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Cognitive therapy for depression in tuberculosis treatment: protocol for multicentre pragmatic parallel arm randomised control trial with an internal pilot

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ABSTRACT

Introduction and objectives There is an unmet need to develop high-quality evidence addressing tuberculosis (TB)-related mental health comorbidity, particularly in the context of lower-middle-income countries. This study aims to examine the effectiveness and cost-effectiveness of cognitive behavioural therapy (CBT) versus enhanced treatment as usual (ETAU) in improving depressive symptoms in people with TB and comorbid depression, enhancing adherence with anti-TB treatment (ATT) and its implementation in the real-world setting of Pakistan.

Methods We will conduct a pragmatic parallel arm randomised control trial with an internal pilot. A brief psychological intervention based on CBT has been developed using a combination of qualitative and ethnographic studies. The inbuilt pilot trial will have a sample size of 80, while we plan to recruit 560 (280 per arm) participants in the definitive trial. Participants who started on ATT within 1 month of diagnosis for pulmonary and extrapulmonary TB or multidrug resistant TB (MDR-TB) and meeting the criteria for depression on Patient Health Questionnaire-9 (PHQ-9) will be randomised with 1:1 allocation to receive six sessions of CBT (delivered by TB healthcare workers) or ETAU. Data on the feasibility outcomes of the pilot will be considered to proceed with the definitive trial. Participants will be assessed (by a blinded assessor) for the following main trial primary outcomes: (1) severity of depression using PHQ-9 scale (interviewer-administered questionnaire) at baseline, weeks 8, 24 and 32 postrandomisation and (2) ATT at baseline and week 24 at the end of ATT therapy.

Ethics and dissemination Ethical approval has been obtained from Keele University Research Ethics Committee (ref: 2023-0599-792), Khyber Medical University Ethical Review Board (ref: DIR/KMU-EB/CT/000990) and National Bioethics Committee Pakistan (ref: No.4–87/NBC-998/23/587). The results of this study will be reported in

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The psychological intervention was developed using an iterative approach, modelled on our previous cognitive behavioural therapy-based approaches used in Pakistan, and will be delivered using easily readable manuals that can be used in populations with low levels of literacy.

⇒ The proposed study aims to test a novel, culturally appropriate, low-cost psychological intervention for the improvement of tuberculosis (TB) and depression outcomes in TB patients who can potentially be scalable in the TB control programmes in real-world settings.

⇒ We will use a multicentre pragmatic hybrid design parallel-arm randomised controlled trial with an internal pilot having clear progression criteria to a fully powered trial. The randomisation at the individual level will enable control of the potential confounding factors and the pragmatic design maximises the external validity, ensuring the generalisability of the results.

⇒ The CONTROL (COgNitive Therapy for depRessiOn in tubercuLosis) intervention will be guided by community engagement and patient and public involvement and engagement activities, as well as feedback from service users at every stage of the implementation of the intervention.

⇒ Both the participants and the TB health workers who provide the intervention will be aware of the treatment and cannot be blinded. This could potentially introduce a bias in the outcomes of the study and there is a possibility of patients dropping out and difficulties with participant's adherence to the cognitive therapy intervention that might introduce attrition bias in the study and compromise the validity of the study's findings.

peer-reviewed journals and academic conferences and disseminated to stakeholders and policymakers.

Trial registration number ISRCTN10761003.

INTRODUCTION

Background and rationale

Tuberculosis (TB) is a leading cause of mortality across the globe, killing more than 1.6 million people in 2021, second only to COVID-19 among infectious diseases.[1] Pakistan, a lower-middle-income country (LMIC) with a population of approximately 230 million, ranks fifth among the TB high-burden countries, with an estimated half a million new cases of TB each year. Pakistan also has the fourth highest burden of multidrug-resistant TB (MDR-TB) globally.[1]

Pakistan has been home to the second largest refugee population in the world.[2] Approximately 3.7 million Afghan refugees are currently living in Pakistan,[3] with the Khyber Pakhtunkhwa province accommodating around 795 958 Afghan refugees across 43 refugee camps.[4] According to Ali *et al*, the prevalence of TB among Afghan refugees is relatively high as they live in overcrowded environments.[5]

Common mental disorders, such as anxiety and depression, are a significant cause of multimorbidity in people with TB in LMICs.[6] The mean-weighted prevalence of depression is 48.9% in people receiving treatment for TB.[7] A systematic review and meta-analysis carried out by Ruiz-Grosso *et al*[8] reported a strong association between depressive symptoms and negative TB treatment outcomes such as loss to follow-up, and non-adherence to TB treatment. Pharmacological treatment of TB in depression is particularly challenging given the significant interactions between anti-TB treatment (ATT) and antidepressants.[9]

Psychological interventions have the potential to enhance treatment adherence, improve quality of life and treatment effectiveness through the mitigation of psychological distress among individuals diagnosed with TB.[10 11] Considering cultural barriers such as lack of awareness and stigma associated with mental health and low literacy levels, cognitive behavioural therapy (CBT) has been suggested as a non-pharmacological treatment of choice for depression and anxiety.[12] It is feasible to incorporate CBT into primary care settings, and its efficacy in treating anxiety and depression in medically ill patients has been demonstrated.[13] A feasibility study carried out using quantitative and qualitative methodological approaches has demonstrated the feasibility and acceptability of a psychosocial support package for people receiving treatment for MDR-TB in Nepal.[14] Zuo *et al*[15] carried out a community-based cluster randomised controlled trial (RCT) to explore the effects of CBT on psychological stress and quality of life in patients with pulmonary TB. It was concluded that CBT can relieve anxiety, and depression symptoms and increase the quality of life in subjects with pulmonary TB.

Farooq *et al*[16] systematically reviewed the literature on psychosocial interventions to treat common mental disorders in TB and reported that these interventions are mainly focused on improving treatment adherence with ATT and had some beneficial effects on mental health outcomes. However, the mental health outcomes were poorly defined in the included studies, and all studies were of low quality. Moreover, mental disorders experienced by people with TB and MDR-TB are overlooked by TB control programmes despite some evidence of psychological interventions being feasible and beneficial.[17] The paucity of high-quality evidence addressing the TB-mental health comorbidity, particularly in the context of LMICs represents a literature gap, requiring the generation of high-quality evidence from such limited resource contexts.

Our proposed study primarily aims to address this gap by developing and testing a psychosocial intervention for the improvement of TB and depression outcomes in TB patients. The core component of CONTROL (COgNitive Therapy for depRessiOn in tubercuLosis treatment) will be a brief psychological intervention based on CBT. We adopt a CBT-based approach as it is a guideline-recommended treatment for depression. The CBT-based approaches for treating depression have also been used for improving adherence to treatment for chronic infections such as HIV.[18] Non-specialists can use these approaches using a task-shifting approach.[19]

The CONTROL will overcome two major public health barriers in TB control activities in an LMIC context, high prevalence of depression, and poor treatment adherence with ATT. Assuming that CONTROL is an effective intervention, implementation data will then inform the implementation strategies for future public health programmes or studies.

Aims and objectives

To improve outcomes for depression and TB in people with TB and MDR-TB, we aim to develop the CONTROL behavioural intervention, test its effectiveness and cost-effectiveness, and examine how the intervention can be implemented in the real-world setting of a Provincial Tuberculosis Control Programme (PTP) in Khyber Pakhtunkhwa, Pakistan. To achieve our aim, we will conduct a pragmatic hybrid design two/parallel-arm single-blinded RCT with an in-built pilot with a specified progression criterion.

Objectives

Objectives of the in-built pilot study

1. To assess the acceptability and feasibility of the CONTROL intervention.
2. To assess and refine the randomisation procedure.
3. To test and refine patient recruitment strategy.
4. To estimate the parameters (eg, recruitment and retention rates), means and SD of the key outcome measures to benchmark potential outcome measures and

update the sample size calculations for the definitive RCT.
5. To gauge the appropriateness and effectiveness of the training provided to TB health workers.

Objectives of the definitive trial

1. To evaluate the effectiveness and cost-effectiveness of CONTROL versus enhanced treatment as usual (ETAU) in improving depressive symptoms in people with TB and depression (TBD) and enhancing adherence with ATT.
2. To examine the effects of implementing CONTROL on the PTP and the wider health system.
3. To complete a process evaluation, refine the intervention and identify barriers and facilitators for implementation and future scale-up.

METHODS AND ANALYSIS

Study design

We will use multicentre pragmatic hybrid design parallel arm RCT with an internal pilot. Hybrid type 1 effectiveness implementation design will be used as it will allow testing of the clinical intervention while gathering information on its delivery during the effectiveness trial and its potential for implementation in a real-world situation.[20 21] It is being increasingly used in evaluating mental health interventions.[22 23] Spirit reporting guidelines were used[24] and the study will be reported using the Consolidated Standards of Reporting Trials (CONSORT) statement for randomised trials of non-pharmacological treatments.

Study setting

We will conduct both the in-built pilot study and the definitive trial in two purposively selected districts of Khyber Pakhtunkhwa (KP) province of Pakistan. The selected districts of KP are Peshawar and Haripur with an estimated population of 4.3 million and 1.01 million, respectively.[25] These districts have been selected due to having a high burden of TB cases with >10 000 new cases in Peshawar and approximately 3000 new cases in Haripur each year. Both districts also have a large population of Afghan refugees living in Pakistan,[26] who also have a high disease burden of TB. For the pilot, we will recruit TB patients from 4 to 6 TB Basic Management Units (BMU) across both districts; for the definitive RCT, we will recruit patients from 10 to 12 BMUs, with the flexibility to include more BMUs, if needed. The BMU is essentially a designated primary healthcare centre that serves as the focal point for TB patient's diagnosis, registration and receipt of treatment and medication. Each BMU has a specialised healthcare professional dedicated to the Directly Observed Therapy (DOTs) for TB, called the DOTs facilitator. The patients on diagnosis of TB are registered with the BMU and are provided free ATT for the next 6 months during which time they have to visit the BMU regularly for health check-ups and medication top-ups (https://ptp.gkp.pk/Pages/previewPdf/Dosage_Chart.pdf).[27]

Randomisation

We will follow the same randomisation protocol for both the inbuilt pilot and definitive trial with a 1:1 allocation to the CONTROL intervention arm and the ETAU arm via random permuted blocks stratified by nationality of the patient and TB or MDR-TB. Randomisation and allocation will be prepared and administered remotely by the trial statisticians.

Sample size

For the pilot study, we will aim to recruit 80 participants, 40 in each study arm. This will ensure reasonable precision of feasibility estimates for example, retention and follow-up rates (as a proportion). A sample size of 80 will enable the 80% one-sided lower confidence bound to be derived to a margin of error of 5% or less. This fits with the criteria for sample size justification and calculation recommendations for pilot and feasibility studies.[28]

To address the multimorbidity between TBD, we have powered the definitive RCT for two primary outcomes for effectiveness.

1. Improvement in depressive symptoms.
2. The treatment adherence with ATT

A sample size of 560 (280 per arm) will provide at least 90% power to detect: (1) a minimal clinically important between-group difference of 2 for the Patient Health Questionnaire-9 (PHQ-9) (assumed SD, 6.5)[29] and (2) a between-group difference of at least 15% in adherence to ATT treatment assuming 65% (two-thirds) adherence in the ETAU group (allowing up to 20% loss to follow-up). This does not assume data clustering/correlation. Because of limited formal data on which to currently base assumptions within the study population in question, the sample size/power will be reassessed and may be recalculated after the inbuilt pilot.

The TB control programme sites included in our trial register about 13 000 new cases of TB each year, based on a conservative estimate we expect about 40% (n=5200) to meet the criteria for depression. Of these, we expect about 80% (n=4160) to meet the study criteria and at least 50% (n=2600) to consent for the study. Based on these estimates, we are confident to recruit the required sample size for the definitive RCT in 9 months. Additionally, the patients will be recruited in proportion to the number of patients from each district and nationality.

