



BMJ Open Culturally adapted cognitive behavioural group therapy for mental disorders in refugees plus problem solving training (ReTreat): study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction Since a high proportion of refugees in Germany suffer from mental disorders, culturally adapted treatments are needed that target a broad range of symptoms. There is much evidence for the efficacy of culturally adapted cognitive behavioural therapy (CA-CBT). Given the promising results of CA-CBT, the combination with problem solving training (CA-CBT+) represents a novel approach that potentially improves the refugees' ability to cope actively with psychosocial problems. This randomised controlled trial evaluates the efficacy of 12-session outpatient CA-CBT+ compared with to treatment as usual (TAU) in a sample of refugees suffering from at least one DSM-5 disorder.

Methods and analysis The present study will be carried out as two-group randomised trial with 1:1 individual allocation to either (1) culturally adapted cognitive behavioural therapy in a group setting (CA-CBT+) or (2) TAU. The study takes place at four sites in Germany, randomising in total 138 adult refugees with at least one primary DSM-5 diagnosis to the treatment conditions. In CA-CBT+ the patients receive 12 sessions of 120 min duration over the course of 12 weeks providing psychoeducation, meditation and other techniques of emotional regulation, stretching and problem solving training. The primary outcome is treatment response operationalised by a clinically significant change in General Health Questionnaire (GHQ-28) score. Follow-up visits will take place 3 and 9 months after the end of the intervention. Secondary outcomes include changes in psychopathological symptoms, somatic symptoms and quality of life. Intention-to-treat analysis will be performed. Adverse and serious adverse events will be analysed. Further, healthcare usage and economic outcomes will be assessed and analysed. Primary and secondary outcomes will be analysed using appropriate statistical methods.

Ethics and dissemination The study has been approved by the Ethics Commission of the German Psychological Society (ref: StangierUlrich2019-1018VA). Results will be disseminated via presentations, publication in international

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A strength of our study is the multicentre randomised controlled design with a relatively large sample size.
- ⇒ Another advantage is that the cultural adaptation was implemented according to a standardised framework and previously published.
- ⇒ Another strength is the evaluation of healthcare usage and the economic analysis.
- ⇒ A major limitation is the lack of an alternative intervention in the control condition.
- ⇒ Another limitation is that the study design does not allow any conclusions about the incremental efficacy of the cultural adaptation compared with regular cognitive behavioural therapy.

journals, and national outlets for clinicians. Furthermore, intervention materials will be available, and the existing network will be used to disseminate and implement the interventions into routine healthcare.

Trial registration number DRKS00021536.

INTRODUCTION

The majority of the refugees from the Middle East in Germany have experienced multiple traumata.¹ Furthermore, the flight itself has often been associated with traumatic, life-threatening experiences. Additional distress is caused by postmigration stressors, such as placement in provisional collective housing and insecure outcome of the asylum proceedings, contributing to the maintenance and aggravation of mental disorders.² Recent studies^{1 3} provide evidence that refugees migrating to Western countries suffer not only from post-traumatic stress disorder

(PTSD, 21%–54%) but also from a variety of other mental disorders with high comorbidity rates, among them depression (20%–56%), anxiety disorders (40%–56%); and also somatoform symptoms (37%). Considering the large spectrum and high comorbidity of mental disorders seen in asylum seekers and refugees, a transdiagnostic approach to psychological treatment appears reasonable.

Another challenge for Western models of mental disorders and psychological treatments is to adapt interventions to the specific needs of ethnic minorities and refugee groups. Qualitative studies with Afghan⁴ and Syrian refugees⁵ indicate that the perception and expression of symptoms, the explanations as well as treatment expectations are linked to the specific culture. The efficacy of psychotherapy is enhanced if treatment is adapted to the culture of origin.^{6–8} In addition, several researchers have developed frameworks to standardise the process of cultural adaptation.^{9 10}

In accordance with these guidelines, the first step of cultural adaptation of the present treatment was screen clinical trials, meta-analyses and systematic reviews on culturally adapted psychological interventions in refugees and asylum seekers. We conducted an electronic literature search using Medline, PsycINFO, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien, Google Scholar and International Clinical Trials Search Portal (date of search: 2 October 2017). Search terms were ‘asylum seekers’, ‘refugees’, ‘group’, ‘psychotherapy’, ‘treatment’ and ‘intervention’ and their combinations for publication date 2000 to present.

According to recent meta-analyses^{11 12} and systematic reviews,¹³ culturally adapted cognitive behavioural therapy (CA-CBT)^{6 14 15} and narrative exposure therapy are the most supported interventions for adult refugees. Whereas narrative exposure therapy has been evaluated exclusively in individual setting, however, only CA-CBT is designed for group setting. Besides, two other studies refer to group psychotherapy. One study evaluated a trauma-focused group day-treatment programme for refugees, combining psychodynamic, cognitive behavioural and a number of other treatment approaches.¹⁶ Although this day-treatment programme was more effective than a waitlisted control group in reducing psychopathological symptoms, its implementation is impeded by the requirements for different treatment components and the high costs for day-treatment setting. Another approach to use group format in a randomised controlled trial (RCT) with refugees from Chechnya involved lay counselling and self-help techniques.¹⁷ Although this approach was not less effective than traditional group CBT in reducing psychopathological symptoms, the validity of the results suffers from low statistical power. No other trials with group treatments were identified in the electronic databases. CA-CBT was evaluated in three trials with Vietnamese refugees,¹⁴ Cambodian refugees,⁶ and female Latino patients with treatment-resistant PTSD,¹⁵ yielding large effect sizes ranging from 1.6 to 2.5. However, its

efficacy in refugee samples in Germany and Europe is still to be determined.

A recent pilot trial indicated that CA-CBT is an effective approach to reduce general psychopathological symptoms and to improve quality of life in Farsi speaking refugees.¹⁸ In addition, the adaptation process was implemented according to a standardised framework for cultural adaptation and previously published.¹⁹ In an ongoing RCT with a waitlist control group the positive findings from the first trial were replicated, indicating CA-CBT+ is an efficient programme in treating refugees.²⁰ However, the RCT trial had a waiting list control condition and a relatively small sample size of 24 participants. Thus, the efficacy of CA CBT+ in refugee groups seen in Germany and Europe is still to be determined with larger patient numbers and an active control condition. In order to evaluate the potential implications for the healthcare system, the assessment of healthcare usage and economic analysis are needed.

Aims and hypotheses

The major goal of the study is to test the efficacy of transdiagnostic, culturally adapted group CBT, augmented with problem solving training (CA-CBT+) in a controlled, randomised multicentre trial, by comparing short-term and long-term outcomes of CA-CBT+ on mental health with treatment as usual (TAU). Furthermore, we will investigate the effect of gender on the outcome of CA-CBT+. Recent findings indicate that male gender is associated with a higher number of non-responders in refugees.²¹ Therefore, we expect that female refugees will benefit significantly more from CA-CBT+ than male refugees. Besides the effects on primary outcome, we will also test the effects of treatment on secondary outcome measures, including psychopathological symptoms and somatic symptoms and quality of life.

The primary hypothesis is that, (1) compared with the TAU, more participants in CA-CBT+ will show reduced general psychiatric symptoms, as well as at both the 3-month and 9-month follow-ups.

Additional analyses will be conducted to address the following secondary hypotheses:

- ▶ Participation in CA-CBT+ will reduce depressive symptoms.
- ▶ Participation in CA-CBT+ will improve quality of life.
- ▶ Female refugees will benefit more from CA-CBT+ than men.

METHODS AND ANALYSIS

Design and setting

The present study is a multicentre, parallel two-group RCT with 1:1 individual allocation to either: (1) culture-sensitive group programme CA-CBT+ or (2) a TAU control group across four study sites in Germany (Frankfurt, Marburg, Münster and München). The study is planned to start on 1 September 2020 and to be concluded on 1 January 2024.

Box 1 Trial entry criteria

Inclusion criteria

- ⇒ At least one primary DSM-5 diagnosis of trauma-related and stressor-related disorders, depressive disorders, anxiety disorders or somatic symptom and related disorders confirmed by the M.I.N.I. for DSM-5.
- ⇒ General Health Questionnaire (GHQ-28) > 11.
- ⇒ Age between 18 and 65 years.
- ⇒ Informed consent.

In case of illiteracy, assistance will be provided in the native language or a language the patient comprehends on an advanced level of proficiency.

Exclusion criteria

- ⇒ Current substance use disorders.
- ⇒ Acute/past manic or psychotic symptoms.
- ⇒ Odd/dramatic personality disorders.
- ⇒ Acute suicidality.
- ⇒ Severe medical conditions.
- ⇒ Concurrent psychotherapy (including interventions from sub-projects 1 and 3).

M.I.N.I., Mini-International Neuropsychiatric Interview.

The Standard Protocol Items: Recommendation for Interventional Trials statement was used for writing this report.

Study population

The target population will comprise adult refugees from different countries of origin, mainly from Afghanistan

and Syria. The full list of participant inclusion and exclusion criteria is provided in [box 1](#).

Participant recruitment

Recruitment of patients will be conducted via established collaborations with service providers for refugees, collaborations with healthcare providers, a project website and via social media. The recruitment period will last for 30 months. The screening of the patients will be performed in the participating study sites. Patients will be enrolled by the local coordinator(s).

Study procedure

Patients will be treated at four outpatient clinics (Frankfurt, Marburg, München and Münster). These participating sites that were selected by the coordinating investigators have adequate staff and experience in treating refugees with mental disorders and in conducting clinical studies. The Frankfurt and Munich sites have already established specialised refugee mental health and counselling outpatient centres. The study sites include experienced therapists regarding the targeted patient population and technical expertise to complete the protocol.

Experienced and trained therapists will administer CA-CBT+. Per site, two fully licensed psychotherapists or psychotherapists in advanced clinical training will administer CA-CBT+. All therapists will attend a 2-day training in CA-CBT+. The study sites include experienced therapists regarding the targeted patient population and technical expertise to complete the protocol. The duration of the study for each subject is expected to be 12 months after randomisation (see also the study flow chart in [figure 1](#)). Included are 3-month intervention period and 9-month follow-up. Screening will be conducted by independent clinical raters and comprises a standardised diagnostic interview (Mini-International Neuropsychiatric Interview (M.I.N.I.)), demographic data and an assisted self-rating of the General Health Questionnaire (GHQ-28). If eligible for participation in the trial, the patient is handed out the patient information and consent form. After giving written consent, the patient completes secondary outcome measures at baseline (assisted self-report). In addition, medical treatment will be assessed, using the TAU protocol. Due to the high number of measures interviewers will be trained in advance and a guideline will be provided, to reduce potential stress for participants.

After completing baseline assessment, patients will be randomised to either CA-CBT+ or TAU. Three months, 6 months and 12 months after randomisation, participants in the CA-CBT+ condition as well as in the TAU condition will complete secondary outcome measures (assisted self-report), and clinical raters will complete TAU protocols. At 12-month follow-up (9 months after treatment), participants with a GHQ-28 ≥ 11 will be offered again the M.I.N.I. to check the persistence of diagnoses at study entry. In case of persisting mental problems, participants will be offered treatment at the outpatient clinics

