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Cognitive therapy for depression in tuberculosis treatment

Submission date
23/11/2023

Recruitment status
No longer recruiting

Registration date
27/11/2023

Overall study status
Ongoing

Last Edited
21/11/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) is the 10th leading cause of death in the world. Pakistan is a Lower-Middle-Income Country (LMIC) with a population of about 230 million and ranks fifth among the TB high-burden countries, with an estimated half a million new cases of TB each year. According to the World Health Organization, Pakistan also has the fourth highest burden of multidrug-resistant TB (MDR-TB) globally. Afghan refugees residing in Pakistan have an even worse TB situation due to the ongoing conflict in Afghanistan. It is estimated that almost 49% of people receiving TB treatment may also have depression. Depression may be caused as a result of TB-related stigma or the side effects of TB treatments. When these conditions co-exist, they may raise the risk of TB reactivation, and contribute to poor adherence to TB treatments and disease progression. Poor treatment adherence results in drug-resistant TB (MDR-TB) which is considered to be a public health crisis.
The CONTROL programme aims to develop, test and implement a brief behavioural intervention to improve the outcomes for depression and TB in people with TB and MDR-TBThe research will be conducted in Pakistan and if the intervention is found to be effective, the researchers also propose a programme of scale-up in similar contexts.

Who can participate?
Participants aged between 18 years and 70 years residing in two districts in Khyber Pakhtunkhwa province of Pakistan: Peshawar and Haripur. Patients may be Pakistani or Afghan refugees living in Pakistan who started on antituberculosis medication (ATT) within 1 month of diagnosis for pulmonary and extrapulmonary TB or started on ATT within 3-6 months of diagnosis for MDR-TB and meet the prespecified criteria for depression.

What does the study involve?
Patients presenting at the selected Basic Management Units (BMUs) in district Peshawar or Haripur will be verbally informed about the study and screened for depression using a questionnaire by the TB Health Workers (TBHWs). Those screened positive will be referred to the CONTROL Research Assistant (RA). The RA will provide the detailed information sheet and arrange a convenient date and time with the potential participants to sign the informed consent and complete the screening assessment to confirm eligibility.
If the participant is eligible for the trial, the RA will arrange another visit within 1 week to

complete the baseline assessment and take demographic details and disease history. Following these assessments, the participant will be randomly allocated to either continue receiving their antituberculosis treatment as usual or to receive six sessions of the CONTROL intervention, along with their usual anti-tuberculosis treatment. The CONTROL intervention will be delivered by TB health workers guided and trained by CONTROL therapists.
Follow-up data will be collected by the RAs (who are blinded to the group collection) at 8-, 24-, and 32 weeks post-randomisation. In total participants will be enrolled in the study for 32 weeks.

What are the possible benefits and risks of participating:
Those who take part may not receive any direct benefit from participating. However, the information from this study will help the CONTROL research team to develop and test a behavioural intervention for the improvement of TB and depression outcomes in TB patients. If CONTROL is found to be an effective intervention, this data may then inform future public health programmes and studies in this area.
There are no anticipated risks involved for those who decide to take part in this study. The study includes sharing personal experiences, which some may find uncomfortable. Participants are under no obligation to answer any questions that make them feel uncomfortable. The information received from the participant will not be used in any way that might cause any harm. Participants will be informed that if there is any problem throughout participation the trained mental health professionals will be available for help. Participants will be informed of their right to withdraw from the study at any time if they find the supervision of treatment or any other part of the study is causing a problem. The withdrawal from the study will not affect their usual care.

Where is the study run from?
Keele University (UK)

When is the study starting and how long is it expected to run for?
November 2021 to June 2026

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Prof. Saeed Farooq, s.farooq@keele.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
NIHR201773

Study information

Scientific Title
Cognitive therapy for depression in tuberculosis treatment, protocol for a multi-centre pragmatic parallel arm randomized control trial with an internal pilot

Acronym
CONTROL

Study objectives
The inbuilt pilot will assess the acceptability and feasibility of the CONTROL intervention, co-developed with key stakeholders in the first phase of the study. It will also assess and refine the randomization procedure and recruitment strategy and gauge the appropriateness and effectiveness of the training provided to tuberculosis (TB) health workers.

