require compensatory analytical approaches.
26 416

27 417 The analysis of the first three of our secondary outcomes will address the feasibility of a definitive
28 418 trial following a similar design to the pilot. Analysis of secondary outcomes four to six addresses the
29 419 intervention, and complements the process evaluation (see below). Analysis of the primary outcome
30 420 and final secondary outcomes around treatment adherence and completion provides initial
31 421 information - given the modest sample size - concerning the effectiveness of the intervention, and
32 422 may assist the sample size calculation for the definitive trial. They can also offer an alert in the
33 423 unlikely event that the intervention is harmful.
34 424

35 425 **Power calculation**

36 426 Although we are undertaking a pilot study and thus the numbers enrolled are small, Table 1
37 427 indicates the power of our primary analysis to detect a range of absolute increases in adherence (10-
38 428 30%) from a variety of baseline values (50-90%).
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3 **431 Table 1- Power calculation for the pilot study**

4 432 Given a sample size of 80 individuals (40 per arm), across a range of baseline levels of adherence and
5 433 absolute increases in that level, the pilot study has the following power.

6 434
7 435

	Baseline adherence	Absolute increase	Power
8 436	70	30	0.98
9 437	60	30	0.88
10 438	50	30	0.82
11 439	80	20	0.86
12 440	70	20	0.61
13 441	60	20	0.49
14 442	90	10	0.54
15 443	80	10	0.24
16 444	70	10	0.18

17 445
18 446
19 447

20 448 **v. Process evaluation**

21 449
22 450 **Evaluation method**

23 451 We will evaluate the implementation process by analysing the challenges and facilitators in
24 452 delivering the package. The impact of the intervention will be assessed by evaluation of adherence
25 453 indicators. We will use the findings of the pilot to assess the costs of delivering the manualised
26 454 intervention in an NHS setting, and to guide development of a proposal for a full RCT.

27 455
28 456 The process evaluation will consist of a description of the process of intervention implementation. It
29 457 will assess how well the manualised intervention achieves its intended aim compared to standard
30 458 care.

31 459
32 460 We will consider:

- 33 461 1) The fidelity of the intervention as delivered in comparison to how it was designed and
34 462 envisaged,
35 463 2) The reach of the intervention (the proportion of the target group receiving it),
36 464 3) The barriers to facilitating implementation of the intervention and how these can be
37 465 addressed,
38 466 4) The pre-existing factors that facilitated implementation.

39 467
40 468 **Process measures, recruitment and eligibility**

41 469 Process measures for each element of the package will be developed once the manual development
42 470 has been completed, and used to assess success. They will include acceptability, uptake and change
43 471 in practice. We will work with patients and staff separately at all four London sites. We will interview
44 472 20 patients (five at each study site i.e. 10 from each arm); and, if possible, 20 health care workers
45 473 (five at each site). The patients will be selected within each site using purposeful sampling of clinic
46 474 lists of every patient with active TB, to enable us to reflect the demographic spread of patients.

47 475
48 476 Key outputs will include a qualitative evaluation of delivery, the development of a narrative
49 477 description of the process of intervention implementation and maintenance and a quantitative
50 478 assessment of adherence-related perceptions and practicalities within intervention and control
51 479 groups.

52 480
53 481 We will invite participation in the process evaluation from patients enrolled in the pilot study or staff

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2
3 482 members treating patients at one of the four London sites also involved in delivering the pilot study.
4 483 They will be included if they are aged 18 or over and able to provide informed consent. This will
5 484 include probing anticipated versus real-life delivery of the intervention.
6 485

8 486 **vi. Cost Analysis and Future Work**

9 487
10 488 In order to generate realistic estimates of the cost of the intervention, cost data from the NHS
11 489 perspective will be collected during the pilot study using a cost data collection tool used by health
12 490 economists (The Client Service Receipt Inventory, CSRI), modified for TB [32].
13 491