Patient eligibility criteria

We will recruit participants who fulfil the following inclusion criteria.

1. Adults aged between 18 and 70 years.
2. Attending a BMU and are Pakistani or Afghan nationals (with refugee status as per their registration in the National Database and Registration Authority of Pakistan) (https://www.nadra.gov.pk/).[30]
3. Started on ATT within 1 month of diagnosis for pulmonary and extrapulmonary TB or MDR-TB and diagnosis of TB following the standard diagnostic procedure of the TB programme (http://ntp.gov.pk/ntp-old/

uploads/National_Guidelines_for_TB_Revised_2019.pdf).[31] We will include both pulmonary and extrapulmonary TB forms.
4. Meeting the criteria for depression (score of 10 or above on PHQ-9): the PHQ-9 is a nine-item instrument measuring the presence and severity of depression during the past 2 weeks.[32] The PHQ-9 questions are derived from the 16-item version. Participants rate their responses on a four-point Likert scale ranging from 'not at all' to 'nearly every day'. The PHQ-9 total severity score ranges from 0 to 27.
5. Score above 16 on WHODAS, questionnaire for functional impairments (WHO Disability Assessment Schedule V.2.0; WHODAS).[33]

The patients meeting one of the following criteria will be excluded:

1. If they meet ICD-10 criteria for current or lifetime bipolar disorder or other forms of severe mental illness, have evidence of learning disability or severe substance abuse (except nicotine dependence), as assessed by a trained psychologist.
2. Receiving any treatment for depression (psychotherapy or antidepressants over the last 6 months
3. Are currently suicidal, as judged by the trained assessor based on the mental health Gap Action Programme (mhGAP) Intervention Guide[34] or made a suicidal attempt within the past 2 years.
4. Have TB directly affected the central nervous system, are severely ill due to TB, or suffer from complications of TB such as pleural effusion or severe pain that prevents them from taking part in the study in view of treating physicians.
5. Are living in the same household as another participant of the study to prevent the risk of contamination between the intervention and control group.
6. Are pregnant or breast- feeding.

Study procedures and data collection

Recruitment

The internal pilot and definitive trial will have the same recruitment procedures. Recruitment will consist of a two-stage process.

Prescreening to identify probable cases of depression

All patients presenting at the selected BMUs will be verbally informed about the study and screened for depression using the PHQ-2 questionnaire[35] by the PTP staff. Those screened positive on PHQ-2 (score 3 or more) will be referred to a psychologist trained by the CONTROL team for screening and confirmation of eligibility criteria.

Screening for eligibility criteria to enter the trial

The psychologist will provide a detailed information sheet and arrange a convenient date and time with the potential participants to get informed consent and to complete the screening assessment. For participants who cannot read and write, there is provision of oral consent. The psychologist will read and explain the information sheet to these patients in simple language, and a thumbprint in lieu of the signature will be used. This approach has been used in our previous trials.[36] The witness will not be a member of the research team. Once informed consent has been obtained from the participant, the psychologists will complete the screening assessment and confirm the eligibility criteria for the trial. Individuals who do not meet the criteria to be included in the study will be given information regarding appropriate healthcare pathways for the treatment of depression. The screening assessments will include the following:

1. The presence and severity of depression during the past 2 weeks using the PHQ-9 scale[32] (score of 10 or above on PHQ-9 will be eligible to participate)
2. Functional impairments using the WHO Disability Assessment Schedule V.2.0 (WHODAS)[33] (score of 16 or above on WHODAS will be eligible to participate).
3. Other assessments for the inclusion and exclusion criteria as outlined above.

Baseline assessment

Participants eligible for inclusion will be required to complete the baseline assessments within 1 week of the screening visit. At the baseline, in addition to demographic details and disease history, all data related to the outcome measures will be taken. Trained research assistants will carry out assessments. They will receive a 5 day training covering administering the instruments, general interview techniques and ethical conduct of research. Ongoing monitoring of assessors' competency will be conducted through regular supervision by field supervisors and the trial manager. The assessments will be delivered in the interview format as many participants are expected to be illiterate. All participants will receive food items worth Pak Rupees (RS-1000 (~£5) for the trial assessments.

Once eligibility is confirmed and baseline assessments are completed, participants will be randomised to either the CONTROL arm or the ETAU arm following the procedure described under randomisation below. The site coordinator at each site will be informed of the allocation status of the patient, and he/she will ask the patient to follow the intervention or control arm care pathway.

After the randomisation, participants in both arms will be seen by the Medical Officer (who is blinded to the allocation status), following the TB control programme procedures. The patients in ETAU will receive the advice on treatment of depression (see description of ETAU below). The site coordinator will ask the patients in the intervention arm to receive the weekly therapy sessions with the TB Healthcare Workers (TBHW) as described in section 'The intervention arm' (see figure 1).

To maintain the blinding and prevent contamination, ATT medicines to the ETAU arm patients will be dispensed by a TBHW who is separate from the ones providing CBT sessions to the CONTROL arm patients. Additionally, the designated space for counselling is separate from the