The definitive trial will evaluate the effectiveness and cost-effectiveness of CONTROL versus Enhanced Treatment as Usual (ETAU) in improving depressive symptoms in people with TB and depression and enhancing adherence with (ATT). It will also examine the effects of implementing CONTROL on the Provincial Tuberculosis Control Programme in Pakistan and the wider health system.
Specifically, the study will aim to answer the following research questions;
1. What is the effect of a CBT-based intervention on:
1.1. Improvement in depression measured by a change in PHQ-9 score over?
1.2. Treatment adherence with ATT at 24 weeks?
2. What is the cost effectiveness of a CBT-based intervention using Service Receipt Inventory (SRI)?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 12/10/2023, National Bioethics Committee for Research NBC-R (Health Research Institute, Shahrah-e-Jamhuriat, Off Constitution Avenue, Sector G-5/2, Islamabad, Sector G-5/2, Pakistan; +92 (0)51 9224325, 9216793; nbcpakistan@nih.org.pk), ref: 4-87/NBC-998/23/587
2. Approved 12/09/2023, KMU-Ethics Board (Phase V Hayatabad Peshawar, Khyber

Pakhtunkhwa, 25100, Pakistan; +92 (0)91-9217258; oric@kmu.edu.pk), ref: DIR/KMU-EB/CT /000990
3. Approved 11/10/2024, Research Ethics Committee, Keele University, UK, REC Project Reference 0599.
4. Approved 24/10/2024, National Bioethics Committee for Research NBC-R (Health Research Institute, Shahrah-e-Jamhuriat, Off Constitution Avenue, Sector G-5/2, Islamabad, Sector G-5/2, Pakistan; +92 (0)51 9224325, 9216793; nbcpakistan@nih.org.pk), ref: Ref: No.4-87/NBC-998/23 /504
5. Approved 13/11/2024, KMU-Ethics Board (Phase V Hayatabad Peshawar, Khyber Pakhtunkhwa, 25100, Pakistan; +92 (0)91-9217258; oric@kmu.edu.pk), ref: KMU/IPHSS/Ethics /2024/CT/226 (dated 04-11-2024)

Study design
Multi-centre pragmatic hybrid design parallel arm randomized control trial with an internal pilot

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Depression in tuberculosis treatment

Interventions
Participants will be randomly allocated to one of the study arms in a 1:1 ratio (via random permuted blocks stratified by patients' nationality and type of TB (i.e. TB or MDR-TB). Randomization and allocation will be prepared and administered remotely by the trial statistician.

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. The content and modes of intervention are adapted based on the Southampton framework and finalised following an iterative process including evidence synthesis, ethnography, qualitative interviews and focus group discussions, and co-design consultative meetings with the stakeholders. The adapted manual emphasizes 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 will be 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. Additional self-help videos and audio material 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. Intervention will be delivered by trained DOTs facilitators/TB Healthcare Workers (TBHW).

Training for the intervention delivery:
The TBHWs will be trained using a cascade model of training. First, a team of senior Psychiatrists and Psychologists with extensive experience in delivering CBT will train 6-8 psychologists as Master Trainers (MTs). 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). 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/).

Control arm Enhanced Treatment as Usual (ETAU):
This arm will include treatment as usual, enhanced by MhGAP training. Treatment as usual for patients presenting with a mental health problem while receiving ATT after diagnosis with TB or MDRTB includes a referral from the treating physician to one of the local mental health teams that offers drug treatment or counselling. This treatment as usual will be enhanced by the mhGAP training for the TB programme staff involved in the trial. The mhGAP is WHO guidance on treating mental disorders in non-specialist health settings using algorithms for clinical decision-making.