14 492 After the pilot study and process evaluation have been completed, a final intervention package will
15 493 be designed for use in a definitive RCT of the manualised package of interventions. The design of this
16 494 final package will be based on the results of the process evaluation and the experience gained during
17 495 the piloting of the intervention, modifying the definitive trial design and/or data collection
18 496 accordingly.
19 497

21 498 **Patient and public engagement**

22 499 As documented above, patient representatives will sit on the IDG for the study. In addition, TB Alert,
23 500 the UK's only national TB charity, has membership of the IDG. The role of the IDG, which will meet
24 501 regularly throughout the study, is described in section iii. At the end of the study, the IDG will be
25 502 involved in commenting on the findings and contributing to the dissemination plan.
26 503

29 504 **Ethics, sponsorship, contact details and dissemination**

30 505 The study is sponsored by the Joint Research Office of University College London and University
31 506 College London Hospitals. This study received ethics approval on 24th December 2018 from
32 507 Camberwell St Giles Ethics Committee (REC reference 18/LO/1818; Level 3, Block B, Whitefriars,
33 508 Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207104 8204; [NRESCCommittee.London-](mailto:NRESCCommittee.London-CamberwellStGiles@nhs.net)
34 509 CamberwellStGiles@nhs.net). Findings will be published and disseminated through peer-reviewed
35 510 publications and conference presentations, published in an end of study report to our funder (the
36 511 National Institute for Health Research, UK), and presented to key stakeholders.
37 512

38 513 For public enquiries, please contact Marcia Darvell, IMPACT Study Project Co-ordinator, Respiratory
39 514 Medicine, The Royal Free London NHS Foundation Trust, UCL Medical School Building, Rowland Hill
40 515 Street, London, NW3 2PF, UK; +4420 8016 8375; m.darvell@ucl.ac.uk
41 516

42 517 For scientific enquiries, please contact the Chief Investigator Professor Marc Lipman (The Royal Free
43 518 London NHS Foundation Trust and University College London), Respiratory Medicine, The Grove
44 519 Centre, The Royal Free London NHS Foundation Trust, Rowland Hill Street, London, NW3 2PF, UK;
45 520 +4420 7472 6452; marclipman@nhs.net.
46 521

49 522 **Data sharing statement**

50 523 The datasets generated during and/or analysed during the current study will be available upon
51 524 request in a de-identified format and after publication of study outcomes and associated permission
52 525 from the funder. Requests for data should be directed to Professor Marc Lipman as per the contact
53 526 details above.
54 527

57 529 **Conclusion**

58 530
59 531 Our study will develop and pilot a manualised intervention to improve adherence to treatment for
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3 532 TB in the UK using a mixed methods, patient-centred and provider-informed approach. This will
4 533 enable us to begin to understand what motivates patients' treatment behaviour, whilst ensuring
5 534 deliverability within the NHS. Our work is based on a robust understanding of the evidence on social,
6 535 cultural and personal factors that influence adherence, and the interventions that are most effective
7 536 in addressing these. The study reflects the geographic spread of TB in the UK and captures not only
8 537 patient and expert clinical and academic experience, but also that of family and carers to develop
9 538 the intervention. A key feature of the study is the co-production of a pragmatic and easy-to-use tool
10 539 that utilises the best evidence on adherence, and allows its application in the clinic setting in a
11 540 dynamic and iterative way.

12 541
13 542 Although the final pilot study may be limited to a relatively small sample size, it is hoped that its
14 543 broad patient-centred perspective will make a useful contribution to our understanding of, and
15 544 ability to deal effectively with, the risks of non-adherence to TB treatment in a population that can
16 545 find this challenging. As many of the factors influencing adherence are likely to be generalisable to
17 546 patients with other conditions in both high and low resource settings, this study also has the
18 547 potential to inform adherence interventions in other disease areas.