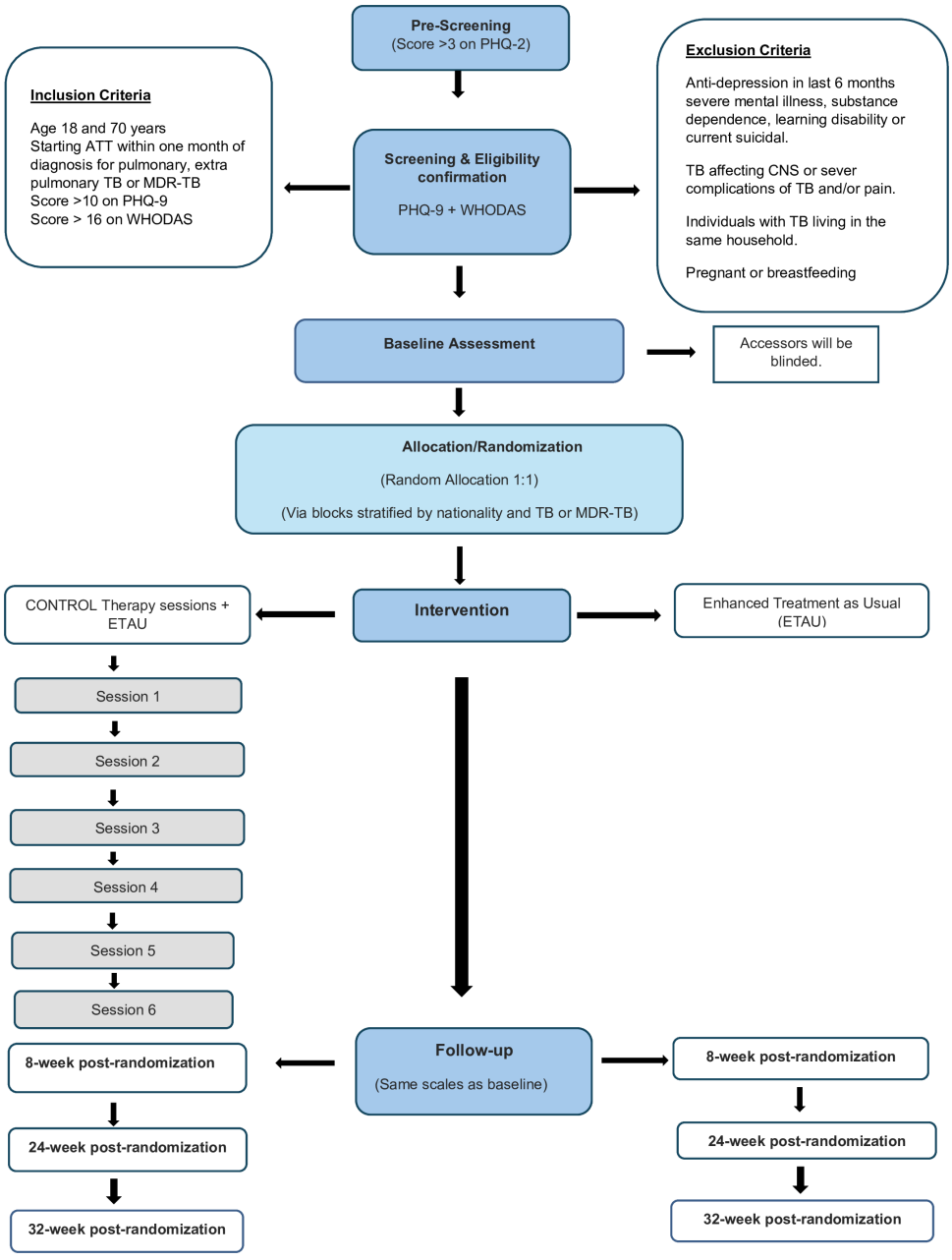

Figure 1 Flow of the CONTROL trial. CONTROL, COgNitive Therapy for depRessiOn in tubercuLosis treatment; CNS, central nervous system; MDR, multidrug resistant; PHQ, Patient Health Questionnaire; TB, tuberculosis; TTB, total TB; WHODAS, WHO Disability Assessment Schedule.

medicine dispensation window, to minimise any possibility that the patients from both arms come in contact at the health facility.

The intervention and control arm

The intervention arm

Patients in the intervention arm will receive six sessions of CBT-based intervention for treating depression and using problem-solving and motivational skills to enhance adherence to ATT. Every session will be delivered individually, and each session will last for 40–60 mins. We have used Theory of Change (TOC) method in the development of the intervention. The content and modes of intervention were adapted based on the Southampton framework used previously in Pakistan[37] and finalised following an iterative process including evidence synthesis, ethnography, qualitative interviews and focus group discussions (FGD) and codesign consultative meetings with the stakeholders. The adapted manual emphasises the three major areas to be considered while delivering culturally sensitive therapy: assessment and engagement, awareness of cultural factors and adjustments in therapy techniques. Culturally appropriate homework assignments have been selected, and patients will be encouraged to attend even if they are unable to complete their homework. Folk stories and examples relevant to the religious beliefs of the local population are used to clarify issues. Guidance videos for

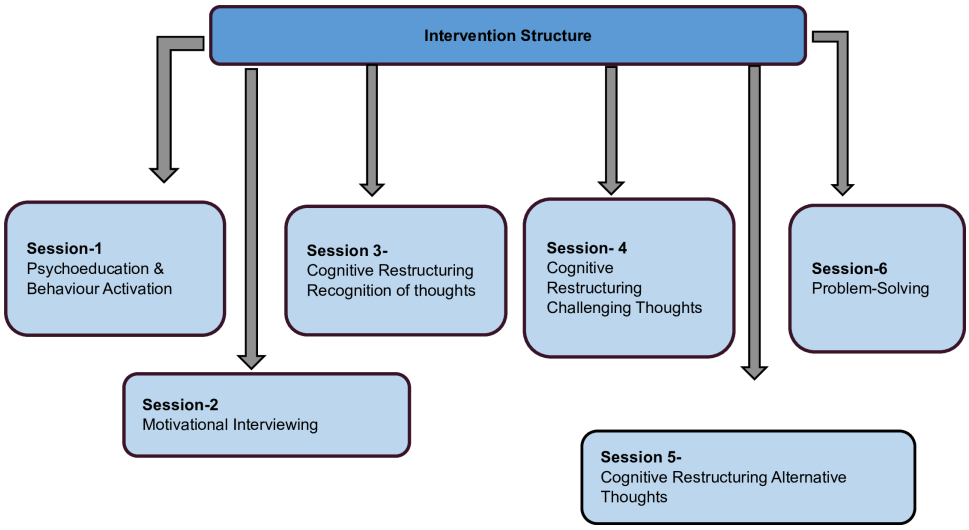

Figure 2 Details of the CBT intervention. CBT, cognitive behavioural therapy.

the intervention providers and audio material for the trial participants will be provided to supplement therapy sessions. The sessions and self-help material are designed for a population with low literacy rates, with approaches used in previous psychological interventions in this population.[36] Intervention will be delivered by trained DOTs facilitators/TBHW. All the details of intervention delivery will be recorded. The TBHW will keep a log of each patient including the details of the sessions delivered (see figure 2).

Training for the intervention delivery

The TBHWs will be trained using a cascade model of training employed successfully in our previous research.[36] First, a team of senior psychiatrists (FN and SF) and a psychologist (MG) with extensive experience in delivering CBT will train 6–8 psychologists as master trainers (MTs). We will use psychologists as MTs with a view to long-term sustainability, as this cadre is already integrated within the TB programme in Pakistan and is a readily available resource. These MTs will train TBHWs to deliver the intervention. As part of the training, we will use face-to-face teaching, case studies, role plays and online and direct clinical supervision. Regular supervision for MTs and TBHWs will be provided throughout the intervention by the senior psychiatrists and psychologists of the trial team. The protocol adherence and treatment integrity will be assessed using the revised Cognitive Therapy Scale (CTS-R).[38] All training will be quality assured by Khyber Medical University (KMU) and follow mhGAP guidelines on the Training of Trainers in resource-poor settings (https://www.who.int/mental_health/mhgap/training_manuals/en/).[34]

Control arm enhanced treatment as usual (ETAU)

This arm will include treatment as usual, enhanced by mhGAP training. After the completion of the screening assessment as outlined above ('Recruitment' section), the patient randomised to the ETAU will be referred to a TBHW who has been trained in mhGAP. Following is a brief description of 'treatment as usual' at BMUs under the TB control programme.

A newly diagnosed TB patient is first seen by the Medical Officer who provides a prescription of ATT for 1 month. The patient is then asked to meet the TBHW, usually DOTs Facilitator. During this first visit, the DOTs facilitator gives brief advice regarding TB treatment and gives the patient his medicines. The drug regimen for TB normally lasts for 6 months with 1 monthly follow-up unless the patient experiences any side effects from the treatment. During each follow-up visit, the patient first reports to the Medical Officer, followed by the TBHW for obtaining a prescription and advice about continuing medication. Treatment as usual for patients presenting with a mental health problem while receiving ATT after diagnosis with TB or MDR-TB is generally limited to the prescription of antidepressants by the medical officer or referral to a local mental health facility for further management. The medical officer and TBHW generally have little training in the detection or management of mental illness.

This 'treatment as usual' will be enhanced by the mhGAP training for TBHW and medical officers working in the participating BMUs. The mhGAP is a WHO guidance on treating mental disorders in non-specialist health settings using algorithms for clinical decision-making. The training for mhGAP is provided in a 2 day workshop aimed at providing training in the detection and management of depressive and anxiety disorders. They will also be trained in signposting the patients to appropriate facilities that can provide treatment for common mental disorders.

Outcome measures

Primary outcome measures for the inbuilt pilot trial

The primary acceptability and feasibility outcomes will be the recruitment rate, retention rates in therapy and the

Table 1 Progression criteria to the definitive trial

	Recruitment to the trial	Retention in therapy sessions	Completion rates for the trial follow-up
Green	80 patients recruited from two sites within 3 months	>70% of patients complete at least four therapy sessions	75% of participants complete follow-up assessments at week 8 and week 24
Amber	40–80 participants recruited from two sites within 3 months	40%–70% complete at least four therapy sessions	40%–75% of participants complete follow-up assessments at week 8 and week 24
Red	Less than 40 participants recruited in 3 months period from two sites	Less than 40% retention in at least four therapy sessions	Less than 40% complete the follow-up assessments at week 8 and week 24

completion rates for the trial follow-up (refer to table 1). These outcomes will be assessed at baseline, at week 8 and week 24 postrandomisation. In addition, data on adherence to ATT and depression score via PhQ-9 will be also collected at week 24 (refer to table 2).

Progression to the definitive trial

Based on the pilot feasibility study outcomes, we will proceed to the definitive trial. A traffic light system is a preferred option as a progression criterion compared with start/stop criteria as it allows a better opportunity for remedial action.[39] We will present the findings from the pilot study to the Independent Advisory Board (IAB) and funders and the decision to progress to the definitive trial will be made according to the following criteria as listed in table 1.

Primary outcome measures for the definitive trial

Two primary effectiveness outcomes will be assessed.

1. Improvement in depression; measured by a change in PHQ-9 score[32] over 8, 24 and 32 weeks postrandomisation; the primary endpoint is 32 weeks. The response will be defined as a ≥50% decrease in the PHQ-9.
2. Treatment adherence with ATT at 24 weeks postrandomisation as the treatment regimen for ATT lasts 6 months. In line with the literature on ATT adherence,[40] a patient will be classified as adherent if no more than 10% of tablets are missed; otherwise, non-adherent. The TB programme utilises various recording and reporting tools, of these the TB01 and TB02 cards, for facility and patients, respectively, are used to track medication adherence. These are filled in routinely by the TB programme staff, we will collect data on ATT medication adherence from these tools.

Secondary outcome measures

Details of all the secondary outcome measures of the pilot and definitive trial are listed in table 2.

Blinding and allocation concealment

It is not possible to blind study participants from their intervention arm allocation. However, they will be instructed to not discuss any treatment details with fellow participants. The assessment team conducting the baseline and follow-up assessments will be blinded to the treatment arm. Assessors will be asked to indicate what treatment they think each participant is receiving at the end of follow-up for each participant. This will provide an estimate of the amount of unblinding that might occur in the RCT. The intervention delivery staff will be instructed not to disclose the treatment that any participants are receiving except with their clinical supervisors. However, in case of an adverse event (AE), the treatment arm of the person can be unblinded.

During all assessments, the primary outcome measures (treatment adherence to ATT and severity of depression) will be completed first to minimise the risk of bias in the event of unmasking and, if it occurs, the point of unmasking will be recorded. Sensitivity analyses will be carried out to assess the effect of unmasking on the primary outcomes. Study statisticians will be blinded to the treatment arm during analysis. The data linking each patient with treatment allocation status will be kept separate from the outcome data set until the time of the final analysis.

Process evaluation

Pilot trial

We will conduct (1) two FGD with TB control staff and health administrators (to assess intervention acceptability and understand the barriers and facilitators to the intervention implementation) and (2) semistructured interviews (n=15) with patients who completed follow-up and those who did not complete all therapy sessions (to assess therapy burden, intervention experience, training and supervision, stigma, satisfaction with training and supervision issues). This will help to refine the intervention and training procedures.

Process evaluation of definitive trial

We will use a combination of qualitative (four FGDs and 20 semistructured interviews) and quantitative approaches for measuring the early implementation outcomes and for the process evaluation. We will focus on the following implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration and sustainability.[41] The choice of these implementation outcomes is based on Proctor's model and recommendations for early implementation assessments. The interview and topic guides for these FGs and semistructured interviews will be based on Proctor's model.[21]

Table 2 Baseline data, primary and secondary outcomes at various study points

Description	Measure	Baseline	8 weeks post randomisation	24 weeks post randomisation	32 weeks post randomisation
Demographic details					
Age	Date of birth	✓			
Gender	Male/female	✓			
Education	Years spent in education	✓			
Marital status	Single/married	✓			
Work status	Employed/unemployed	✓			
Acceptability and feasibility outcomes of the pilot trial					
Recruitment rate	Feasible if the sample size of 80 participants within a 3 month time frame is recruited	✓			
Retention in therapy	70% of participants completing at least four sessions		✓		
Completion rates for the trial follow-up	Feasible if at least 75% of participants are followed up and complete the 24 week follow-up assessment			✓	
The degree of completion of screening at routine TB treatment visits	Indicated by at least a 65% compliance rate	✓			
Compliance in completing the outcome measures for mental health	Indicated by at least a 65% compliance rate.	✓	✓		✓
The willingness of TB health workers	Number of TBHW approached. Completing a training programme in both arms (intervention/ETAU)	✓	✓		✓
The acceptability of trial procedures	Adherence to trial procedures and completion of the assessments	✓	✓		✓
Fidelity to intervention	Assessed using the revised Cognitive Therapy Scale[38]		✓		✓
Evaluation of PHQ-2 subscale for the sufficient and adequate screen for depression in this population	The sensitivity and specificity of the PHQ-2[35] against the PHQ-9[32] (proxy gold-standard) diagnosis of depression	✓			
Primary outcomes of definitive trial and clinical outcomes of pilot trial					
Presence and severity of depression	Measured by a change in PHQ-9 score. Response defined as a ≥50% decrease in the PHQ-9[32]	✓	✓	✓	✓
Adherence with ATT	The patient will be classified as adherent if no more than 10% of tablets are missed[40]			✓	
Secondary outcome measures of definitive trial					
Cost-effectiveness	Service Receipt Inventory[51] assesses service utilisation during the time preceding the assessment	✓	✓		✓
Functional impairment	WHODAS[33]	✓	✓		✓

Continued

Table 2 Continued

Description	Measure	Baseline	8 weeks post randomisation	24 weeks post randomisation	32 weeks post randomisation
The severity of anxiety symptoms	Generalised Anxiety Disorder Scale (GAD-7)[52]	✓	✓		✓
Quality of life	EuroQoL EQ5D[42]	✓	✓		✓
Traumatic stress symptoms	Harvard Trauma Questionnaire (HTQ)[53]	✓	✓		✓
Caregiver's burden-if caregiver is present	Zarit Burden Interview Scale[54]	✓	✓		✓
Perceived stigma	Internalised Stigma of Mental Illness Scale[55]	✓	✓		✓
Mental health outcome in routine TB care	Measures developed for mental health outcome in routine TB care			✓	
Implementation outcome measures					
Appropriateness	Intervention Appropriateness Measure (IAM)[56] and interviews with TBHW and patients				✓
Feasibility	Feasibility of Intervention Measure (FIM)[56] and The Applied Mental Health Research Group (AMHR) feasibility subscale[57]				✓
Acceptability	The Applied Mental Health Research Group (AMHR) acceptability subscale and trial data[57]	✓	✓	✓	✓
Fidelity	An independent ratter using a checklist and The Cognitive Therapy Scale (CTS-R)[38]		✓		✓
Penetration and sustainability	Acceptance of Mental Health Measures in Routine TB Health Outcomes				✓

ATT, anti-TB treatment; ETAU, enhanced treatment as usual; PHQ-2, Patient Health Questionnaire; TB, tuberculosis; TBHW, TB Healthcare Workers ; WHODAS, WHO Disability Assessment Schedule.

Withdrawal criteria

All participants will be informed about their right to withdraw from the study at any time, without providing a reason. They will be informed that such a decision will not have any repercussions on their clinical care. Participants will be withdrawn from the study in the event of any of the following:

1. Non-compliance with the study protocol results in a serious breach of protocol (GCP or other), which can compromise data integrity or significantly affect the scientific value of the reported results. Immediate action will be taken with the participant excluded from the study.
2. Any serious incident that has a bearing on the patient's safety. Data collected up to that point of discontinuation from the study will be reported as such.
3. Patients who experience exacerbation of the symptoms and may require hospitalisation will not be discontinued from the study, provided that the procedure is as advised by their treating physician and the patient continues to consent to the study.

Patient and public involvement

The CONTROL comprises a novel culturally appropriate intervention that will involve community engagement (CE) and Patient and Public Involvement and Engagement (PPIE) at every stage of the research project (intervention development, pilot RCT, progression to definitive trial, conduct and evaluation of the definitive trial, dissemination and implementation of the findings, etc). We received substantial input from the PPIE advisory group in designing the intervention. The involvement of PPIE allowed us to identify the barriers to the implementation of psychosocial interventions for depression in TB in the context of regular TB care. Subsequently, we successfully recognised it and integrated elements of the CONTROL intervention to overcome these obstacles. A plain language summary report of the research findings,

codeveloped with PPI representatives, will be produced. The service user groups and the PPIE team in Pakistan will work closely with the Keele PPIE team throughout the research project.