Intervention Type
Behavioural

Primary outcome(s)
Current primary outcome measures as of 25/01/2024:
Acceptability and feasibility outcomes of the inbuilt pilot which determines the progression criteria will include:
1. Recruitment rate, measured by the number of patients recruited at baseline
2. Retention rates in therapy, are measured by the percentage of participants completing at least four sessions. This will be measured at week 8 post-randomization.
3. Completion rates for the trial follow-up, measured by the percentage of participants who are followed up and complete the 24-week post-randomization follow-up assessment.

Progression criteria:
The results from the pilot study will be presented to the Trial Steering Committee and the funders. The researchers will proceed to the main trial without major modification if:
1. Sample size of 40-80 participants recruited within the 3-month time frame.
2. If 40-70% of the patients complete at least four therapy sessions
3. And if 40-75% of the participants complete the follow-up assessments at week 8 and week 24 post-randomization
If any major modification is required to the intervention design or delivery, the researchers will recommend that the internal pilot is changed to an external pilot with afresh recruitment to the main trial based on the substantial re-design.

Other acceptability and feasibility outcomes of the inbuilt pilot will include:
4. The degree of completion of screening at routine TB treatment visits, indicated by at least a 65% compliance rate, measured at baseline.
5. Compliance in completing the outcome measures for mental health, indicated by at least a 65% compliance rate. This will be measured at baseline, week 8, and week 32 post-randomization.
6. The willingness of TB health workers: the number of TBHWs approached, completing a training program in both arms. This will be measured at baseline, week 8, and week 32 post-

randomization.
7. The acceptability of trial procedures: adherence to trial procedures and completion of the assessments. This will be measured at baseline, week 8, and week 32 post-randomization.
8. intervention fidelity assessed using the revised Cognitive Therapy Scale at week 8 and week 32 post-randomization
9. Evaluation of PHQ-2 sub-scale for sufficient screening: the sensitivity and specificity of the PHQ-2 against the PHQ-9 (proxy gold- -standard) diagnosis of depression will be measured at baseline.

Primary outcome measures for the definitive RCT and clinical outcomes of the pilot trial:
1. Depressive symptoms measured using PHQ-9 at baseline, week 8, week 24, and week 32 post-randomization; response defined as a ≥50% decrease in the PHQ-9 from baseline score.
2. Treatment adherence with ATT, measured by getting the data from TB health centres at week 24 post-randomization. In line with the literature on ATT adherence a patient will be classified as adherent if no more than 10% of tablets are missed; otherwise, non-adherent. At each participating centre, patients collect anti-TB treatment every month from their DOTS supervisor, who will inform the study RA about the estimate while maintaining blindness.

Previous primary outcome measures:

Acceptability and feasibility outcomes for the inbuilt pilot will include:
1. Recruitment rate, measured by the number of patients recruited at baseline
2. Retention rates in therapy, measured by the number of therapy sessions patients attended. This will be measured at week 8 post-randomisation
3. Completion rates for the trial follow-up, measured by the number of follow-up sessions patients attended at week 8 and week 24 post-randomisation

Progression criteria:
The results from the pilot study will be presented to the Trial Steering Committee and the funders. The researchers will proceed to the main trial without major modification if:
1. Sample size of 40-80 participants recruited within 3 months' time frame
2. If 40-70% of the patients complete at least four therapy sessions
3. And if 40-75% of the participants complete the follow-up assessments at week 8 and week 24 post-randomisation
If any major modification is required to the intervention design or delivery, the researchers will recommend that the internal pilot is changed to an external pilot with afresh recruitment to the main trial based on the substantial re-design.