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550 **Authors' contributions**

551 ML, IA, RH, KK and HRS conceived of the work. HRS, IA, AC, RH, KK, MM, AS, NV, FW, HK, EP and ML
552 designed the work. HRS, CNJC, MD, RH, KK, drafted the manuscript. All authors critically revised the
553 manuscript and gave final approval of the version of the protocol manuscript to be published. All
554 authors agree to be accountable for all aspects of the work in ensuring that questions related to the
555 accuracy or integrity of any part are appropriately investigated and resolved.

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560
561 The views expressed are those of the author(s) and not necessarily those of the National Health
562 Service, UK, the NIHR or the Department of Health and Social Care.

563
564 This is an abridged version of the full study protocol, which can be accessed at
565 <https://www.fundingawards.nihr.ac.uk/award/16/88/06>

567 **Competing interests statement**

568 IA, MD, HK, KK, ML, MM, EP, AS, FW have no competing interests to declare.

569
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574 Sharp Dohme, Novartis, Pfizer, Roche, Shire Pharmaceuticals and TEVA. RH is Founding Director of a
575 UCL-Business spin-out company (Spoonful of Sugar Ltd) providing consultancy on treatment
576 engagement and patient support programmes to healthcare policy makers, providers and industry.

577
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579 Health Research (NIHR), UK, during the conduct of the study; other from Korean CDC and Johnson
580 and Johnson (makers of Bedaquiline), other from Latvian Society Against Tuberculosis (funding
581 through Otsuka and Johnson and Johnson), outside the submitted work.

582
583 CNJC reports personal fees from Public Health England, outside the submitted work.

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588 england
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3 **675 Figure legends**
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6 **677 Figure 1- The IMPACT study**

7 678 The six mixed-methods elements of the IMPACT [Intervening with a Manualised Package to Achieve
8 679 treatment adherence in people with Tuberculosis] study and the relationships between them. The
9 680 study is guided by a steering group, which has oversight over the entire process and culminates in a
10 681 pilot study with associated evaluatory elements.
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For peer review only

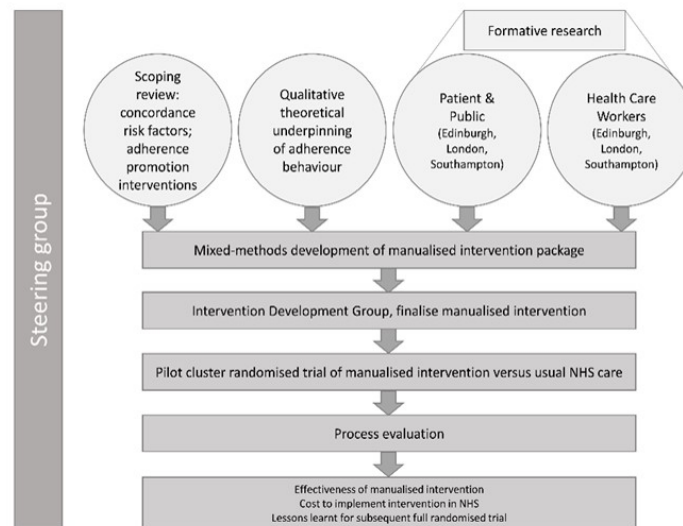


Figure 1- The IMPACT study

The six mixed-methods elements of the IMPACT [Intervening with a Manualised Package to Achieve treatment adherence in people with Tuberculosis] study and the relationships between them. The study is guided by a steering group, which has oversight over the entire process and culminates in a pilot study with associated evaluatory elements.