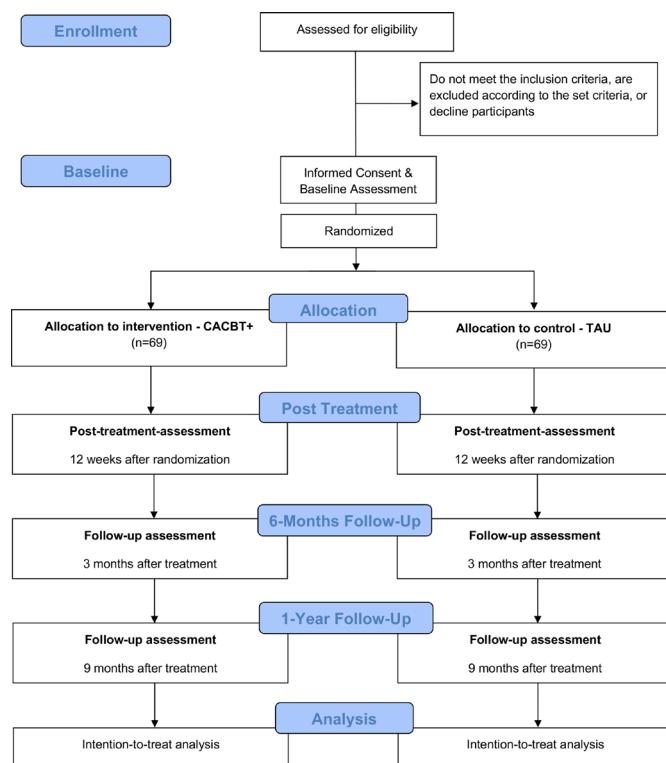


Figure 1 Study flow chart of ReTreat randomised controlled trial. CA-CBT+, culturally adapted cognitive behavioural therapy; TAU, treatment as usual.

of the trial sites or cooperating clinics and psychiatric services.

Patient and public involvement

No patient involved.

Randomisation

Randomisation will be performed centrally by the central office of the Coordinating Centre for Clinical Studies in Marburg. The randomisation of an eligible patient can take place if all inclusion criteria and none of the exclusion criteria are fulfilled.

The chance for allocation to the intervention group and the control group is 1:1. The randomisation will be stratified by gender and study site to ensure balance between the two study arms across all four investigation sites. The Coordination Center for Clinical trials (KKS) in Marburg informs the centre about the randomisation result and the local coordinator(s) will assign patients to study groups. Each participant will be given a unique study code by the KKS.

INTERVENTION

CA-CBT+ consists of 12 weekly sessions of 120 min duration.²² The standard session length of 120 min accommodates the need to use interpreter services in treatment. CA-CBT+ includes the following interventions: psychoeducation, meditation and other techniques of emotional regulation, cognitive techniques (eg, identification of the relationship between thoughts, emotions and somatic complaints), and stretching. All components target 'thinking too much' as a transcultural concept of mental suffering. Furthermore, we added problem solving training to the intervention. A focus group that was conducted after the pilot trial, revealed the lack of interventions that address post migration stressors. The implementation of problem solving techniques intended to enable patients to take independent actions within their social contexts. As a less intense intervention delivered by non-professional helpers, problem management+has been successfully applied in the treatment of traumatised earthquake survivors in Iran²³ and in the prevention of PTSD in a conflict-affected area in Pakistan.²⁴ We incorporated simplified, easier accessible rationales for depression and PTSD symptoms²⁵ which take into account cultural values of the participants (eg, collective vs individual benefit) or the varying mental health literacy.

Based on interviews, we adapted the contents of psychoeducation such as explanations of causes, interpretations of symptoms, and therapeutic practices and concepts, to the Afghan/Iranian or Syrian/Iraqi culture (for further details see¹⁹). Cultural idioms of distress are used to describe mental disorders. Culture-specific causal explanations are used as a rationale for interventions (eg, 'thinking too much' for meditation). Finally, interventions are referred to culturally embedded, behavioural patterns (eg, seeking social support).

Based on data from qualitative studies and focus groups with refugees conducted at the Frankfurt trial site of the Female Refugee Study, gender-specific topics were included in the psychoeducation (gender-specific role behaviours, family relationships, education of children, discrimination, violence and abuse, participation in public life). The use of mental health services is often avoided due to stigma barriers, shame and taboos. We therefore present the programme as a training to increase resilience, to support coping with problems and to reduce distress.

Per site, two fully licensed psychotherapists or psychotherapists in advanced clinical training will administer CA-CBT+. All therapists will attend an additional 2-day CA-CBT+ workshop. Sessions will be audiotaped and evaluated for adherence by independent raters. Regular supervision two times a month at the four centres as well as telephone case consultation for all therapists two times a month will ensure treatment adherence.