Primary outcome measures for the definitive RCT:
1. Depressive symptoms, measured using PHQ-9 at baseline, week 8, week 24 and week 32 post-randomisation; response defined as a ≥50% decrease in the PHQ-9 from baseline score.
2. Treatment adherence with ATT, measured by getting the data from TB health centres at week 24 post-randomisation. In line with the literature on ATT adherence a patient will be classified as adherent if no more than 10% of tablets are missed; otherwise, non-adherent. At each participating centre, patients collect anti-TB treatment every month from their DOTS supervisor, who will inform the study RA about the estimate while maintaining blindness.

Key secondary outcome(s))

Current secondary outcome measures as of 25/01/2024:
1. Cost-effectiveness measured using the Service Receipt Inventory (SRI) at baseline, week 8, and week 32 post-randomisation
2. Severity of anxiety symptoms assessed using the Generalized Anxiety Disorder scale (GAD-7)

at baseline, week 8, and week 32 post-randomization
3. Caregivers' burden assessed by Zarit Burden interview at baseline, week 8, week 32 post-randomization
4. Perceived stigma assessed using the Internalized Stigma of Mental Illness scale at baseline, week 8, week 32 post-randomisation
5. Quality-adjusted life years (QALY) and general health status measured using the EuroQoL EQ5D at baseline, week 8, and week 32 post-randomization
6. Traumatic stress symptoms will be measured using the Harvard Trauma Questionnaire (HTQ) at baseline, week 8, and week 32 post-randomization
7. Functional impairment measured using WHODAS at baseline, week 8, and week 32 post-randomization
8. Clinical outcomes will be assessed using measures developed and successfully incorporated in routine TB programme recording tools at 24 weeks post-randomization
10. Acceptability of trial procedures measured by the adherence to trial procedures and completion of the assessments at baseline, 8 weeks, 24 weeks, and 32 weeks post-randomization
11. Implementation outcomes for appropriateness measured using the Intervention Appropriate Measure (IAM) scale at week 32 post-randomization
12. Implementation outcomes for feasibility and acceptability will be measured using the Applied Mental Health Research Group (AMHR) feasibility Scale at week 32 post-randomization
13. Intervention Fidelity, measured using an independent ratter using a checklist and The Cognitive Therapy Scale (CTS-R), at week 8 & week 32 post-randomization
14. Penetration and sustainability of the intervention will be measured using the acceptance of Mental Health Measures in Routine TB Health outcomes at week 32 post-randomization

Previous secondary outcome measures:
1. Cost-effectiveness measured using the Service Receipt Inventory (SRI) at baseline, week 8, and week 32 post-randomisation
2. Severity of anxiety symptoms assessed using the Generalized Anxiety Disorder scale (GAD-7) at baseline, week 8, and week 32 post-randomisation
3. Caregivers' burden assessed by Zarit Burden interview at baseline, week 8, week 32 post-randomisation
4. Perceived stigma assessed using the Internalized Stigma of Mental Illness scale at baseline, week 8, week 32 post-randomisation
5. Quality-adjusted life years (QALY) and general health status measured using the EuroQoL EQ5D at baseline, week 8, and week 32 post-randomisation
6. Traumatic stress symptoms measured using the Harvard Trauma Questionnaire (HTQ) at baseline, week 8, and week 32 post-randomisation
7. Functional impairment measured using WHODAS at baseline, week 8, and week 32 post-randomisation
8. Clinical outcomes assessed using measures developed and successfully incorporated in routine TB programme recording tools at 24 post-randomisation
9. Willingness of TB health workers measured by the number of TBHWs approached and completing a training programme in both arms. This will be measured at baseline
10. Acceptability of trial procedures measured by the adherence to trial procedures and completion of the assessments at baseline, 8 weeks, 24 weeks and 32 weeks post-randomisation
11. Implementation outcomes for appropriateness measured using the Intervention Appropriate Measure (IAM) scale at week 32 post-randomisation
12. Implementation outcomes for feasibility and acceptability measured using the Applied Mental Health Research Group (AMHR) feasibility Scale at week 32 post-randomisation