Study timeline

The pilot RCT began on 22 January 2024. Recruitment started as soon as the trial commenced and will continue until the required sample size is achieved. The outcomes will be assessed at baseline, week 1, week 8, week 24 and week 32 postrandomisation. We anticipate that the analysis will start around November 2024 and the definitive trial will commence approximately around January 2025.

End of trial

The end of the study is defined as when the 32 weeks postrandomisation assessments and all quantitative and qualitative implementation and process outcome measures have been completed. Once the study comes to an end, the Keele University ethics and the local ethics board will be informed.

Data management

All data will be managed by the protocol and will be safely stored according to KMU and Keele University's standard data storage and confidentiality policy. Participants will be assigned unique identification numbers, and the data will not contain identifiable information. Data will be kept confidential and not shared without participant consent. Data access will be restricted to members of the Keele and KMU study teams. Personal information, including names, addresses and National ID card numbers, will be securely stored separately from the research data. The Office of Research, Innovation and Commercialisation at KMU will be responsible for protecting the data, complying with the Personal Data Protection Bill 2020 of Pakistan, the General Data Protection Regulation, 2016, and the United Kingdom's Data Protection Act, 2018. Research data will be securely stored for 10 years at KMU and will be discarded in line with the Data Protection Act of Pakistan.

Data analysis

Quantitative analysis

Between-group mean differences in PHQ-9 change scores at 8 weeks, 24 weeks and 32 weeks postrandomisation will be evaluated by linear mixed model adjusting for baseline PHQ-9, MDR-TB/TB status and nationality (including random effect for participant ID (taking into account repeated measure data) and for therapist ID (if data clustering by the therapist is observed)). Similar linear mixed model analysis adjusting for the same fixed-effect covariates and corresponding baseline scores (and random effects) will be used to analyse secondary numerical outcome measures. For categorical outcomes, we will use generalised linear mixed models adjusting for baseline PHQ-9, MDR-TB/TB status, nationality and (as applicable) corresponding baseline factor. For the dichotomised outcomes (PHQ-9 response (<50% change/≥50% change) and adherence to ATT treatment (yes/no)), the analysis will be via logistic models where we will derive OR estimates. Furthermore, the results of the two logistic regression analyses will be used to derive absolute per cent differences (using the ETAU as the reference group) from which we will calculate the number needed to treat statistics across both dichotomised outcomes. Statistical significance will be given at the 5% two-tailed level (including the two coprimary outcomes which are separate measures).

Sensitivity analysis will be carried out to address potential attrition bias via multiple imputations (MI analysis). Exploratory subgroup analyses will model the interaction of subgroup factors (including MDR-TB/TB status and Pakistani/Afghan nationality) and treatment group concerning the contrast in between-group mean PHQ difference and OR for treatment adherence across subgroups. The principal analysis is by intention-to-treat (ITT), analysing all participants as per randomised allocation. The mixed models allow data to be analysed following an ITT approach with missing data being modelled under the assumption that missingness is missing-at-random (MAR). MI analysis will explore deviations from the MAR assumptions.

Health economic evaluation

The study will link costs to outcomes to determine if the CONTROL intervention is cost-effective. Outcomes will be evaluated using WHODAS[33] and EuroQoL EQ5D-5L.[42] Cost-effectiveness planes and acceptability curves will assess uncertainty in estimates and the probability of the intervention being cost-effective at different willingness-to-pay thresholds. Healthcare and societal health economic perspectives will be considered.

Qualitative data analysis

All interviews and FGDs will be digitally recorded and fully transcribed. We will subject the data to rigorous thematic analysis, following grounded theory principles[43] and we will seek to integrate the findings with the other data sets in phase 3. The researchers who will collect and analyse the interview data are fluent in the local language and are trained in qualitative research methods in our previous studies involving adaptation and evaluation of a psychological intervention for those affected by conflict in the region and explanatory models of psychosis.[36 44]

Trial management and monitoring

A Project Management Committee (PMC) comprising all investigators from the partner institutions has been instituted to oversee the management of the trial. The PMC will meet every second month to discuss the trial set-up, monitoring of study progress, monitoring of trial conduct, resolution of any issues and chalking the way forward. The trial will be monitored in line with the protocol and the trial standard operating procedures. An IAB will be established to independently monitor trial progress and advise the team on the way forward.

Safety and adverse events reporting

A Data and Safety Monitoring Board (DSMB) will be established to oversee and monitor trial conduct, meeting twice a year to ensure participant safety and data validity. The research team will record and report any AEs or serious adverse events (SAEs) as defined by the Health Research Authority (HRA) in the UK. The study outlines a standard operating procedure or reporting potential SAEs to the research clinician, the advisory board and the TB BMU staff. The clinician will ensure participant safety, while the advisory board will review SAEs within 48 hours. Staff will receive safety training. Participants will be informed about reporting mechanisms. Potential SAEs will be reported to the trial coordinator within 24 hours, and to the KMU REC, DSMB and IAB within 15 days. AEs that are not categorised as SAE will be routinely collected using an AE form and AE log and reported to the DSMB and IAB periodically according to their requirements.

Ethics and dissemination

This study has obtained ethical approval from the KMU Ethical Review Board (ref: DIR/KMU-EB/CT/000990), and National Bioethics Committee Pakistan (ref: No.4–87/NBC-998/23/587). It has been registered in the Trial registry (ISRCTN10761003). The study aims to engage the academic audience and global health community by publishing the trial results in high-impact peer-reviewed journals, presenting them at international public and global health conferences, and publishing an abstract on partner institutions' websites. Major academic outputs include a paper describing the study protocol, a study describing the definitive trial results, a publication based on the implementation outcomes analysis of CONTROL and a paper describing process outcomes. The project will also incorporate implementation science learning into academic lectures in partner institutions. Stakeholder and patient advisory groups will be involved in the project's dissemination and recommendations. Results will be shared with provincial and national governments, and a report will be published in English and Urdu.