Control group

In the TAU condition, patients will be referred to institutions of public mental healthcare, and will be monitored at the corresponding measurement points as for CA-CBT+. Referral will be made through a standardised information leaflet. TAU may include drug treatment, and supportive counselling. If patients are dissatisfied with their treatment after the last follow-up assessment 9 months post-TAU treatment, they will be offered CA-CBT+. Patients allocated to TAU will be contacted 3, 6 and 12 months after randomisation, and changes in medication and adverse events will be assessed using the TAU protocol.

Outcome measures

All questionnaires will be given in the most commonly spoken native languages of the refugees. For the other questionnaires, the original versions will be translated and back-translated by different native Farsi and Arabic speakers and discrepancies clarified, in accordance with standard procedure.²⁶ All measures not yet translated will be translated and back-translated as is standard. When needed, the questionnaires will be employed with support from a native-speaking or interpreter-assisted psychologist. A detailed overview of the assessments and time points is presented in [table 1](#).

Diagnoses will be determined by the M.I.N.I. 7.0^{27 28} adapted to DSM-5. Culturally sensitive assessment of general psychopathology will be implemented by the Afghan Symptom Checklist²⁹ or the Arab Symptom Checklist.³⁰

An additional objective of the study is to identify predictors for short-term outcome, by using the Thinking a Lot Questionnaire³¹ as a predictor and changes in GHQ-28 as dependent variable.

For economic analysis of CA-CBT+, costs will be measured by a brief version of the Client Sociodemographic and Service Receipt Inventory,³² utilities will be

Table 1 Summary of assessment schedule

Visit	Screen.	Baseline	Random assignment by KKS	Intervention visits 1–12												End of intervention	FU1	FU2
				1	2	3	4	5	6	7	8	9	10	11	12			
Week	0	0		1	2	3	4	5	6	7	8	9	10	11	12	24	52	
Day	0	1		7	14	21	28	35	42	49	56	63	70	77	84	168	364	
M.I.N.I.	D																	
Demographic data	D																	
GHQ-28	P														P	P	P	
PHQ-9		P													P	P	P	
ITQ		P													P	P	P	
SSS-8		P													P	P	P	
Therapy expectations		P																
EQ-5D		P													P	P	P	
CSSRI		P													P	P	P	
CSSRI brief															P			
PMLDC		P													P	P	P	
ASCL/ArSCL		P													P	P	P	
CSQ-8		P													P		P	
TALQ										T								
Diagnosis, meeting inclusion criteria	D																	
Informed consent	P																	
Adherence and competence rating										T	T	T	T	T	T	T	T	
TAU protocols	D														D	D	D	

ArSCL, Arab Symptom Checklist; ASCL, Afghan Symptom Checklist; CSQ-8, Client Satisfaction Questionnaire; CSSRI, Client Sociodemographic and Service Receipt Inventory; EQ-5D, EuroQol; FU, follow-up; GHQ-28, General Health Questionnaire; ITQ, International Trauma Questionnaire; M.I.N.I., Mini-International Neuropsychiatric Interview; PHQ-9, Patient Health Questionnaire; PMLDC, Post-Migration Living Difficulties Checklist; SSS-8, Somatic Symptom Scale; TALQ, Thinking a Lot Questionnaire; TAU, treatment as usual.

assessed by the EuroQol (EQ-5D).³³ Healthcare usage will be monetarily valued by unit costs. By synthesising costs and (clinical) outcomes, the cost analyses will be extended to a cost-effectiveness analysis or/and a cost-utility analysis depending on data quality. Economic outcomes include the incremental cost-effectiveness ratio and cost-effectiveness acceptability curves based on net-benefit regression to adjust for potential confounding. Therapy expectations will be assessed via four items.

Primary endpoint

The GHQ-28³⁴ is a widely used instrument for the assessment of psychiatric symptoms in general population surveys, primary care, and general medical outpatients. It consists of 28 items grouped into four subscales: somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. The items are rated on a 4-point Likert scale, which is recommended to be transformed into a binary scale (0, 1=0; 2, 3=1). The GHQ-28 has also been validated for Arabic³⁵ and Afghan populations,³⁶ and as a measure to assess clinically significant change in psychiatric patients, using the Present State Examination as criterion. Therefore, we based the definition of treatment response on the GHQ-28. Definition of response to treatment was derived from the findings of Ormel *et al.*³⁷ In their study, patients from a psychiatric sample underwent psychiatric treatment and were classified as recovered, unchanged or deteriorated. Based on these findings, we defined clinical significant improvement either as a decrease in the GHQ-28 score of -5 or more or change to recovery by decreasing below the threshold for psychiatric conditions of less than 5.

Secondary endpoints

Sociodemographic data such as information on gender, age, education, country of origin, duration of stay in Germany, command of language, family status, residence status and current living conditions are collected during screening from all participants.

Depressive symptoms will be assessed using the Patient Health Questionnaire (PHQ-9).³⁸ The International Trauma Questionnaire (ITQ)³⁹ is a brief self-report measure and contains 12 items. It measures the core features of PTSD and Complex PTSD and is consistent with the criteria from International Classification of Diseases (ICD-11). The Somatic Symptom Scale (SSS-8) will be used to measure somatic symptoms.^{40 41} Health-related quality of life will be assessed using the international standard EQ-5D.³³ Good psychometric properties of the EQ-5D have been reported in different languages, including Arabic. The Post-Migration Living Difficulties Checklist⁴² is a self-report questionnaire used to assess recent adverse life experiences typical of migration. The Client Satisfaction Questionnaire,⁴³ an 8-item self-report instrument constructed to measure satisfaction with health services, will be used at postassessment. To assess long-term effects of treatment, the measurements will be taken at 3 and 9 months after treatment. A 3-month

follow-up reflects the standard in studies with refugees. However, a 9-month interval after randomisation allows for the assessment of long-term maintenance of treatment effects.

Blinding

To avoid detection bias, study personnel conducting the assessments will be blinded. Blinding of therapists and patients is not possible. To avoid detection bias, treatment effects will be assessed by using self-report measures. However, participants will be assisted by psychologists who are blinded to group allocation. Additionally, to prevent selection bias, randomisation will be performed externally by the KKS.

Sample size

Our sample size calculation is based on the assumption that the primary endpoint will take on higher values in women than in men. In accordance with demographic data in Germany the gender ratio in the participants is estimated as 67% men versus 33% women. Estimates for percentage of patients with response are as follows: (1) women: CA-CBT=66.0%, TAU=32.65%; (2) men: CA-CBT=58.1%, TAU=25.7%. In order to detect an OR of 4 in each stratum between groups at a two-sided α of 5% with a power of 80%, 82 persons (41 per group) are required (Cochran Mantel-Haenszel test, software PASS 14, V.14.0.4, NCSS, LLC). Compensating for 40% dropouts, 138 patients have to be randomised. Participants who did not attend to 50% of appointments or at least four consecutive appointments will be classified as dropouts.

Adverse events

Complications are divided into serious adverse events (SAEs) and adverse events (AEs). The following events are categorised as SAEs: (1) suicide; (2) other cause of death; (3) severe self-harm; (4) harm of others; (5) suicide attempt; (6) life-threatening event (participant is in acute risk of death) and (7) event that led to severe physical disability. The following events are categorised as AEs: (1) occurrence of new symptoms of a severe mental disorder; (2) unforeseen or prolonged hospitalisation due to psychiatric problems and (3) clinically significant worsening of clinical symptoms such as exacerbation of PTSD symptoms, suicidal ideation, psychotic symptoms indications of substance misuse or body symptoms that have to be medically evaluated (eg, cardiac arrhythmia).

(S)AEs are documented if reported. All SAEs and AEs will be recorded in the participant file and the electronic case report form (e-CRF) for the duration of the participant's direct involvement in the trial. All SAEs and AEs must be reported to the coordinating investigators, and the central project manager within 24 hours on notice of the event.

End of protocol treatment

Study treatment of a patient may also be terminated by the investigator for one of the following reasons: (1)

severe serious complications which makes it necessary to stop the study treatment, (2) abnormal test procedure result(s) which make it necessary to stop study treatment or (3) non-compliance with the study protocol. Study treatment must be terminated for one of the following reasons: (1) withdrawal of patient's consent to study treatment or (2) study treatment termination by the investigator. If the investigator terminates the treatment of the patient prematurely, he has to inform the patient about his decision and has to record the primary reason for withdrawal in the patient file and to document the end of treatment in the CRF. If the patient caused the premature withdrawal the data collected before termination may be used if the patient agrees and an informed consent for follow-up is signed by the patient.

Data management

The trial will use an e-CRF (EDC-System) for data collection and documentation, which is hosted by KKS Marburg. The data will be entered directly via web browser to the e-CRF and are transferred via encryption (HTTPS (TLS/SSL)) to the central database. Access to the e-CRF is only allowed for persons who are documented as trial personnel and have received necessary training. Each person who is allowed to make entries in the e-CRF receives a personal username and the URL for database login on request (user-ID request).

The given data will be checked electronically for its plausibility and consistency in a multistage procedure. Detected inconsistencies and missing or implausible data will be clarified with queries (electronically or paper-based) and necessary changes will be carried out. The EDC system has an implemented audit trail. This assures that any documentation and/or changes to database items are traceable anytime. At the end of trial, the database will be closed after data cleaning process. This process will be documented according to SOPs of KKS Marburg. The pseudonymised patient data recorded in the e-CRF are stored by the KKS Marburg in accordance with legal requirements.

Statistical analysis

Primary outcome

The null hypothesis 'no difference in the primary endpoint between the CA-CBT+ and TAU group' will be tested against the alternative hypothesis 'difference in the primary endpoint between the CA-CBT+ and TAU group' by a two-sided Cochran Mantel-Haenszel test stratified for gender at $\alpha=5\%$. Estimates for the primary endpoint in each group and corresponding 95% CIs will be presented. In addition, multivariable binary logistic regression analyses will be performed to analyse the influence of baseline covariates and the language of adaptation (Farsi vs Arabic). In addition, a mixed analysis of variance (ANOVA) will be conducted to test for language-specific group effects on the GHQ-28. The analysis will also be performed for the per-protocol population as sensitivity analysis.

Secondary outcome

Both absolute changes in continuous scores as well as categorical assessments of GHQ-28 total score and subscales for Depression, Somatic Symptoms, Anxiety and the ITQ from T1 to T2, Client Satisfaction Scale at T2 will be analysed by appropriate hierarchical regression models (ie, Poisson or Binomial model) adjusting for baseline covariates. Furthermore, longitudinal analyses will be performed by applying (generalised) linear mixed models with first order autoregressive covariance matrices (repeated measures analyses) and random effects for patient and centre, main effects for group, gender and time, as well as interaction terms for group-by-time and group-by-gender. All efficacy analyses will be performed for the intention-to-treat population.

Safety and tolerability endpoints

Multiple imputation of missing values will be applied according to Rubin's concept (data missing completely at random, missing at random and missing not at random). Sensitivity analyses will be performed to investigate the effect of different modelling strategies for the imputation of missing values on the primary endpoint.

Monitoring

An independent Data Safety and Monitoring Board (DSMB) has been established. The DSMB will periodically review the accumulating data and patient safety. Based on their review, the DSMB will determine if the trial should be modified and make recommendations to the coordinating investigators. The DSMB independent from the study organisers and sponsors.

Ethics and dissemination

The study has been approved by the Ethics Commission of the German Psychological Society (ref: StangierUlrich2019-1018VA). Results will be disseminated via presentations, publication in international journals, and national outlets for clinicians. Furthermore, intervention materials will be available, and the existing network will be used to disseminate and implement the interventions into routine healthcare.

The trial will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and will follow the principles of Good Clinical Practice. Members of the DSMB, the principal investigators, as well as the KKS Marburg will ensure adherence to these guidelines.

After trial completion and publication of the study results, data requests can be submitted to the principal investigators.

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Competing interests None declared.

Patient and public involvement No patient involved.

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