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-11
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	12

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4 5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and 14
5 interpretation of data; writing of the report; and the decision to submit the report for publication,
6 including whether they will have ultimate authority over any of these activities
7

8
9 The key roles and responsibilities are listed in the full protocol, available online and referenced at the
10 end of the paper <https://www.fundingawards.nihr.ac.uk/award/16/88/06>
11

12 (The page number indicated refers to the location in the manuscript of the link to the full protocol)
13

- 14 5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint 14
15 adjudication committee, data management team, and other individuals or groups overseeing the trial,
16 if applicable (see Item 21a for data monitoring committee)
17

18 The management of the study is described in the full protocol.
19

20 An Intervention Development Group overseeing the development of the content for the manualised
21 intervention and advising on the design of the pilot study is also described in the full protocol.
22

23 (The page number indicated refers to the location in the manuscript of the link to the full protocol)
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29 **Introduction**

- 30
31 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of 4
32 relevant studies (published and unpublished) examining benefits and harms for each intervention
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34 6b Explanation for choice of comparators 5
35
36 Objectives 7 Specific objectives or hypotheses 4-5
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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
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Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
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	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8/9
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[The withdrawal procedure is outlined in detail in the main protocol.](#)

[\(The second page number indicated refers to the location in the manuscript of the link to the full protocol\).](#) 14

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8/9
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4	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
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9	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10
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12	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
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[The randomisation procedure is described in the full protocol.](#) 14

[\(The second page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

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Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
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[The randomisation procedure is described in the full protocol.](#)

[\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
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Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial	8
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
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[These will all be available as appendices in the full protocol. The Case Report Form will be added to the study protocol before the pilot study begins.](#)

[\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

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4		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
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7			This is described in the full protocol.	
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10			(The page number indicated refers to the location in the manuscript of the link to the full protocol).	
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13	Data	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.	14
14	management			
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18			Details for data management are listed in the full protocol.	
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21			(The page number indicated refers to the location in the manuscript of the link to the full protocol).	
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24	Statistical	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
25	methods			
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27		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
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29		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
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Methods: Monitoring

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Data
monitoring

21a

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

[A formal data monitoring committee is not required for this study. See 5d for Steering committee oversight.](#)

21b

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

[This is a pilot study with limited power to detect important changes in outcome and therefore there are no plans to terminate the trial early based on interim results.](#)

Harms

22

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct 14

[Adverse event reporting is described in the full protocol.](#)

[\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

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4 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be 14
5 independent from investigators and the sponsor

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8 [Outlined in the full protocol.](#)

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10 [\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

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13 **Ethics and dissemination**

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15 Research 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval 12
16 ethics
17 approval

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21 Protocol 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria,
22 amendments outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial
23 registries, journals, regulators)

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27 [Approval for any modification to the protocol will be sought from the sponsor, REC, and](#)
28 [subsequently communicated to the Research Offices at all study sites.](#)

29
30 Consent or 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates,
31 assent and how (see Item 32)

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33 26b Additional consent provisions for collection and use of participant data and biological specimens in N/A
34 ancillary studies, if applicable

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Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
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[Outlined in the full protocol.](#)

[\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
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Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
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[Outlined in the full protocol.](#)

[\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
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[Outlined in the full protocol.](#)

[\(The page number indicated refers to the location in the manuscript of the link to the full protocol\).](#)

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4 31b Authorship eligibility guidelines and any intended use of professional writers

5
6 [Academic papers will be published according to UCL's policy on publications](https://www.ucl.ac.uk/library/open-access/ucl-publications-policy-2012)
7 <https://www.ucl.ac.uk/library/open-access/ucl-publications-policy-2012>

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9 Professional writers will not be used.

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13 31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical
14 code

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17 The full protocol is available on the NIHR website <https://fundingawards.nihr.ac.uk/award/16/88/06>.
18 All research outputs will be deposited in the UCL repository in Open Access. We have no plans for
19 the dataset to be made available.
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24 **Appendices**

25			
26	Informed	32	Model consent form and other related documentation given to participants and authorised surrogates
27	consent		
28	materials		Model consent form and PIS will be made available on the study website.
29			
30	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or
31	specimens		molecular analysis in the current trial and for future use in ancillary studies, if applicable
32			N/A

33
34 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on
35 the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative
36 Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.
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