DISCUSSION

TB is a communicable disease that is responsible for a significant burden of morbidity and mortality worldwide.[45] A significant majority, exceeding 80% of reported cases and deaths are concentrated within LMICs. Estimates suggest that the total TB incidence in Pakistan in 2021 was 265 per 100 000 population with 339 256 new and relapsed cases.[1] TBD are commonly observed comorbidities, where the presence of one disease enhances the risk of adverse consequences for the other.[7] Untreated depression at baseline is independently associated with more significant disability, poorer quality of life[46 47] and TB treatment default.[46] Poor adherence to TB treatment leads to MDR-TB, which is a health security threat.[1]

Van Rensburg *et al*[48] conducted a scoping review on 'person-centred care interventions' for common mental diseases and TB and found only two studies from LMIC that included these interventions. There is a lack of high-quality evidence on the effectiveness and implementation feasibility of psychological interventions among TB patients in resource-poor settings. However, there is an urgent requirement for governmental and non-governmental organisations to develop strategies that necessitate the incorporation of psychological interventions as a compulsory component of TB treatments.[10] To the best of our knowledge, this is the first study designed to examine the effectiveness of a psychosocial intervention to improve the outcomes both for depression and TB in people with TB and MDR-TB, test its effectiveness and cost-effectiveness and assess how the intervention can be implemented in the real-world setting of a TB Control Programmes (PTP) in LMIC setting.

CONTROL will significantly contribute to mitigating the social and economic impact of TB. By assessing the feasibility of integrating psychological intervention into the current healthcare delivery system and evaluating its cost-effectiveness, this study aims to alleviate the heavy burden of TB on healthcare. The proposed research has four major innovations: (1) screening to identify probable cases of depression by TBHWs using (PHQ-2); (2) developing culturally appropriate CBT intervention by using a combination of methods, including evidence synthesis, ethnography, qualitative interviews, FGD and codesign consultative meetings with the stakeholders; (3) training of DOTs facilitators/TBHWs by psychologists as MTs using a well-structured cascade model of a training programme and (4) using a task-sharing and task-shifting approach involving PTP staff, psychologists and psychiatrists.

It is crucial to understand how the context influences the implementation of the intervention and the possibility of expansion or scaling up, particularly in complex population health systems.[49] The CONTROL study will include an extensive process evaluation with implementation outcomes of the study after the pilot is completed and it will be assessed again after the completion of the definitive trial. The results of the pilot study and process evaluation will inform the planning and conduct of a definitive pragmatic RCT. The development of a prospective model, which can be effectively implemented with the assistance of PTP staff, is anticipated to yield significant economic and social benefits. Moreover, it is expected that this model will be well received by the individuals utilising these services. The impact of research can be optimised by fostering a collaborative relationship among patients, members of the public and researchers. It will be carried out successfully by recognising and accepting the varied contributions that service users make in different phases of the research process, including prioritisation, design, data collection, analysis, and dissemination of findings.

The application of psychological interventions to TB patients and implementation must be operationalised at various levels.[10] At the community level, identification of vulnerable people and delivery of intervention at the individual level using effective communication would aid in addressing mental health outcomes such as depression and anxiety, while improving medication adherence, quality of life and reducing the caregiver burden and perceived stigma. At the institutional level, not only the provision of necessary training and capacity-building programmes for PTP staff but also regular supervision, training need assessment and monitoring is crucial to deliver the psychological intervention more efficiently. The proposed CONTROL study includes all these vital aspects. At the national level, formulation of guidelines, protocols and policies would further strengthen the incorporation of psychological intervention in the existing TB control programme. The CONTROL study has already established stakeholder and patient advisory groups in both study districts, who would support us in the dissemination of our findings and uptake of our recommendations. Results will be shared with provincial and national government, and key policy implications will be published. With all these collaborative effects and holistic approaches, in the development and implementation of the CBT intervention, our study will help to improve the outcomes both for depression and TB in people with TB and MDR-TB in resource-poor settings.

Strengths and limitations of the proposed study

The proposed study design has several strengths. A hybrid design will be used as it examines both effectiveness and implementation outcomes within a study.[19] An internal pilot is being conducted with a specified progression criterion as pilot studies that are properly planned and carried out will provide valuable insights into improving the design and methods before the a fully powered RCT is carried out.[50] An extensive intervention development phase using a combination of qualitative, ethnographic methods and involvement of stakeholders will lead to development of CONTROL intervention that is likely to be implementable and sustainable in future.

The proposed study aims to evaluate an approach that can be used for scaling up the treatment of depression in TB in resource-poor settings and specifically addresses a major gap in TB care that affects both mortality and morbidity in the condition. The intervention involves a task-sharing approach. Importantly, the trial is powered for two primary outcomes that are relevant to TB and mental health, that is, treatment adherence with ATT and improvement in drug treatment for TB.

One potential limitation of the study is that there may be possible contamination between the intervention and control groups. We have adopted the procedures to keep the intervention and control groups separate during the trial recruitment and follow-up, having separate teams for assessing the outcomes but this would not eliminate the possibility of contamination between the group. The measurement of treatment adherence is based on a subjective measure, that is, reporting from patients and carers that cannot be objectively validated.

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Contributors SF conceived the study idea, and SF and ZKh are the colead in the CONTROL programme of research. SF and ZKh wrote the grant application, obtained funding and designed the methodology. SF, ZKh, NF, ML, SS and GY contributed to writing the draft article. ML and GY provided the statistical expertise and contributed to designing the study and methodological details of the RCT and wrote the analysis plan and economic evaluation part of the protocol. NS and FA contributed to designing and developing the methodology for the qualitative and anthropological studies for intervention development and process evaluation. SF, ZKh, ML, ZU-H, MU-H, NS, FN, MB, SA, IKo, CM and IKe contributed significantly to obtaining the funding for the study, conceived and developed the intervention and study design, and led the creation of the team. MFK and MH provided the clinical input in intervention development. NF, ZKi, MR, MM, AM and SS contributed to writing the ethics application, developing and designing participants' information sheets, and consent forms for the ethics application, submitting all ethics applications, obtaining the ethics and governance approvals and submitting the article. The initial and final manuscripts have been read, revised and approved by all named authors.

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