Completion date

30/06/2026

Eligibility

Key inclusion criteria

Current inclusion criteria as of 19/11/2024:

Based on the findings from the pilot trial, the eligibility criteria for the definitive trial have been updated as follows:
1. Adults aged 18 – 70 years old
2. Are Pakistani or Afghan nationals (with refugee status as per their registration in the National Database and Registration Authority of Pakistan)
3. Started on ATT within 1 month of diagnosis for pulmonary and extrapulmonary 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). We will include both pulmonary and extra-pulmonary TB forms.
4. Started on ATT within 3-6 months of diagnosis for Multi-Drug Resistance TB.
5. 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 (Kroenke and Spitzer, 2002). 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.
6. Score above 16 on WHODAS, questionnaire for functional impairments (WHO Disability Assessment Schedule 2.0; WHODAS) (Üstün et al., 2010).

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Previous inclusion criteria as of 20/02/2024:

1. Adults aged between 18 and 70 years
2. Are Pakistani or Afghan nationals (with refugee status as per their registration in the National Database and Registration Authority of Pakistan)
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 program (http://ntp.gov.pk/ntp-old/uploads/National_Guidelines_for_TB_Revised_2019.pdf). The researchers will include both pulmonary and extra-pulmonary TB forms
4. Meeting the criteria for depression (score of 10 or above on PHQ-9)
5. Score above 16 on WHODAS, questionnaire for functional impairments (WHO Disability Assessment Schedule 2.0; WHODAS)

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Previous inclusion criteria:

1. Adults aged 18 years and above
2. Are Pakistani or Afghan nationals (with refugee status as per their registration in the National Database and Registration Authority of Pakistan)
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 program (http://ntp.gov.pk/ntp-old/uploads/National_Guidelines_for_TB_Revised_2019.pdf). The researchers will include both pulmonary and extra-pulmonary TB forms

4. Meeting the criteria for depression (score of 10 or above on PHQ-9)
5. Score above 16 on WHODAS, questionnaire for functional impairments (WHO Disability Assessment Schedule 2.0; WHODAS)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Total final enrolment
575

Key exclusion criteria
Current exclusion criteria as of 19/11/2024:

1. Meeting ICD-10 criteria for current or lifetime bipolar disorder, other forms of severe mental illness, have evidence of learning disability or severe substance abuse (except nicotine dependence)
2. Receiving any treatment for depression (psychotherapy or antidepressants over the last 6 months
3. Are currently suicidal, as defined in the mhGAP Intervention Guide, or made a suicidal attempt within the past 2 years
4. Have TB directly affecting the CNS, are severely ill and suffer from complications of TB such as pleural effusion or in 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. Pregnant or breast-feeding mothers will not be excluded in the definitive trial.

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Previous exclusion criteria:

1. Meeting ICD-10 criteria for current or lifetime bipolar disorder, other forms of severe mental illness, have evidence of learning disability or severe substance abuse (except nicotine dependence)
2. Receiving any treatment for depression (psychotherapy or antidepressants over the last 6 months

3. Are currently suicidal, as defined in the mhGAP Intervention Guide, or made a suicidal attempt within the past 2 years
4. Have TB directly affecting the CNS, are severely ill and suffer from complications of TB such as pleural effusion or in 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 breastfeeding

Date of first enrolment
31/12/2023

Date of final enrolment
18/11/2025

Locations

Countries of recruitment
Pakistan

Study participating centre
Khyber Medical University
Phase V
Hayatabad
Peshawar
Khyber Pakhtunkhwa
Pakistan
25100

Sponsor information

Organisation
National Institute for Health and Care Research

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated or analysed during the current study will be available on request from Professor Saeed Farooq (s.farooq@keele.ac.uk). The data-sharing plan will be uploaded as an additional file to the record once drafted.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/06/2024	19/06/2024	Yes	No
Other publications		05/10/2025	06/10/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes