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Modular-Based Psychotherapy (MoBa) versus Cognitive Behavioural Therapy (CBT) for patients with comorbid depression and a history of childhood maltreatment: Study protocol for a randomised controlled feasibility trial

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Abstract

Introduction: In depression treatment, most patients do not reach response or remission with current psychotherapeutic approaches. Major reasons for individual non-response are interindividual heterogeneity of etiological mechanisms and pathological forms, and a high rate of comorbid disorders. Personalised treatments targeting comorbidities as well as underlying transdiagnostic mechanisms and factors like early childhood maltreatment may lead to better outcomes. A Modular-Based Psychotherapy (MoBa) approach provides a treatment model of independent and flexible therapy elements within a systematic treatment algorithm to combine and integrate existing evidence-based approaches. By optimally tailoring module selection and application to the specific needs of each patient, MoBa has great potential to improve the currently unsatisfying results of psychotherapy as a bridge between disorder-specific and personalised approaches.

Methods and analysis: In a randomized controlled feasibility trial (RCT), N=70 outpatients with episodic or persistent major depression, comorbidity and childhood maltreatment are treated in 20 individual sessions with MoBa or standard Cognitive Behavioural Therapy (CBT) for depression. The three modules of MoBa focus on deficits associated with early childhood maltreatment: the systems of negative valence, social processes, and arousal. According to a specific questionnaire-based treatment algorithm, elements from Cognitive Behavioral Analysis System of Psychotherapy (CBASP), Mentalization-Based Psychotherapy (MBT) and/or Mindfulness (MBCT) are integrated for a personalised modular procedure.

As a proof of concept, this trial will provide evidence for the feasibility and efficacy (post-treatment and six month follow-up) of a modular add-on approach for patients with depression, comorbidities and a history of childhood maltreatment. Crucial feasibility aspects include targeted psychopathological mechanisms, selection (treatment algorithm), sequence and application of modules, as well as training and supervision of the study therapists.

Ethics and dissemination: This study obtained approval from independent Ethics Committees. All findings will be disseminated broadly via peer-reviewed articles in scientific journals and contributions to national and international conferences.

Trial registration: German Clinical Trials Register (www.drks.de): DRKS00022093.

Keywords: Modular-Based Psychotherapy | Cognitive Behavioural Therapy | Depression | Childhood Maltreatment | Treatment Algorithm | Personalised | Randomised Controlled Trial | Cognitive Behavioral Analysis System of Psychotherapy | Mentalization-Based Psychotherapy | Mindfulness

Abstract Summary

Strengths and limitations of this study

- This is the first study to investigate the feasibility of a Modular-Based Psychotherapy (MoBa) approach for patients with comorbid depression and a history of childhood maltreatment.
- Besides feasibility, this RCT will prove initial evidence for the efficacy of MoBa and generate pilot data for a subsequent multicentre confirmatory trial.
- If successful, clinicians will be provided with an evidence-based treatment algorithm to combine and integrate available treatment modules systematically instead of ad libitum eclecticism.
- Using Cognitive Behavioural Therapy (CBT) as control condition represents a strong comparator for a rigorous evaluation with a high generalizability to the clinical reality.
- Since no a priori values are established, the algorithm cut-offs used here are based on general population means of self-rated questionnaires.

Introduction

Until recently, depressive disorders have been predominantly conceptualized and researched with a focus on the primary diagnosis. This has led to the development of several disorder-specific approaches such as the Cognitive Behavioural Therapy (CBT) [1] and the Interpersonal Psychotherapy (IPT) [2]. While these approaches (among others) have proven efficacy in unipolar major depression, there is a large proportion of patients who do not respond (more than 50%) or do not reach full remission (about two thirds) with first line treatment [3], even when the procedure is in accordance with treatment guidelines [4,5]. Major reasons for individual non-response and non-remission include interindividual heterogeneity of etiological mechanisms of depression and high rates of comorbid disorders of up to 80% in clinical and epidemiological studies [6-8]. Particularly anxiety disorders and Cluster C personality disorders are highly prevalent in Major depressive disorder (MDD) [9]. These comorbid disorders typically predict poorer treatment outcomes for MDD [10-13] or longer time to remission [14].

Childhood maltreatment

One major transdiagnostic factor associated with cognitive, emotional, behavioural and interpersonal dysfunctions common to a wide range of disorders is childhood maltreatment (CM). CM has most frequently been operationalized based on the Childhood Trauma Questionnaire (CTQ) [15], defined as onset reported before the age of 18 and meeting the criterion of at least “moderate to severe” on one of the five trauma subtypes (emotional abuse, emotional neglect, physical abuse, physical neglect, sexual abuse). In depressive disorders, CM is highly prevalent (~46%) [16], especially in early-onset and persistent depression with up to 80% [17,18]. An emerging body of evidence suggests a significant relationship between emotional maltreatment (abuse and/or neglect) in particular and depression [19-22]. Maltreated individuals are 2.7 to 3.7 times more likely to develop depression in adulthood, have an earlier depression onset and are twice as likely to develop a chronic or treatment-resistant course [16]. CM was also associated with an elevated risk for comorbid disorders [23,18]. Treated with psychotherapy and pharmacotherapy, the probability of non-response is 1.9 times

higher in depressed patients with early trauma compared to those without [16]. Taken together, study results indicate that interpersonal trauma exposure complicates the treatment of depression and reduces the impact of traditional cognitive therapy or treatments such as psychoeducation, TAU, or pharmacotherapy [24]. However, some approaches like Mindfulness Based Cognitive Therapy (MBCT) [25] or the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) [26-28] show promising results in the subgroup of depressed patients with CM.

Impact of childhood maltreatment on social and emotional functioning

A growing body of evidence links interpersonal trauma in both youth and adults to difficulties in social and emotional functioning [24]. Among other sequelae, CM usually results in marked avoidance behaviour [9] with negative social consequences and in concomitant retardation of emotional maturational growth [28,29]. These deficits are also expressed in terms of social threat hyperresponsivity (i.e. being highly sensitive to social rejection and anxiously expecting, readily perceiving, and overreacting to it) [30-33], social stress and avoidance behaviour [34,35], lack of empathy and theory-of-mind [36-38] and emotional dysregulation [39,40]. These emotional and social dysfunctions are mediated in common brain circuits for emotion and salience regulation, fear, and mentalising, suggesting that abnormalities in these functional pathways may be induced by CM [41,42]. Despite these severe consequences of CM and their important implications for treatment, disorder-specific approaches for depression such as CBT or IPT do not specifically address the role of CM and the affected dimensions of functioning.

Personalised Treatments

This calls for personalised treatments that target both comorbidities as well as underlying mechanisms and factors, which are central to the development and maintenance of psychological disorders. One of the challenges in the development of personalised approaches is to select treatment modules for targeted dysfunctions and to determine whether and in which sequence to combine them with standard treatment. In daily practice, it is left to the clinical

judgement and expertise of the therapist to address the patient´s individual needs and comorbidities by adding various therapeutic strategies to the disorder-specific interventions. However, this choice of add-on strategies is not backed up by empirical evidence and thus hardly conveyable to usual clinical practice in a systematic way [43]. Driven by these concerns, there has been growing consensus that a novel approach is needed in the way we classify, formulate, treat, and prevent depression and other mental disorders [44,45]. Insel and Cuthbert [46] postulated the concept of Research Domain Criteria (RDoC) to move "toward a new classification system" of studying and validating transdiagnostic, dimensional constructs since psychiatric diagnosis seem to be no longer optimal as long as they remain restricted to symptoms and signs. The transdiagnostic procedure focuses on identifying the common and core maladaptive temperamental, cognitive, emotional, interpersonal and behavioural characteristics that underpin a broad array of diagnostic presentations [47] and addresses them via specific modules in treatment [48]. In this sense, a modular-based psychotherapy provides a structured approach of tailoring treatments to fit patient needs by allowing greater flexibility to consider interindividual differences and comorbidity [49,50]. The modules, as sets of independent but combinable functional units, focus on common transdiagnostic dysfunctions and offer skills to improve e.g. emotion regulation, social competence, empathy, or self-motivation. There is only one study [51] in which emotion regulation skills were successfully added to CBT in depressed patients that had sufficient statistical power to detect a clinically significant effect.

Modular-Based Psychotherapy (MoBa)

Empirical support for the effectiveness of modular approaches following decision flowcharts is emerging lately [50,52]. For instance, Weisz and colleagues [49] conducted a large randomized controlled trial (RCT) in which a Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH) outperformed standard manual treatment as well as care as usual (CAU). The superiority of MATCH was found to be sustained in a two-year follow-up [53] and was replicated in a more recent trial [54]. Another example of a modular approach to psychotherapy is Behavioural Interventions for Anxiety in Children with

Autism (BIACA) [55]. By using a modular format and including an algorithm to guide the selection of modules, it offers a treatment approach for several anxiety disorders and obsessive-compulsive disorder for youths on the autism spectrum. BIACA was superior to waitlist and CAU in several RCTs (e.g. [56]). In adults, a still ongoing RCT [57] assesses the feasibility of a modular transdiagnostic intervention for mood, stressor-related and anxiety disorders (HARMONIC trial) in preparation for a later-stage trial. This represents early signs of a significant paradigm shift away from single-diagnosis approaches towards dimensional, transdiagnostic, and modular-based conceptualizations [58,46].

The here proposed rationale for a modular-based psychotherapy (MoBa) for depressed patients with comorbidity and a history of CM is two-fold: First, to include patients regularly seen in clinical practice showing a) more often comorbid and heterogeneous complaints than the samples usually included in RCTs and b) a limited treatment response to standard disorder-specific approaches. Second, tailoring the treatment to the specific characteristics and needs of patients with CM and comorbid depression can ensure that the psychotherapeutic process is responsive and may reach better treatment results. The MoBa intervention aims at interpersonal and emotional maturation by overcoming social threat hypersensitivity and interpersonal avoidance patterns and improving poor mentalization as well as poor emotion regulation capacities. The rationale is supported by previous trials with empirically supported treatments such as CBASP for chronic depression [59-62], MBCT for depression prevention and treatment [63-66], and Mentalization-Based Therapy (MBT) [67] for borderline personality disorder [68,69]. In the here used design, MoBa complements standard CBT with modules compiling specific elements from CBASP, MBCT, and MBT focusing on three disturbed systems (Figure 1). Those systems are part of the RDoC model and have been shown to be critically related to CM:

I) the negative valence system (acute, potential, and sustained threat): social threat response and avoidance behaviour [34,9];

II) the system of social processes: perception and understanding of self and others (understanding mental states), social communication, attachment [70,37,38];

III) the arousal system: emotion awareness and arousal regulation [40,71-73].

[FIGURE 1]

Objectives

This pilot study has a number of objectives appropriate to its status as a feasibility study:

1. Providing initial evidence for the efficacy of MoBa (reduction of clinician-rated depressive symptoms) as well as generating pilot data for the power calculation in terms of effect and sample size for a subsequent multicentre confirmatory trial.
2. Investigating the planned study design regarding the feasibility of recruitment, feasibility of applying cut-off values of self-reported deficits to select the modules, acceptability of the program to therapists and patients as well as patient ratings of 'usefulness' (both overall and in terms of individual modules). A crucial goal is to refine the algorithm for the selection of modules based on questionnaires.
3. Explore potential moderators of the primary outcome (in a hypothesis-generating exercise and to help refine the intervention).

Methods and analysis

Study design

The bicentric study will be conducted at the Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Germany, and the Department of General Psychiatry, University Medical Center Heidelberg, Germany. It is a parallel-arm RCT (N=70) comparing MoBa with CBT in 20 individual sessions over 16 weeks of treatment (twice weekly in weeks 1-4, then once per week in weeks 5-16). Participants will be assessed at screening, baseline, post-treatment and follow-up (six months after end of treatment).

Study population and recruitment

Seventy outpatients with episodic/persistent major depression, comorbidity and childhood maltreatment will be recruited. Key inclusion and exclusion criteria are:

Inclusion criteria:

1. Age eligibility: 18-65 years.
2. Episodic or persistent MDD or MDD superimposed on Dysthymia ("Double Depression") as the primary diagnosis (according to the SCID-5) [74].
3. A score of > 18 on the Hamilton Rating Scale for Depression (HRSD-24) [75].
4. History of CM: at least moderate to severe in one or more of the five CTQ-categories (emotional neglect, emotional abuse, physical neglect, physical abuse, sexual abuse) [15].
5. Any psychiatric comorbidity according to the SCID-5 except for those described in the exclusion criteria below.
6. Exceeding the 'cut-off' value of at least one of the following measures (module questionnaires): 1) Rejection Sensitivity Questionnaire (RSQ, [76]) ≥ 9.88, 2) Interpersonal Reactivity Index (IRI, [77]) < 45, or 3) Difficulties in Emotion Regulation Scale-16 (DERS-16, [78]) ≥ 55.73.
7. Written informed consent.

Exclusion criteria:

1. Acute risk of suicide.
2. Other current psychiatric disorders as primary diagnosis.
3. Comorbid schizophrenia, bipolar I disorder, organic disorder or substance dependence fulfilling criteria within the last 6 months.
4. Antisocial or borderline personality disorder (BPD). For BPD, up to three traits are allowed.
5. Severe cognitive impairment.
6. Serious medical condition (interfering with participation in regular sessions).
7. Other ongoing psychotherapy or psychotropic medication except antidepressant (e.g. selective serotonin reuptake inhibitor (SSRI) / serotonin–norepinephrine reuptake inhibitor (SNRI)) and/or sleep-inducing treatment at baseline if stable for at least three

weeks before inclusion (four weeks for fluoxetine). Rescue medication is benzodiazepine for a maximum of 2 weeks or on-demand.

Patients will be recruited through psychiatric and psychotherapeutic outpatient clinics and private practices by announcement of the psychotherapy treatment offers. Approximately 120 patients will be pre-screened for eligibility by research assistants via telephone with a brief pre-screening guide that has been successfully used in prior depression studies. A total of N=70 patients will be randomised (Figure 2).

[FIGURE 2]

Sample size

Due to the exploratory nature of the design and the lack of comparable studies, no formal sample size calculation is possible. One of the major aims of this trial is to generate pilot data for a subsequent sample size calculation for a confirmatory study. With reference to Billingham et al. [79] a medium sample size of 30 patients per group in pilot trials seems to be reasonable for the generation of pilot data for such estimation. That results in a total of 60 patients. Non-compliance and/or dropout of patients after randomization are assumed to be at most 14%. Therefore, 70 patients have to be randomized to observe the desired number of compliant patients, split in two groups for each of the two participating centres (FR=35, HD=35; Figure 2).

Outcomes

The primary endpoint is the *HRSD-24* measured by blind, independent raters at the conclusion of the 16-week treatment period. All secondary endpoints are describe in Table 1.

Table 1: Primary and secondary endpoints and corresponding measures.

Endpoint	Measure
Severity of depression (post treatment)	**Primary Endpoint**: Hamilton Rating Scale for Depression (HRSD-24) [75] at the end of treatment rated by trained and blinded clinicians.
Feasibility	Assessed by recruitment rates, distribution rates to the modules, and therapists' as well as patients' ratings (Therapeutic Element Checklist; WAI-SR, [80])
Severity of depression (FUP)	HRSD-24 six months after end of treatment rated by trained and blinded clinicians.
Social threat response system	**Module questionnaire:** The Rejection Sensitivity Questionnaire (RSQ) is a self-report questionnaire comprising 18 hypothetical interpersonal interactions with potential rejections by others (e.g. "You ask someone you don't know well out on a date"). It assesses the level of anxiety the patient feels about the outcome of each situation on a six point Likert scale ranging from "very

	unconcerned" to "very concerned". The RSQ shows good internal consistency and test-retest reliability, and is a reliable measure of the anxious-expectations-of-rejection component of rejection sensitivity. For the German version, the original has been translated, adapted, and shown to be a homogeneous measure with good psychometric properties [81].
Mentalizing of others' mental states / empathy	**Module questionnaire:** The Interpersonal Reactivity Index (IRI) is a 28-item self-report instrument that measures both cognitive and emotional aspects of empathy. Items are rated on a five-point Likert scale ranging from 0 ("does not describe me well") to 4 ("describes me very well"). The questionnaire comprises 4 subscales (7 items each): Perspective Taking (e.g. "I sometimes find it difficult to see things from the 'other guys' point of view."), Fantasy (e.g. "I daydream and fantasize, with some regularity, about things that might happen to me."), Empathic Concern (e.g. "I often have tender, concerned feelings for people less fortunate than me."), and Personal Distress (e.g. "I sometimes feel helpless when I am in the middle of a very emotional situation."). The German version of the IRI [82] was reduced to only four items per scale and showed good psychometric properties.
	The Mentalization Questionnaire (MZQ) [83] is a self-rating instrument for the assessment of mentalization in patients with mental disorders and consists of 15 items. The MZQ can be considered a practicable instrument with acceptable reliability and sufficient validity to assess mentalization in patients with mental disorders [83].
Emotion awareness and regulation	**Module questionnaire:** A validated shorter version of the DERS [84,78] with 16 items. For each of the DERS-16 items, participants are asked to "indicate how much it applies to your emotions right now" with response options ranging from 1 ("not at all") to 5 ("completely"). The questionnaire has four subscales: Non-acceptance (i.e., non-acceptance of current emotions), Modulate (i.e., difficulties modulating emotional and behavioural responses in the moment), Awareness (i.e., limited awareness of current emotions), and Clarity (i.e., limited clarity about current emotions). Results of the study provide support for the reliability and validity of the DERS-16 as a measure of emotion regulation difficulties.
Response and remission rates	Response is defined as a reduction in the HRSD-24 score by at least 50% from baseline and a total score of less than 16; remission is defined a priori as an HRSD-24 score of ≤ 8.
Social and Occupational Functioning	The clinician-rated Social and Occupational Functioning Assessment Scale (SOFAS) [85] assesses social role functioning irrespective of psychopathology.
Quality of Life	The WHO Quality of Life Instrument (WHOQOL-BREF) [86] is a short form tool consisting of 26 items divided into 4 domains (physical health, psychological health, social relationships, and the environment) to measure quality of life.
Self-rated depressive and anxiety symptoms	Self-ratings of depressive and anxiety symptoms will be obtained using the Beck Depression Inventory (BDI-II) [87] and the Beck Anxiety Inventory (BAI) [88].
Body connectedness	Self-ratings of body awareness and bodily dissociation will be obtained using the Scale of Body Connectedness (SBC) [90].
Therapeutic alliance	The Working Alliance Inventory-Short Revised (WAI-SR) [80] assesses three key aspects of the therapeutic alliance: (a) agreement on the tasks of therapy, (b) agreement on the goals of therapy and (c) development of an affective bond.
Course of depressive symptoms	Patients will fill out the Patient Health Questionnaire-9 (PHQ-9) [91] before every session to constantly monitor depressive symptom severity as a proxy of therapy progress or deterioration.
Therapeutic Element Checklist	All elements/strategies/components will be recorded immediately after each session including the approximate time the therapist used for applying those interventions using a Therapeutic Element Checklist designed for this feasibility trial.

A comprehensive overview about the frequency and scope of all trial visits including all assessments and measures is depicted below (figure 3).

[FIGURE 3]

Adherence

Study psychotherapists are in a completed or far advanced stage of psychotherapy training. All therapist will execute CBT as well as MoBa interventions after thorough training to ensure a high treatment quality (1.5-day training course in CBT, 2.5-day training course in MoBa). All trainings are led by clinical experts in the field. The training process for therapists includes the supervision of one pilot case in each arm and an adherence rating for study certification. To check for adherence in the further process and to support the supervision, a "Therapeutic Element Checklist" is filled out by the therapists immediately after each session. Supervisors will review the "Therapeutic Element Checklist" regularly in ongoing supervision. All therapy sessions will be videotaped for adherence and supervision. Every 5th session will be supervised by the responsible supervisor in biweekly video conference meetings and/or by written feedback. Two clinical experts will conduct the diagnostic training of raters in SCID-5, HRSD-24 and SOFAS and interrater reliability will be ensured.

Experimental intervention: Modular-Based Psychotherapy

The MoBa model complements standard CBT for depression with modules aiming at socio-emotional cognitive deficits and compiling specific strategies from CBASP, MBT and mindfulness (figure 1). Content and implementation of the three modules are illustrated in Table 2.

Table 2: Content and implementation of modules.

CBASP-Module	**Corresponding RDoC domain:**	Negative Valence System: Social Threat Response
	Indicative questionnaire:	Rejection Sensitivity Questionnaire (RSQ)
	Objective:	"Re-training" the negative valence system (social threat response) and reducing avoidance behaviour
The CBASP-Module includes interpersonal discrimination training between abusing and well meaning others based on continued safety signals given by the therapist [28]. As a first step, a so-called "*Significant Other History*" (SOH) is conducted, a short procedure listing significant others who left an interpersonal-emotional "stamp" in the patient's learning history. From the SOH, causal conclusions are derived (e.g. "Growing up with my mother led to the pervasive assumption that I have nothing to expect from others"). Based on the patient's assumptions about relationships the patient experienced in his/her history with abusive significant others, a proactive "*transference hypothesis*" is formulated stating the patient's most relevant interpersonal expectation/fear regarding the therapist-patient encounter The transference hypothesis is then systematically contrasted with the therapist´s actual behaviour in "*hot spot situations*", applying the structured "*Interpersonal Discrimination Exercise*". By means of this exposure procedure, the patient learns to differentiate the abusive significant other (generalized to his/her social environment) from current non-abusive or well-intended persons by discrimination learning. Thus, the patient is enabled to overlearn dysfunctional expectations and reprogram the conditioned social threat systems. In addition, by enriching safety signals in therapists' behaviour and re-establishing the perception of operant interpersonal contingencies, this intervention is designed to provide a secure learning environment to decrease interpersonal threat sensitivity. In addition, teaching the patient the mechanisms of complementary interpersonal processes illustrated by *Kiesler's circumplex model* [92] enables the patient to recognize the consequences of his/her own behaviour on other persons and to develop empathy ("reading		

others") and social problem-solving skills (element of CBASP). Genuine empathy and theory of mind skills are furthermore facilitated by the therapist´s "*Disciplined Personal Involvement*" (DPI) and more specifically "*Contingent Personal Reactivity*" (CPR), i.e. expressing personal emotional reactions to the patients´ dysfunctional behaviour patterns in a disciplined way (including considering a teachable moment and relating it to the patient´s core pathology) and offering alternative behaviour. The key objective of this module is social fear extinction by overlearning conditioned associations and avoidance behaviour.

Mentalising-Module	**Corresponding RDoC domain:**	System for Social Processes
	Indicative questionnaire:	Interpersonal Reactivity Index (IRI)
	Objective:	Enhancing perception and understanding of self and others (understanding mental states) and social communication

The Mentalising-Module contains modelling and teaching mentalising by learning to "read" others' behaviour and thereby re-connecting the patient to his/her social environment and creating social competence. To promote mentalised affectivity (i.e. mentalising own emotional states as described by MBT), the therapist introduces repetitive sequences to stimulate basic mentalising functions in the patient. Based on empathy, the therapist uses a "*not knowing*" stance of exploration of the patients' experiences and identifies context-related emotional reactions, raising "*what-questions*" rather than "why-questions". Two typical interventions to engage mentalising are the „*Stop and Stand*" and the „*Stop, Re-wind, Explore*" sequences [67]. In the first case, the therapist stops a patient who is stuck in drawing non-mentalising assumptions (e.g. "everybody hates me") by surprise or humour to subsequently help the patient to mentalise about his/her experiences. The second sequence generates a joined attention on the patient´s past experiences by shifting the focus back and forth within an episodic experience to make it accessible for the mentalising process. Genuine empathy and theory of mind skills are furthermore facilitated by the therapist´s "*Disciplined Personal Involvement*" (DPI; and more specifically "Contingent Personal Reactivity" (CPR) as an element of CBASP as well. The key objective of this module is to improve mentalising capabilities in social interactions.

Mindfulness-Module	**Corresponding RDoC domain:**	Arousal System: Hyperarousal
	Indicative questionnaire:	Difficulties in Emotion Regulation (DERS-16)
	Objective:	Reducing the arousal system (hyperarousal) referring to emotion awareness and regulation

This module integrates mindfulness-based exercises, which focus on a) observing non-judgmentally internal and external stimuli, b) shifting attention away from trauma-related inner "movies" and monitoring skills to c) overcome hyperarousal and experiential avoidance or being run over by one's emotions. Mindfulness-based interventions aim to change a person's perspective on his or her emotions and cognitions. This process is facilitated through mindfulness meditation (e.g., body scan, formal sitting meditation) in which close attention is paid to the present moment whilst thoughts, feelings and body sensations are noted with an attitude of curiosity, non-judgement, and acceptance of psychological experiences. Mindfulness has been suggested to be effective via four mechanisms: attention regulation, body awareness, changes in perspective on the self, and emotion regulation [93,94]. Mindfulness training enhances positive affect [95], decreases negative affect, and reduces maladaptive automatic emotional responses [96] being associated with changes in areas of the brain responsible for affect regulation and stress impulse reaction [97,93]. The key objective of this module is to improve emotion awareness and regulation in order to mitigate hyperarousal.

Selection of modules

The application of the modular intervention is preceded by a structured diagnostic assessment of the patient´s impaired systems (negative valence system, system of social processes, or arousal system) according to the scores on the 1) Rejection Sensitivity Questionnaire (RSQ; social threat response); 2) Interpersonal Reactivity Index (IRI; mentalization, empathy), and 3) Brief Version of the Difficulties in Emotion Regulation Scale (DERS-16; emotion awareness and regulation). The corresponding modular interventions will be applied if the cut-off value in one or more of these measures is exceeded. Since no a priori values are established, the cut-offs used here are defined as one standard deviation above the general population mean, i.e.

the upper 16% [81,78]. The problem(s) thus identified is/are assigned as the target for one, two or three of the modules (figure 3) according to the systematic treatment algorithm (figure 4).

[FIGURE 4]

Application of modules (time distribution)

The modules are not simply added as separate components, but rather integrated into the therapeutic process and course as add-on to the standard CBT procedure. Consequently, the amount of time spent with single CBT-techniques (e.g. cognitive restructuring) will be reduced with increasing number of modules and the procedure will be condensed to behavioural activation (e.g. identifying and promoting pleasant activities) as the most effective component of CBT [98]. Depending on the selected number of modules, approximately one third of the time will be spent with basic CBT procedures and two thirds of the time with the application of modules. Therapists will document the time, which is spent with CBT procedures or with single modules, after each session.

Control intervention: CBT

CBT will be delivered according to the German standard manual by Hautzinger [99]. The main CBT elements are 1. establishing therapeutic relationship, 2. psychoeducation, 3. behaviour activation, 4. cognitive restructuring, and 5. maintenance and relapse prevention. CBT has been shown to be efficacious in depressed patients in prior clinical trials [100,101], but not specifically in this subgroup of depressed and comorbid patients exposed to CM.

Randomisation

The randomisation code will be generated by the Clinical Trials Unit Freiburg (CTU) using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Randomisation will be performed, stratified by site, in blocks of variable length in a ratio of 1:1. The block lengths will be documented separately and will not be disclosed to the sites. The randomisation code will be produced by validated programs

based on the Statistical Analysis System (SAS). This dataset is included in Redcap so that patients can be randomised directly in the eCRF.

Blinding

All clinical ratings will be completed by trained and independent raters blinded to treatment assignment. Each of the sites implements procedures to mask a patient treatment assignment from the person who will evaluate the results of the clinical ratings through the following: 1) locating the raters at a separate physical location, and 2) reminding the patients at each visit not to mention anything that might reveal their treatment condition to the independent evaluator.

Data Management and Monitoring

Study data will be entered in pseudonymised form in a study database by authorized and trained members of the study team via electronic case report forms (eCRF). The data management will be performed with REDCap™ Version 9, a fully web based remote data entry system based on web forms, which is developed and maintained by the REDCap Consortium (redcap@vanderbilt.edu). This system uses built-in security features to prevent unauthorized access to patient data, including an encrypted transport protocol for data transmission from the participating sites to the study database. An audit trail provides a history of the data entered, changed, or deleted, indicating the processor and date. Monitoring is performed by CTU. Risk-based monitoring will be done according to ICH-GCP E6 (R2) and standard operating procedures (SOP) to ensure patient`s safety and integrity of clinical trial data.

Statistical Analysis

Before the start of the final analysis, a detailed statistical analysis plan will be prepared. This will be completed during the 'blind review' of the data, at the latest. The primary efficacy analysis will be performed according to the intention-to-treat (ITT) principle and will therefore be based on the full analysis set including all randomized patients. Patients are analysed as randomised regardless of any protocol deviations. This analysis corresponds to the analysis of the treatment policy estimand. The effects of CBT and MoBa with respect to the HRSD-24

score after 16 weeks of treatment (primary endpoint) will be estimated within a linear regression model, and the two-sided 95% confidence interval will be calculated for the treatment effect. The model will include treatment and study centre as independent variables, as well as baseline HRSD-24 score. A conservative assumption of the effect size anticipated for the subsequent confirmative trial will be derived from these analyses by a combination of clinical and statistical judgement. Secondary endpoints will be analysed descriptively in a similar fashion as the primary outcome, using regression models as appropriate for the respective type of data. Treatment effects will be calculated with two-sided 95% confidence intervals. All secondary analyses are exploratory and are interpreted in a descriptive fashion.

The safety analysis includes calculation and comparison of frequencies and rates of serious adverse events. Furthermore, statistical methods are used to assess the quality of data and the homogeneity of intervention groups. Data should be collected regardless of the patients' adherence to the protocol, especially on the clinical outcome, to obtain the best approximation to the full analysis set. Data should also be collected on other therapies received post dropout. Patients with missing follow-up will be excluded. As the only available measurement of the patient is taken at baseline and the primary aim is feasibility, this can be considered as an adequate strategy. The reasons for missing post baseline values will be collected and will be taken into consideration for the subsequent confirmatory trial.

Study results will be reported according to CONSORT guidelines. Further details of the statistical analysis will be fixed before data base lock and start of the analysis. The responsible biostatistician will remain blind for treatment allocation throughout the study. For further information regarding the statistical analysis, see the extensive study protocol publicly accessible at https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00022093.

Ethics and dissemination:

This study obtained approval from the independent Ethics Committees of the University of Freiburg in August 2020 and the University of Heidelberg in October 2020. Additionally, the administrative department for governance and quality of the University Medical Center

Freiburg verified GCP conformity. All findings will be disseminated broadly via peer-reviewed articles in scientific journals and contributions to national and international conferences.

Consent to participate

At first contact, all prospects will be informed about the study in detail and will receive standardized participant information sheets. At screening, voluntary written informed consent for study participation and storage, evaluation and transfer of study-related data will be obtained from each study participant by research associates of the respective study centre. Withdrawal of written consent is possible at any time, without giving reasons. In the event of a withdrawal of the informed consent, patients can decide whether their data should be deleted or destroyed or whether they can be used in anonymised form for this research project.

Safety/harms

Side effects of evidence- based psychotherapies are fortunately rather rare (e.g. [102,103]). According to the most recent meta-analysis, only approximately 5% of patients deteriorate while in psychotherapeutic treatment [3]. Adverse Events (AE; e.g. private/occupational stress or conflicts in the patient-therapist relationship) and Serious Adverse Events (SAE; e.g. severe events requiring stationary medical treatment or with potential permanent damage) are screened for at every assessment or therapy session. AEs have to be reported to the principal investigators (ES, SH) and SAEs to the independent experts. In addition, on-site data monitoring will be regularly conducted by a clinical monitor from CTU to ensure patients' safety and integrity of the clinical data in adherence to the study protocol, as well as to check data quality and accuracy. Individual trial participation will be stopped if one of the following discontinuation criteria occurs:

a) Active suicidality
b) The physical health of the patient is at risk according to clinical judgment
c) Occurrence of an AE/SAE with therapeutic implications incompatible with the study
d) Newly occurring exclusion criteria (demanding further procedures not compatible with the continuation of the study participation)

e) Withdrawal of the informed consent

If the study principal investigator or the co-principal investigator have serious ethical concerns because of the performance at one of the sites or severe safety concerns become apparent to the independent experts, the whole trial will be discontinued.

Trial Status

Official study begin was in May 2020. The first patient was included in December 2020. Within the first months of recruiting, there were no difficulties regarding the recruitment and inclusion of eligible patients, or the implementation of the MoBa and CBT treatments. Due to the ongoing COVID-19 pandemic, all in person contacts (assessments as well as psychotherapy sessions) are done while wearing appropriate face masks (surgical or FFP2) according to the national guidelines and the respective guidelines of the University Medical Centers in Freiburg and Heidelberg. The end of treatment is expected for July 2022 and data collection aims to be completed in March 2023.

Discussion

Most evidence-based treatment protocols are single-disorder-specific manuals disregarding common comorbidities and transdiagnostic clinical phenomena as sequelae of early trauma and childhood adversities. This leaves a mismatch between the available disorder-specific manuals and the clinical reality. Many clinicians consider the use of evidence-based manuals as challenging or even inadequate for their daily work and report resistances to the 'oversimplified', 'rigid', 'inflexible' or 'flawed' rationales and the 'extensive efforts' needed to maintain up-to-date knowledge by ongoing training [104]. Even attending evidence-based workshops has little impact on clinicians' decisions to use evidence-based treatment protocols in their practice resulting in the well-known underutilization in community settings [105,106]. In contrast to conventional evidence-based treatment protocols, a modular-based psychotherapy supports the eclectic approach of most clinicians by providing them with an evidence-based treatment algorithm to combine and integrate available treatment modules as independent but combinable sets of functional units systematically. This reduces the perceived challenges of

using evidence-based approaches by ensuring a high flexibility and goodness-of-fit within a systematic framework for personalised treatments. By optimally tailoring module selection and application to the specific needs of each patient, MoBa has great potential to improve the currently unsatisfying results of psychotherapeutic treatments in research and clinical practice as a bridge between disorder-specific and personalised approaches.

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Patient and public involvement

Neither patients nor public were systematically involved in designing this study. Feedback is constantly collected from participants on their experience of participating and implemented in conducting this trial. The main results will be disseminated to trial participants and systematic patient and public involvement in the development of a subsequent multicentre confirmatory trial will be implemented.

Competing interests

The authors declare the following competing interests: ME received minor book royalties. SH received minor royalties for books with chapters on modular psychotherapy. HP and CJ declare no competing interests. MH received book royalties from several publishers. ES received book royalties and honoraria for workshops and presentations relating to Interpersonal Psychotherapy and CBASP.

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Authors contributions

ME, ES and SH were the main contributors in drafting this manuscript. ES and SH were the main contributors in designing this study with support by ME. CJ provided expertise on data monitoring, data management and statistical analyses. All authors provided feedback on the initial draft of the manuscript and read and approved the final version.

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Figure and Table Legends

Figure 1: Overview of the targeted RDoC domains and their corresponding objectives, assessments and modules. A detailed description of the modules is given below.

Figure 2: Trial design and flow of patients.

Table 1: Primary and Secondary Endpoints and corresponding measures.

Figure 3. Frequency and scope of trial visits.

Figure 4: Decision Tree Algorithm for Modular-Based Psychotherapy.

Table 2: Content and implementation of modules.

Figure 1: Overview of the targeted RDoC domains and their corresponding objectives, assessments and modules. A detailed description of the modules is given below.

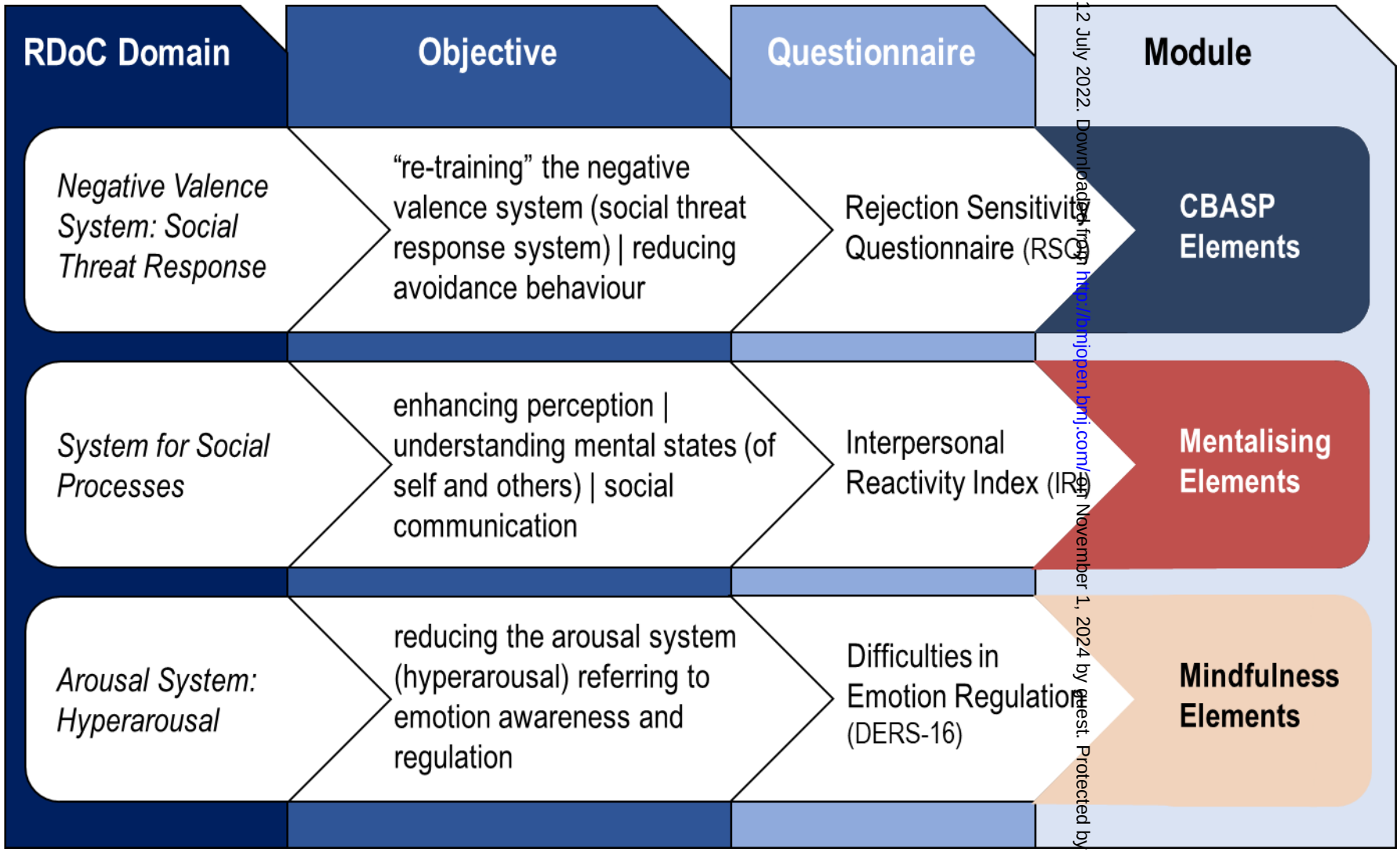


Figure 2: Trial design and flow of patients.

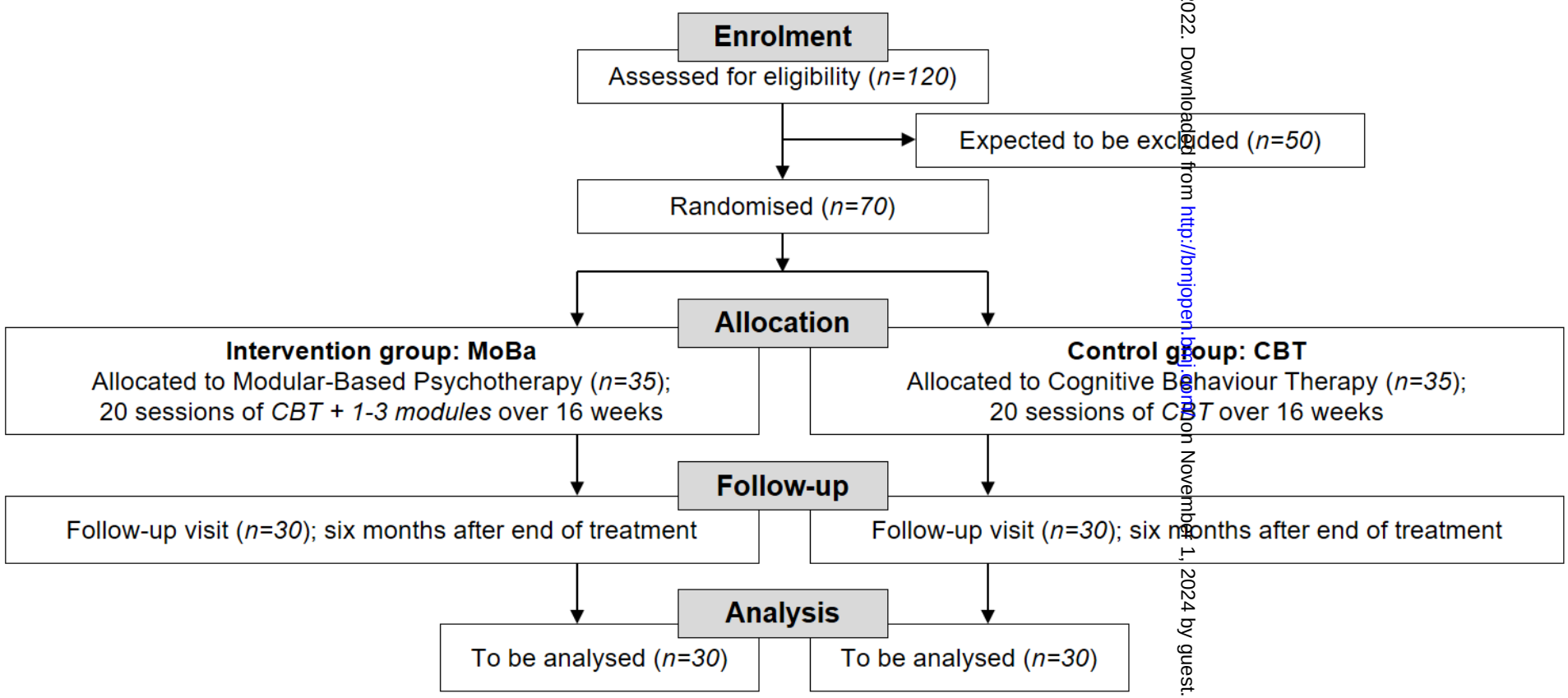
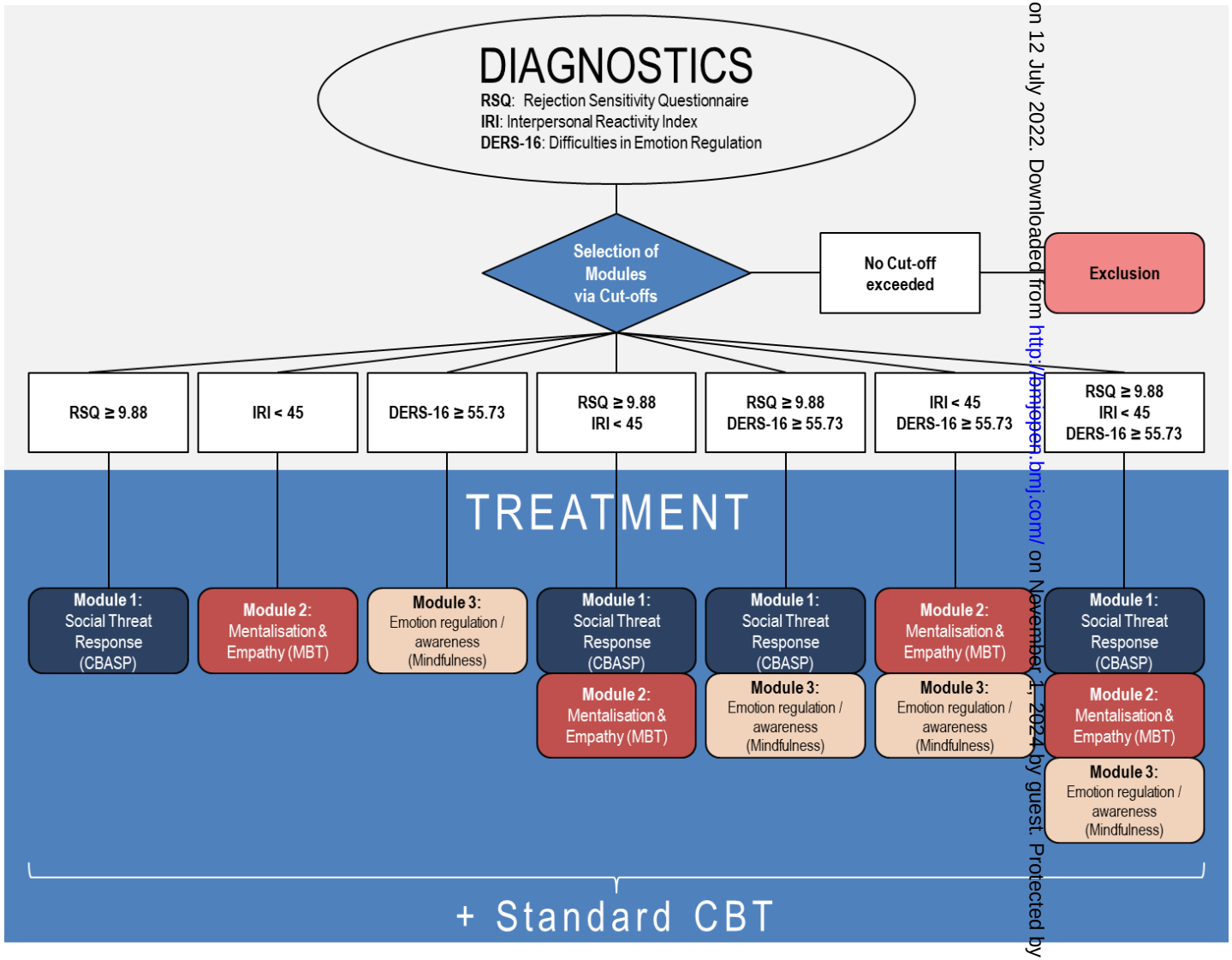


Figure 3. Frequency and scope of trial visits.

		Visits	Pre-screening	Screening	T0 Baseline	*Treatment: MoBa vs. CBT*			T1 Post	T2 Follow-up
		Week(s)	-	-	0	1-4	5-15	16	16	42
THERAPISTS		Sessions per week				2	1	1		
	Questionnaires	Therapeutic Element Checklist				X	X	X		
	Questionnaires	AE / SAE				X	X	X		
	Questionnaires	PHQ-9				X	X	X		
	Questionnaires	WAI-P / WAI-T						X		
RATERS	Interview	telephone screening	(X)							
	Interview	SCID-5 (CV/PD)		X						
	Interview	HRSD-24		X	(X)				X	X
	Interview	SOFAS			X				X	X
	Interview	AE / SAE			(X)				X	X
	Questionnaires	CTQ		X						
	Questionnaires	RSQ		X					X	X
	Questionnaires	IRI		X					X	X
	Questionnaires	DERS-16		X					X	X
	Questionnaires	MZQ			X				X	X
	Questionnaires	BDI-II			X				X	X
	Questionnaires	BAI			X				X	X
	Questionnaires	WHOQoL-BREF			X				X	X
	Questionnaires	PHQ-9			X				X	X
	Questionnaires	ECR-RD8			X				X	X
	Questionnaires	SBC			X				X	X

Figure 4: Decision Tree Algorithm for Modular-Based Psychotherapy.



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	p.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	19-20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	19-20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19-20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-8
	6b	Explanation for choice of comparators	4-8
Objectives	7	Specific objectives or hypotheses	8

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-16
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17-18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15/17-18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16-17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16/19
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	17/19
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

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

BMJ Open

Modular-Based Psychotherapy (MoBa) versus Cognitive Behavioural Therapy (CBT) for patients with comorbid depression and a history of childhood maltreatment: Study protocol for a randomised controlled feasibility trial

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Modular-Based Psychotherapy (MoBa) versus Cognitive Behavioural Therapy (CBT) for patients with comorbid depression and a history of childhood maltreatment: Study protocol for a randomised controlled feasibility trial

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Abstract

Introduction: In depression treatment, most patients do not reach response or remission with current psychotherapeutic approaches. Major reasons for individual non-response are interindividual heterogeneity of etiological mechanisms and pathological forms, and a high rate of comorbid disorders. Personalised treatments targeting comorbidities as well as underlying transdiagnostic mechanisms and factors like early childhood maltreatment may lead to better outcomes. A Modular-Based Psychotherapy (MoBa) approach provides a treatment model of independent and flexible therapy elements within a systematic treatment algorithm to combine and integrate existing evidence-based approaches. By optimally tailoring module selection and application to the specific needs of each patient, MoBa has great potential to improve the currently unsatisfying results of psychotherapy as a bridge between disorder-specific and personalised approaches.

Methods and analysis: In a randomised controlled feasibility trial (RCT), N=70 outpatients with episodic or persistent major depression, comorbidity and childhood maltreatment are treated in 20 individual sessions with MoBa or standard Cognitive Behavioural Therapy (CBT) for depression. The three modules of MoBa focus on deficits associated with early childhood maltreatment: the systems of negative valence, social processes, and arousal. According to a specific questionnaire-based treatment algorithm, elements from Cognitive Behavioral Analysis System of Psychotherapy (CBASP), Mentalization-Based Psychotherapy (MBT) and/or Mindfulness (MBCT) are integrated for a personalised modular procedure.

As a proof of concept, this trial will provide evidence for the feasibility and efficacy (post-treatment and six month follow-up) of a modular add-on approach for patients with depression, comorbidities and a history of childhood maltreatment. Crucial feasibility aspects include targeted psychopathological mechanisms, selection (treatment algorithm), sequence and application of modules, as well as training and supervision of the study therapists.

Ethics and dissemination: This study obtained approval from the independent Ethics Committees of the University of Freiburg and the University of Heidelberg. All findings will be

disseminated broadly via peer-reviewed articles in scientific journals and contributions to national and international conferences.

Trial registration: German Clinical Trials Register (www.drks.de): DRKS00022093.

Keywords: Modular-Based Psychotherapy | Cognitive Behavioural Therapy | Depression | Childhood Maltreatment | Treatment Algorithm | Personalised | Randomised Controlled Trial | Cognitive Behavioral Analysis System of Psychotherapy | Mentalization-Based Psychotherapy | Mindfulness

Abstract Summary

Strengths and limitations of this study

- This is the first study to investigate the feasibility of a Modular-Based Psychotherapy (MoBa) approach for patients with comorbid depression and a history of childhood maltreatment generating effect estimates for subsequent confirmatory trials.
- Clinicians will be provided with an evidence-based treatment algorithm to combine available treatment modules systematically instead of ad libitum eclecticism.
- Using Cognitive Behavioural Therapy (CBT) as control condition represents a strong comparator for a rigorous evaluation with a high generalizability to the clinical reality.
- Since no a priori values are established, the algorithm cut-offs used here are based on general population means of self-rated questionnaires.
- Due to the limited sample size of this feasibility study (N=70), statistical analyses will be limited to exploratory comparisons of MoBa versus CBT, since tests between different modules within the MoBa intervention arm are not sufficiently powered.

Introduction

Until recently, depressive disorders have been predominantly conceptualized and researched with a focus on the primary diagnosis. This has led to the development of several disorder-specific approaches such as the Cognitive Behavioural Therapy (CBT) [1] and the Interpersonal Psychotherapy (IPT) [2]. While these approaches (among others) have proven efficacy in unipolar major depression, there is a large proportion of patients who do not respond (more than 50%) or do not reach full remission (about two thirds) with first line treatment [3], even when the procedure is in accordance with treatment guidelines [4,5]. Major reasons for individual non-response and non-remission include interindividual heterogeneity of etiological mechanisms of depression and high rates of comorbid disorders of up to 80% in clinical and epidemiological studies [6-8]. Particularly anxiety disorders and Cluster C personality disorders are highly prevalent in Major depressive disorder (MDD) [9]. These comorbid disorders typically predict poorer treatment outcomes for MDD [10-13] or longer time to remission [14].

Childhood maltreatment

One major transdiagnostic factor associated with cognitive, emotional, behavioural and interpersonal dysfunctions common to a wide range of disorders is childhood maltreatment (CM). CM has most frequently been operationalized based on the Childhood Trauma Questionnaire (CTQ) [15], defined as onset reported before the age of 18 and meeting the criterion of at least “moderate to severe” on one of the five trauma subtypes (emotional abuse, emotional neglect, physical abuse, physical neglect, sexual abuse). In depressive disorders, CM is highly prevalent (~46%) [16], especially in early-onset and persistent depression with up to 80% [17,18]. An emerging body of evidence suggests a significant relationship between emotional maltreatment (abuse and/or neglect) in particular and depression [19-22]. Maltreated individuals are 2.7 to 3.7 times more likely to develop depression in adulthood, have an earlier depression onset and are twice as likely to develop a chronic or treatment-resistant course [16]. CM was also associated with an elevated risk for comorbid disorders [23,18]. Treated with psychotherapy and pharmacotherapy, the probability of non-response is 1.9 times

higher in depressed patients with early trauma compared to those without [16]. Taken together, study results indicate that interpersonal trauma exposure complicates the treatment of depression and reduces the impact of traditional cognitive therapy or treatments such as psychoeducation, TAU, or pharmacotherapy [24]. However, some approaches like Mindfulness Based Cognitive Therapy (MBCT) [25] or the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) [26-28] show promising results in the subgroup of depressed patients with CM.

Impact of childhood maltreatment on social and emotional functioning

A growing body of evidence links interpersonal trauma in both youth and adults to difficulties in social and emotional functioning [24]. Among other sequelae, CM usually results in marked avoidance behaviour [9] with negative social consequences and in concomitant retardation of emotional maturational growth [28,29]. These deficits are also expressed in terms of social threat hyperresponsivity (i.e. being highly sensitive to social rejection and anxiously expecting, readily perceiving, and overreacting to it) [30-33], social stress and avoidance behaviour [34,35], lack of empathy and theory-of-mind [36-38] and emotional dysregulation [39,40]. These emotional and social dysfunctions are mediated in common brain circuits for emotion and salience regulation, fear, and mentalising, suggesting that abnormalities in these functional pathways may be induced by CM [41,42]. Despite these severe consequences of CM and their important implications for treatment, disorder-specific approaches for depression such as CBT or IPT do not specifically address the role of CM and the affected dimensions of functioning.

Personalised Treatments

This calls for personalised treatments that target both comorbidities as well as underlying mechanisms and factors, which are central to the development and maintenance of psychological disorders. One of the challenges in the development of personalised approaches is to select treatment modules for targeted dysfunctions and to determine whether and in which sequence to combine them with standard treatment. In daily practice, it is left to the clinical

judgement and expertise of the therapist to address the patient´s individual needs and comorbidities by adding various therapeutic strategies to the disorder-specific interventions. However, this choice of add-on strategies is not backed up by empirical evidence and thus hardly conveyable to usual clinical practice in a systematic way [43]. Driven by these concerns, there has been growing consensus that a novel approach is needed in the way we classify, formulate, treat, and prevent depression and other mental disorders [44,45]. Insel and Cuthbert [46] postulated the concept of Research Domain Criteria (RDoC) to move "toward a new classification system" of studying and validating transdiagnostic, dimensional constructs since psychiatric diagnosis seem to be no longer optimal as long as they remain restricted to symptoms and signs. The transdiagnostic procedure focuses on identifying the common and core maladaptive temperamental, cognitive, emotional, interpersonal and behavioural characteristics that underpin a broad array of diagnostic presentations [47] and addresses them via specific modules in treatment [48]. In this sense, a modular-based psychotherapy provides a structured approach of tailoring treatments to fit patient needs by allowing greater flexibility to consider interindividual differences and comorbidity [49,50]. The modules, as sets of independent but combinable functional units, focus on common transdiagnostic dysfunctions and offer skills to improve e.g. emotion regulation, social competence, empathy, or self-motivation. There is only one study [51] in which emotion regulation skills were successfully added to CBT in depressed patients that had sufficient statistical power to detect a clinically significant effect.

Modular-Based Psychotherapy (MoBa)

Empirical support for the effectiveness of modular approaches following decision flowcharts is emerging lately [50,52]. For instance, Weisz and colleagues [49] conducted a large randomized controlled trial (RCT) in which a Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH) outperformed standard manual treatment as well as care as usual (CAU). The superiority of MATCH was found to be sustained in a two-year follow-up [53] and was replicated in a more recent trial [54]. Another example of a modular approach to psychotherapy is Behavioural Interventions for Anxiety in Children with

Autism (BIACA) [55]. By using a modular format and including an algorithm to guide the selection of modules, it offers a treatment approach for several anxiety disorders and obsessive-compulsive disorder for youths on the autism spectrum. BIACA was superior to waitlist and CAU in several RCTs (e.g. [56]). In adults, a recent RCT [57] assessed the feasibility and efficacy of a modular transdiagnostic intervention for mood, stressor-related and anxiety disorders (HARMONIC trial) in preparation for a later-stage trial. The modular transdiagnostic intervention demonstrated superiority with moderate effect sizes compared to psychological treatment-as-usual [58]. This represents early signs of a significant paradigm shift away from single-diagnosis approaches towards dimensional, transdiagnostic, and modular-based conceptualizations [59,46].

The here proposed rationale for a modular-based psychotherapy (MoBa) for depressed patients with comorbidity and a history of CM is two-fold: First, to include patients regularly seen in clinical practice showing a) more often comorbid and heterogeneous complaints than the samples usually included in RCTs and b) a limited treatment response to standard disorder-specific approaches. Second, tailoring the treatment to the specific characteristics and needs of patients with CM and comorbid depression can ensure that the psychotherapeutic process is responsive and may reach better treatment results. The MoBa intervention aims at interpersonal and emotional maturation by overcoming social threat hypersensitivity and interpersonal avoidance patterns and improving poor mentalisation as well as poor emotion regulation capacities. The rationale is supported by previous trials with empirically supported treatments such as CBASP for chronic depression [60-63], MBCT for depression prevention and treatment [64-67], and Mentalization-Based Therapy (MBT) [68] for borderline personality disorder [69,70]. In the here used design, MoBa complements standard CBT with modules compiling specific elements from CBASP, MBCT, and MBT focusing on three disturbed systems (Figure 1). Those systems are part of the RDoC model and have been shown to be critically related to CM:

I) the negative valence system (acute, potential, and sustained threat): social threat response and avoidance behaviour [34,9];

II) the system of social processes: perception and understanding of self and others (understanding mental states), social communication, attachment [71,37,38];

III) the arousal system: emotion awareness and arousal regulation [40,72-74].

[FIGURE 1]

Objectives

This pilot study has a number of objectives appropriate to its status as a feasibility study:

1. Providing initial evidence for the efficacy of MoBa (reduction of clinician-rated depressive symptoms) as well as generating pilot data for the power calculation in terms of effect and sample size for a subsequent multicentre confirmatory trial.
2. Investigating the planned study design regarding the feasibility of recruitment, feasibility of applying cut-off values of self-reported deficits to select the modules, acceptability of the program to therapists and patients as well as patient ratings of 'usefulness' (both overall and in terms of individual modules). A crucial goal is to refine the algorithm for the selection of modules based on questionnaires.
3. Explore potential moderators of the primary outcome (in a hypothesis-generating exercise and to help refine the intervention).

Methods and analysis

Study design

The bicentric study will be conducted at the Department of Psychiatry and Psychotherapy, University Medical Centre Freiburg, Germany, and the Department of General Psychiatry, University Medical Centre Heidelberg, Germany. It is a parallel-arm RCT (N=70) comparing MoBa with CBT in 20 individual sessions over 16 weeks of treatment (twice weekly in weeks 1-4, then once per week in weeks 5-16). Participants will be assessed at screening, baseline, post-treatment and follow-up (six months after end of treatment).

Study population and recruitment

Seventy outpatients with episodic/persistent major depression, comorbidity and childhood maltreatment will be recruited. Key inclusion and exclusion criteria are:

Inclusion criteria:

1. Age eligibility: 18-65 years.
2. Episodic or persistent MDD or MDD superimposed on Dysthymia ("Double Depression") as the primary diagnosis (according to the SCID-5) [75].
3. A score of > 18 on the Hamilton Rating Scale for Depression (HRSD-24) [76].
4. History of CM: at least moderate to severe in one or more of the five CTQ-categories (emotional neglect, emotional abuse, physical neglect, physical abuse, sexual abuse) [15].
5. At least one psychiatric comorbidity or more according to the SCID-5 (except for those described in the exclusion criteria below).
6. Exceeding the 'cut-off' value of at least one of the following measures (module questionnaires): 1) Rejection Sensitivity Questionnaire (RSQ, [77]) ≥ 9.88, 2) Interpersonal Reactivity Index (IRI, [78]) < 45, or 3) Difficulties in Emotion Regulation Scale-16 (DERS-16, [79]) ≥ 55.73.
7. Written informed consent.

Exclusion criteria:

1. Acute risk of suicide.
2. Other current psychiatric disorders as primary diagnosis.
3. Comorbid schizophrenia, bipolar I disorder, neurocognitive disorder or substance dependence fulfilling criteria within the last 6 months.
4. A diagnosis of antisocial personality disorder or more than three traits of borderline personality disorder (BPD) according to SCID-5 PD.
5. Severe cognitive impairment.
6. Serious medical condition (interfering with participation in regular sessions).

7. Other ongoing psychotherapy or psychotropic medication except antidepressant (e.g. selective serotonin reuptake inhibitor (SSRI) / serotonin–norepinephrine reuptake inhibitor (SNRI)) and/or sleep-inducing treatment at baseline if stable for at least three weeks before inclusion (four weeks for fluoxetine). The continuous intake of benzodiazepine is prohibited; the selective use of benzodiazepine as rescue medication on-demand for a maximum of two weeks is permitted.

Patients will be recruited through psychiatric and psychotherapeutic outpatient clinics and private practices by announcement of the psychotherapy treatment offers. Approximately 120 patients will be pre-screened for eligibility by research assistants via telephone with a brief pre-screening guide that has been successfully used in prior depression studies. A total of N=70 patients will be randomised (Figure 2).

[FIGURE 2]

Sample size

Due to the exploratory nature of the design and the lack of comparable studies, no formal sample size calculation is possible. One of the major aims of this trial is to generate pilot data for a subsequent sample size calculation for a confirmatory study. With reference to Billingham et al. [80] a medium sample size of 30 patients per group in pilot trials seems to be reasonable for the generation of pilot data for such estimation. That results in a total of 60 patients. Non-compliance and/or dropout of patients after randomization are assumed to be at most 14%. Therefore, 70 patients have to be randomized to observe the desired number of compliant patients, split in two groups for each of the two participating centres (FR=35, HD=35; Figure 2).

Outcomes

The primary endpoint is the *HRSD-24* measured by blind, independent raters at the conclusion of the 16-week treatment period. All secondary endpoints are describe in Table 1.

Table 1: Primary and secondary endpoints and corresponding measures.

Endpoint	Measure
Severity of depression	**Primary Endpoint**: Hamilton Rating Scale for Depression (HRSD-24) [76] at the end of treatment rated by trained and blinded clinicians.

(post treatment)	
Feasibility	Assessed by recruitment rates, distribution rates to the modules, and therapists' as well as patients' ratings (Therapeutic Element Checklist; WAI-SR, [81])
Severity of depression (FUP)	HRSD-24 six months after end of treatment rated by trained and blinded clinicians.
Social threat response system	**Module questionnaire:** The Rejection Sensitivity Questionnaire (RSQ) is a self-report questionnaire comprising 18 hypothetical interpersonal interactions with potential rejections by others (e.g. "You ask someone you don't know well out on a date"). It assesses the level of anxiety the patient feels about the outcome of each situation on a six point Likert scale ranging from "very unconcerned" to "very concerned". The RSQ shows good internal consistency and test-retest reliability, and is a reliable measure of the anxious-expectations-of-rejection component of rejection sensitivity. For the German version, the original has been translated, adapted, and shown to be a homogeneous measure with good psychometric properties [82].
Mentalising of others' mental states / empathy	**Module questionnaire:** The Interpersonal Reactivity Index (IRI) is a 28-item self-report instrument that measures both cognitive and emotional aspects of empathy. Items are rated on a five-point Likert scale ranging from 0 ("does not describe me well") to 4 ("describes me very well"). The questionnaire comprises 4 subscales (7 items each): Perspective Taking (e.g. "I sometimes find it difficult to see things from the 'other guys' point of view."), Fantasy (e.g. "I daydream and fantasize, with some regularity, about things that might happen to me."), Empathic Concern (e.g. "I often have tender, concerned feelings for people less fortunate than me."), and Personal Distress (e.g. "I sometimes feel helpless when I am in the middle of a very emotional situation."). The German version of the IRI [83] was reduced to only four items per scale and showed good psychometric properties.
	The Mentalization Questionnaire (MZQ) [84] is a self-rating instrument for the assessment of mentalisation in patients with mental disorders and consists of 15 items. The MZQ can be considered a practicable instrument with acceptable reliability and sufficient validity to assess mentalisation in patients with mental disorders [84].
Emotion awareness and regulation	**Module questionnaire:** A validated shorter version of the DERS [85,79] with 16 items. For each of the DERS-16 items, participants are asked to "indicate how much it applies to your emotions right now" with response options ranging from 1 ("not at all") to 5 ("completely"). The questionnaire has four subscales: Non-acceptance (i.e., non-acceptance of current emotions), Modulate (i.e., difficulties modulating emotional and behavioural responses in the moment), Awareness (i.e., limited awareness of current emotions), and Clarity (i.e., limited clarity about current emotions). Results of the study provide support for the reliability and validity of the DERS-16 as a measure of emotion regulation difficulties.
Response and remission rates	Response is defined as a reduction in the HRSD-24 score by at least 50% from baseline and a total score of less than 16; remission is defined a priori as an HRSD-24 score of ≤ 8.
Social and Occupational Functioning	The clinician-rated Social and Occupational Functioning Assessment Scale (SOFAS) [86] assesses social role functioning irrespective of psychopathology.
Quality of Life	The WHO Quality of Life Instrument (WHOQOL-BREF) [87] is a short form tool consisting of 26 items divided into 4 domains (physical health, psychological health, social relationships, and the environment) to measure quality of life.
Self-rated depressive and anxiety symptoms	Self-ratings of depressive and anxiety symptoms will be obtained using the Beck Depression Inventory (BDI-II) [88] and the Beck Anxiety Inventory (BAI) [89].
Attachment	The Experiences in Close Relationships – Revised (ECR-R) [90] scale assesses attachment in adults.
Body connectedness	Self-ratings of body awareness and bodily dissociation will be obtained using the Scale of Body Connectedness (SBC) [91].
Therapeutic alliance	The Working Alliance Inventory-Short Revised (WAI-SR) [81] assesses three key aspects of the therapeutic alliance: (a) agreement on the tasks of therapy, (b) agreement on the goals of therapy and (c) development of an affective bond.
Course of depressive symptoms	Patients will fill out the Patient Health Questionnaire-9 (PHQ-9) [92] before every session to constantly monitor depressive symptom severity as a proxy of therapy progress or deterioration.
Therapeutic Element Checklist	All elements/strategies/components will be recorded immediately after each session including the approximate time the therapist used for applying those interventions using a Therapeutic Element Checklist designed for this feasibility trial.

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A comprehensive overview about the frequency and scope of all trial visits including all assessments and measures is depicted below (figure 3).

[FIGURE 3]

Adherence

Study psychotherapists are in a completed or far advanced stage of psychotherapy training. All therapist will execute CBT as well as MoBa interventions after thorough training to ensure a high treatment quality (1.5-day training course in CBT, 2.5-day training course in MoBa). All trainings are led by clinical experts in the field. The training process for therapists includes the supervision of one pilot case in each arm and an adherence rating for study certification. To check for adherence in the further process and to support the supervision, a "Therapeutic Element Checklist" is filled out by the therapists immediately after each session. Supervisors will review the "Therapeutic Element Checklist" regularly in ongoing supervision. All therapy sessions will be videotaped for adherence and supervision. Every 5th session will be supervised by the responsible supervisor in biweekly video conference meetings and/or by written feedback. Two clinical experts will conduct the diagnostic training of raters in SCID-5, HRSD-24 and SOFAS and interrater reliability will be ensured.

Experimental intervention: Modular-Based Psychotherapy

The MoBa model complements standard CBT for depression with modules aiming at socio-emotional cognitive deficits and compiling specific strategies from CBASP, MBT and mindfulness (figure 1). Content and implementation of the three modules are illustrated in Table 2.

Table 2: Content and implementation of modules.

CBASP-Module	**Corresponding RDoC domain:**	Negative Valence System: Social Threat Response
	Indicative questionnaire:	Rejection Sensitivity Questionnaire (RSQ)
	Objective:	"Re-training" the negative valence system (social threat response) and reducing avoidance behaviour
The CBASP-Module includes interpersonal discrimination training between abusing and well meaning others based on continued safety signals given by the therapist [28]. As a first step, a so-called "*Significant Other History*" (SOH) is conducted, a short procedure listing significant others who left an interpersonal-emotional "stamp" in the patient's learning history. From the SOH, causal conclusions are derived (e.g. "Growing up with my mother led to the pervasive assumption that I have nothing to expect from others"). Based on the patient's assumptions about relationships the patient experienced in his/her history with abusive significant others, a proactive "*transference hypothesis*" is formulated stating the patient's most relevant interpersonal expectation/fear regarding the therapist-patient		

encounter The transference hypothesis is then systematically contrasted with the therapist´s actual behaviour in "*hot spot situations*", applying the structured "*Interpersonal Discrimination Exercise*". By means of this exposure procedure, the patient learns to differentiate the abusive significant other (generalized to his/her social environment) from current non-abusive or well-intended persons by discrimination learning. Thus, the patient is enabled to overlearn dysfunctional expectations and reprogram the conditioned social threat systems. In addition, by enriching safety signals in therapists' behaviour and re-establishing the perception of operant interpersonal contingencies, this intervention is designed to provide a secure learning environment to decrease interpersonal threat sensitivity. In addition, teaching the patient the mechanisms of complementary interpersonal processes illustrated by *Kiesler's circumplex model* [93] enables the patient to recognize the consequences of his/her own behaviour on other persons and to develop empathy ("reading others") and social problem-solving skills (element of CBASP). Genuine empathy and theory of mind skills are furthermore facilitated by the therapist´s "*Disciplined Personal Involvement*" (DPI) and more specifically "*Contingent Personal Reactivity*" (CPR), i.e. expressing personal emotional reactions to the patients´ dysfunctional behaviour patterns in a disciplined way (including considering a teachable moment and relating it to the patient´s core pathology) and offering alternative behaviour. The key objective of this module is social fear extinction by overlearning conditioned associations and avoidance behaviour.

Mentalising-Module	**Corresponding RDoC domain:**	System for Social Processes
	Indicative questionnaire:	Interpersonal Reactivity Index (IRI)
	Objective:	Enhancing perception and understanding of self and others (understanding mental states) and social communication

The Mentalising-Module contains modelling and teaching mentalising by learning to "read" others' behaviour and thereby re-connecting the patient to his/her social environment and creating social competence. To promote mentalised affectivity (i.e. mentalising own emotional states as described by MBT), the therapist introduces repetitive sequences to stimulate basic mentalising functions in the patient. Based on empathy, the therapist uses a "*not knowing*" stance of exploration of the patients' experiences and identifies context-related emotional reactions, raising "*what-questions*" rather than "why-questions". Two typical interventions to engage mentalising are the „*Stop and Stand*" and the „*Stop, Re-wind, Explore*" sequences [68]. In the first case, the therapist stops a patient who is stuck in drawing non-mentalising assumptions (e.g. "everybody hates me") by surprise or humour to subsequently help the patient to mentalise about his/her experiences. The second sequence generates a joined attention on the patient´s past experiences by shifting the focus back and forth within an episodic experience to make it accessible for the mentalising process. Genuine empathy and theory of mind skills are furthermore facilitated by the therapist´s "*Disciplined Personal Involvement*" (DPI; and more specifically "Contingent Personal Reactivity" (CPR) as an element of CBASP as well. The key objective of this module is to improve mentalising capabilities in social interactions.

Mindfulness-Module	**Corresponding RDoC domain:**	Arousal System: Hyperarousal
	Indicative questionnaire:	Difficulties in Emotion Regulation (DERS-16)
	Objective:	Reducing the arousal system (hyperarousal) referring to emotion awareness and regulation

This module integrates mindfulness-based exercises, which focus on a) observing non-judgmentally internal and external stimuli, b) shifting attention away from trauma-related inner "movies" and monitoring skills to c) overcome hyperarousal and experiential avoidance or being run over by one's emotions. Mindfulness-based interventions aim to change a person's perspective on his or her emotions and cognitions. This process is facilitated through mindfulness meditation (e.g., body scan, formal sitting meditation) in which close attention is paid to the present moment whilst thoughts, feelings and body sensations are noted with an attitude of curiosity, non-judgement, and acceptance of psychological experiences. Mindfulness has been suggested to be effective via four mechanisms: attention regulation, body awareness, changes in perspective on the self, and emotion regulation [94,95]. Mindfulness training enhances positive affect [96], decreases negative affect, and reduces maladaptive automatic emotional responses [97] being associated with changes in areas of the brain responsible for affect regulation and stress impulse reaction [98,94]. The key objective of this module is to improve emotion awareness and regulation in order to mitigate hyperarousal.

Selection of modules

The application of the modular intervention is preceded by a diagnostic assessment of the patient´s impaired systems (negative valence system, system of social processes, or arousal system) according to the scores on the self-rated 1) Rejection Sensitivity Questionnaire (RSQ; social threat response); 2) Interpersonal Reactivity Index (IRI; mentalisation, empathy), and 3) Brief Version of the Difficulties in Emotion Regulation Scale (DERS-16; emotion awareness

and regulation). The corresponding modular interventions will be applied if the cut-off value in one or more of these measures is exceeded. Since no a priori values are established, the cut-offs used here are defined as one standard deviation above the general population mean, i.e. the upper 16% [82,79]. The problem(s) thus identified is/are assigned as the target for one, two or three of the modules (figure 3) according to the systematic treatment algorithm (figure 4).

[FIGURE 4]

Treatment modules are selected according to the evidence-based treatment algorithm on the basis of the self-rated module-specific questionnaires. However, the selection of specific treatment strategies or techniques *within* a specific module (e.g. BA or cognitive restructuring in CBT, use of Kiesler's circumplex model or interpersonal discrimination exercise in CBASP) and the sequence of treatment strategies or techniques *between* modules are based on the clinical judgement and expertise of the therapist and the supervisors, since there is no reliable evidence to implement a data-driven decision algorithm for sequencing yet. The individual case conceptualizations are formulated in consultation with the supervisors who regularly check on the weekly intraindividual PHQ-9 courses and the utilisation of treatment techniques within each session according to the Therapy Elements Checklist (TEC) and the video recordings.

Application of modules (time distribution)

The modules are not simply added as separate components, but rather integrated into the therapeutic process and course as add-on to the standard CBT procedure as basis for both interventions. Consequently, the amount of time spent with single CBT-techniques (e.g. cognitive restructuring) will be reduced with increasing number of modules and the procedure will be condensed to behavioural activation (e.g. identifying and promoting pleasant activities) as the most effective component of CBT [99]. Depending on the selected number of modules, approximately one third of the time will be spent with basic CBT procedures and two thirds of the time with the application of modules. Therapists will document the time, which is spent with CBT procedures or with single modules, after each session.

Control intervention: CBT

CBT will be delivered according to the German standard manual by Hautzinger [100]. The main CBT elements are 1. establishing therapeutic relationship, 2. psychoeducation, 3. behaviour activation, 4. cognitive restructuring, and 5. maintenance and relapse prevention. CBT has been shown to be efficacious in depressed patients in prior clinical trials [101,102], but not specifically in this subgroup of depressed and comorbid patients exposed to CM.

Randomisation

The randomisation code will be generated by the Clinical Trials Unit Freiburg (CTU) using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Randomisation will be performed, stratified by site, in blocks of variable length in a ratio of 1:1. The block lengths will be documented separately and will not be disclosed to the sites. The randomisation code will be produced by validated programs based on the Statistical Analysis System (SAS). This dataset is included in Redcap so that patients can be randomised directly in the eCRF.

Blinding

All clinical ratings will be completed by trained and independent raters blinded to treatment assignment. Each of the sites implements procedures to mask a patient treatment assignment from the person who will evaluate the results of the clinical ratings through the following: 1) locating the raters at a separate physical location, and 2) reminding the patients at each visit not to mention anything that might reveal their treatment condition to the independent evaluator.

Data Management and Monitoring

Study data will be entered in pseudonymised form in a study database by authorized and trained members of the study team via electronic case report forms (eCRF). The data management will be performed with REDCap™ Version 9, a fully web based remote data entry system based on web forms, which is developed and maintained by the REDCap Consortium (redcap@vanderbilt.edu). This system uses built-in security features to prevent unauthorized

access to patient data, including an encrypted transport protocol for data transmission from the participating sites to the study database. An audit trail provides a history of the data entered, changed, or deleted, indicating the processor and date. Monitoring is performed by CTU. Risk-based monitoring will be done according to ICH-GCP E6 (R2) and standard operating procedures (SOP) to ensure patient`s safety and integrity of clinical trial data.

Statistical Analysis

Before the start of the final analysis, a detailed statistical analysis plan will be prepared. This will be completed during the 'blind review' of the data, at the latest. The primary efficacy analysis will be performed according to the intention-to-treat (ITT) principle and will therefore be based on the full analysis set (FAS) including all randomized patients. Patients are analysed as randomised regardless of any protocol deviations. This analysis corresponds to the analysis of the treatment policy estimand. The effects of CBT and MoBa with respect to the HRSD-24 score after 16 weeks of treatment (primary endpoint) will be estimated within a linear regression model, and the two-sided 95% confidence interval will be calculated for the treatment effect. The model will include treatment and study centre as independent variables, as well as baseline HRSD-24 score. A conservative assumption of the effect size anticipated for the subsequent confirmative trial will be derived from these analyses by a combination of clinical and statistical judgement. Secondary endpoints will be analysed descriptively in a similar fashion as the primary outcome in the FAS, using regression models as appropriate for the respective type of data. Treatment effects will be calculated with two-sided 95% confidence intervals. All secondary analyses are exploratory and are interpreted in a descriptive fashion.

The safety analysis includes calculation and comparison of frequencies and rates of serious adverse events. Furthermore, statistical methods are used to assess the quality of data and the homogeneity of intervention groups. Data should be collected regardless of the patients' adherence to the protocol, especially on the clinical outcome, to obtain the best approximation to the full analysis set. Data should also be collected on other therapies received post dropout. Patients with missing follow-up will be excluded. As the only available measurement of the patient is taken at baseline and the primary aim is feasibility, this can be considered as an

adequate strategy. The reasons for missing post baseline values will be collected and will be taken into consideration for the subsequent confirmatory trial.

Study results will be reported according to CONSORT guidelines. Further details of the statistical analysis will be fixed before data base lock and start of the analysis. The responsible biostatistician will remain blind for treatment allocation throughout the study. For further information regarding the statistical analysis, see the extensive study protocol publicly accessible at https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00022093.

Ethics and dissemination:

This study obtained approval from the independent Ethics Committees of the University of Freiburg in August 2020 and the University of Heidelberg in October 2020. Additionally, the administrative department for governance and quality of the University Medical Centre Freiburg verified GCP conformity. All findings will be disseminated broadly via peer-reviewed articles in scientific journals and contributions to national and international conferences.

Consent to participate

At first contact, all prospects will be informed about the study in detail and will receive standardized participant information sheets. At screening, voluntary written informed consent for study participation and storage, evaluation and transfer of study-related data will be obtained from each study participant by research associates of the respective study centre. Withdrawal of written consent is possible at any time, without giving reasons. In the event of a withdrawal of the informed consent, patients can decide whether their data should be deleted or destroyed or whether they can be used in anonymised form for this research project.

Safety/harms

Side effects of evidence- based psychotherapies are fortunately rather rare (e.g. [103,104]). According to the most recent meta-analysis, only approximately 5% of patients deteriorate while in psychotherapeutic treatment [3]. Adverse Events (AE; e.g. private/occupational stress or conflicts in the patient-therapist relationship) and Serious Adverse Events (SAE; e.g. severe events requiring stationary medical treatment or with potential permanent damage) are

screened for at every assessment or therapy session. AEs have to be reported to the principal investigators (ES, SH) and SAEs to the independent experts. In addition, on-site data monitoring will be regularly conducted by a clinical monitor from CTU to ensure patients' safety and integrity of the clinical data in adherence to the study protocol, as well as to check data quality and accuracy. Individual trial participation will be stopped if one of the following discontinuation criteria occurs:

a) Active suicidality
b) The physical health of the patient is at risk according to clinical judgment
c) Occurrence of an AE/SAE with therapeutic implications incompatible with the study
d) Newly occurring exclusion criteria (demanding further procedures not compatible with the continuation of the study participation)
e) Withdrawal of the informed consent

If the study principal investigator or the co-principal investigator have serious ethical concerns because of the performance at one of the sites or severe safety concerns become apparent to the independent experts, the whole trial will be discontinued.

Trial Status

Official study begin was in May 2020. The first patient was included in December 2020. Within the first months of recruiting, there were no difficulties regarding the recruitment and inclusion of eligible patients, or the implementation of the MoBa and CBT treatments. Due to the ongoing COVID-19 pandemic, all in person contacts (assessments as well as psychotherapy sessions) are done while wearing appropriate face masks (surgical or FFP2) according to the national guidelines and the respective guidelines of the University Medical Centres in Freiburg and Heidelberg. The end of treatment is expected for August 2022 and data collection aims to be completed in April 2023.

Discussion

Most evidence-based treatment protocols are single-disorder-specific manuals disregarding common comorbidities and transdiagnostic clinical phenomena as sequelae of early trauma

and childhood adversities. This leaves a mismatch between the available disorder-specific manuals and the clinical reality. Many clinicians consider the use of evidence-based manuals as challenging or even inadequate for their daily work and report resistances to the 'oversimplified', 'rigid', 'inflexible' or 'flawed' rationales and the 'extensive efforts' needed to maintain up-to-date knowledge by ongoing training [105]. Even attending evidence-based workshops has little impact on clinicians' decisions to use evidence-based treatment protocols in their practice resulting in the well-known underutilization in community settings [106,107]. In contrast to conventional evidence-based treatment protocols, a modular-based psychotherapy supports the eclectic approach of most clinicians by providing them with an evidence-based treatment algorithm to combine and integrate available treatment modules as independent but combinable sets of functional units systematically. This reduces the perceived challenges of using evidence-based approaches by ensuring a high flexibility and goodness-of-fit within a systematic framework for personalised treatments. By optimally tailoring module selection and application to the specific needs of each patient, MoBa has great potential to improve the currently unsatisfying results of psychotherapeutic treatments in research and clinical practice as a bridge between disorder-specific and personalised approaches. Due to the limited sample size of this feasibility study, statistical analyses will be limited exclusively to comparisons of MoBa versus CBT, since tests between different modules within the MoBa intervention arm are not sufficiently powered. While the modules are selected based on our evidence-based algorithm, the selection of specific treatment strategies or techniques *within* a specific module and the sequencing *between* modules are based on individual case conceptualisations, since there is no reliable evidence to implement a data-driven decision algorithm for sequencing yet.

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Patient and public involvement

Neither patients nor public were systematically involved in designing this study. Feedback is constantly collected from participants on their experience of participating and implemented in conducting this trial. The main results will be disseminated to trial participants and systematic patient and public involvement in the development of a subsequent multicentre confirmatory trial will be implemented.

Competing interests

The authors declare the following competing interests: ME received minor book royalties. SH received minor royalties for books with chapters on modular psychotherapy. HP and CJ declare no competing interests. MH received book royalties from several publishers. ES received book royalties and honoraria for workshops and presentations relating to Interpersonal Psychotherapy and CBASP.

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Authors contributions

ME, ES and SH were the main contributors in drafting this manuscript. ES and SH were the main contributors in designing this study with support by ME. CJ provided expertise on data monitoring, data management and statistical analyses. HP and MH provided important feedback on all manuscript versions. All authors approved the final version.

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Figure and Table Legends

Figure 1: Overview of the targeted RDoC domains and their corresponding objectives, assessments and modules. A detailed description of the modules is given below.

Figure 2: Trial design and flow of patients.

Table 1: Primary and Secondary Endpoints and corresponding measures.

Figure 3. Frequency and scope of trial visits.

Figure 4: Decision Tree Algorithm for Modular-Based Psychotherapy.

Table 2: Content and implementation of modules.

Figure 1: Overview of the targeted RDoC domains and their corresponding objectives, assessments and modules. A detailed description of the modules is given below.

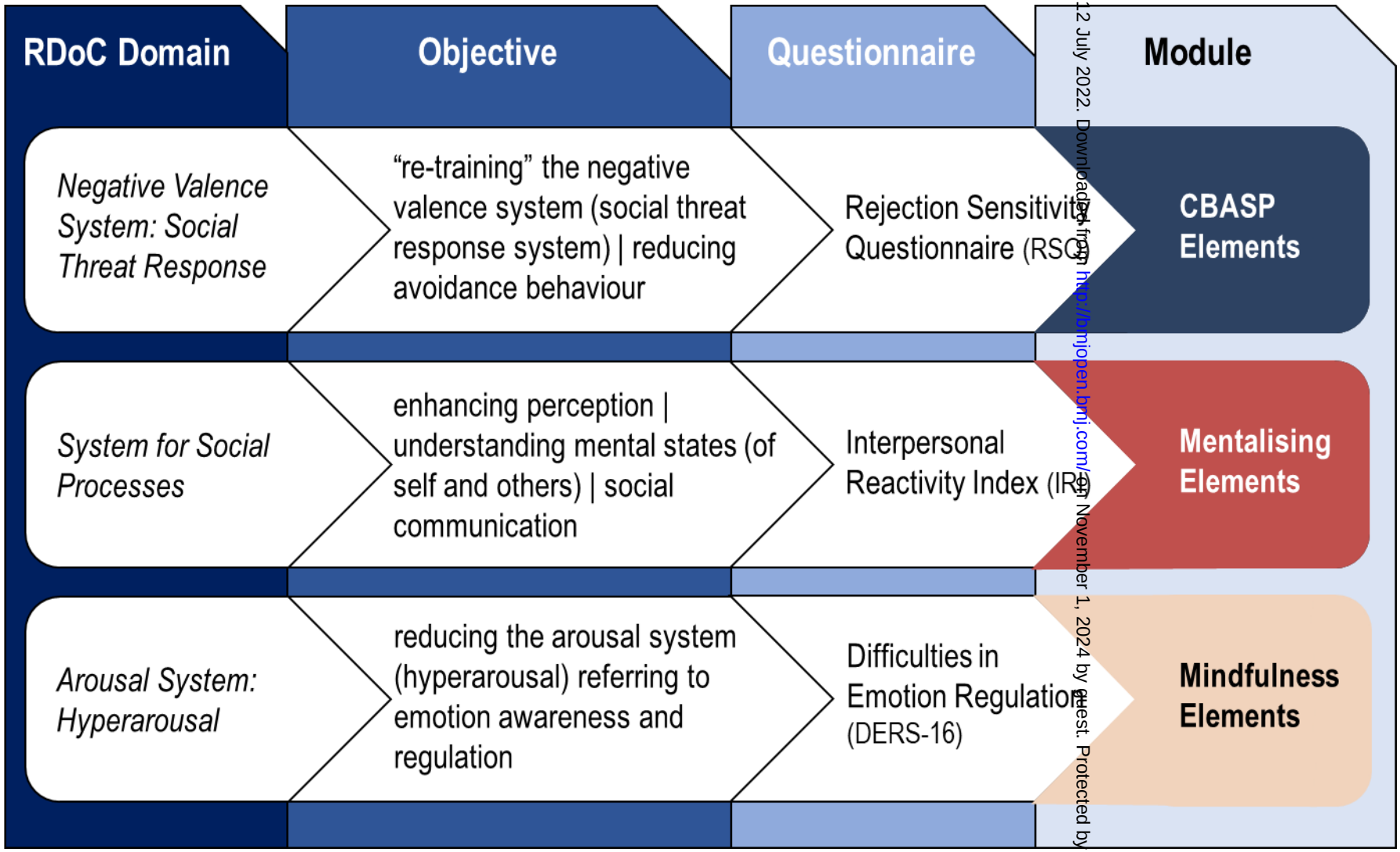


Figure 2: Trial design and flow of patients.

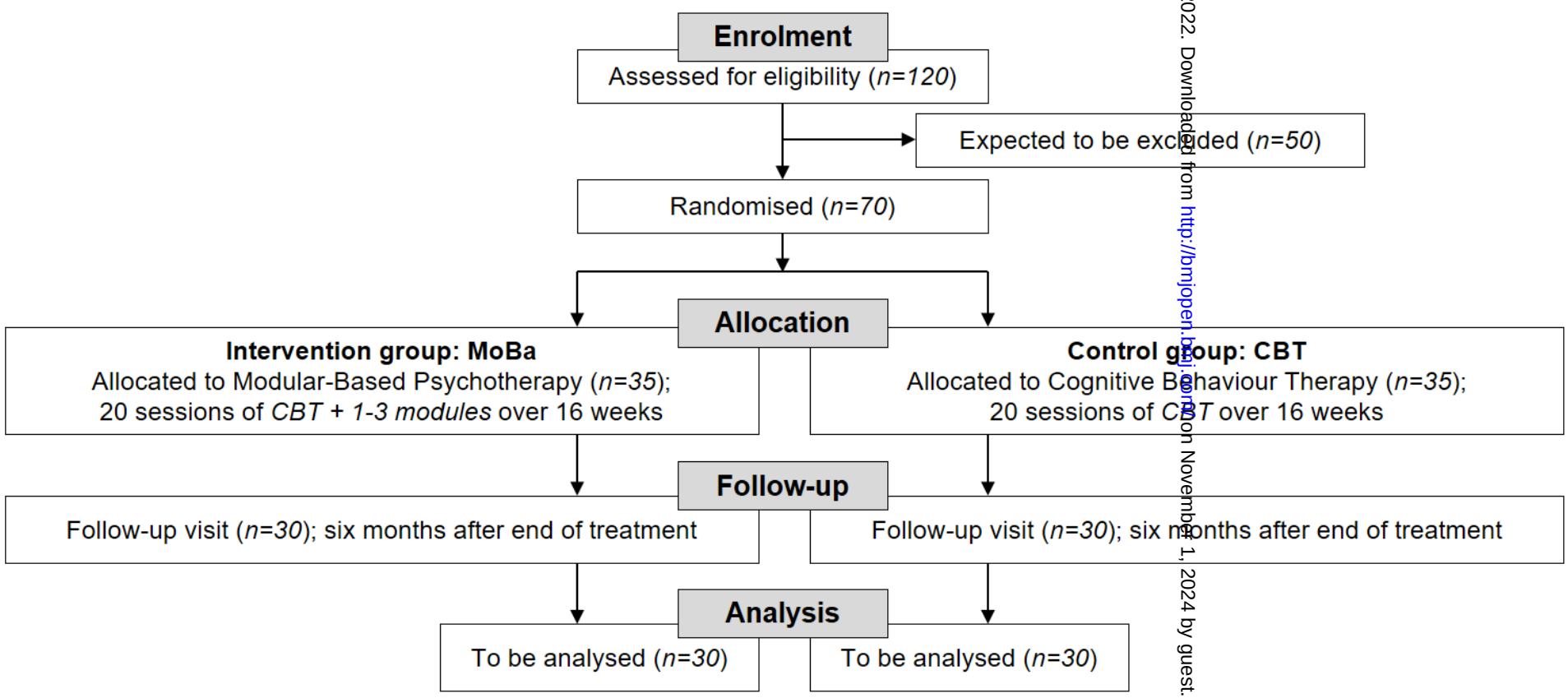
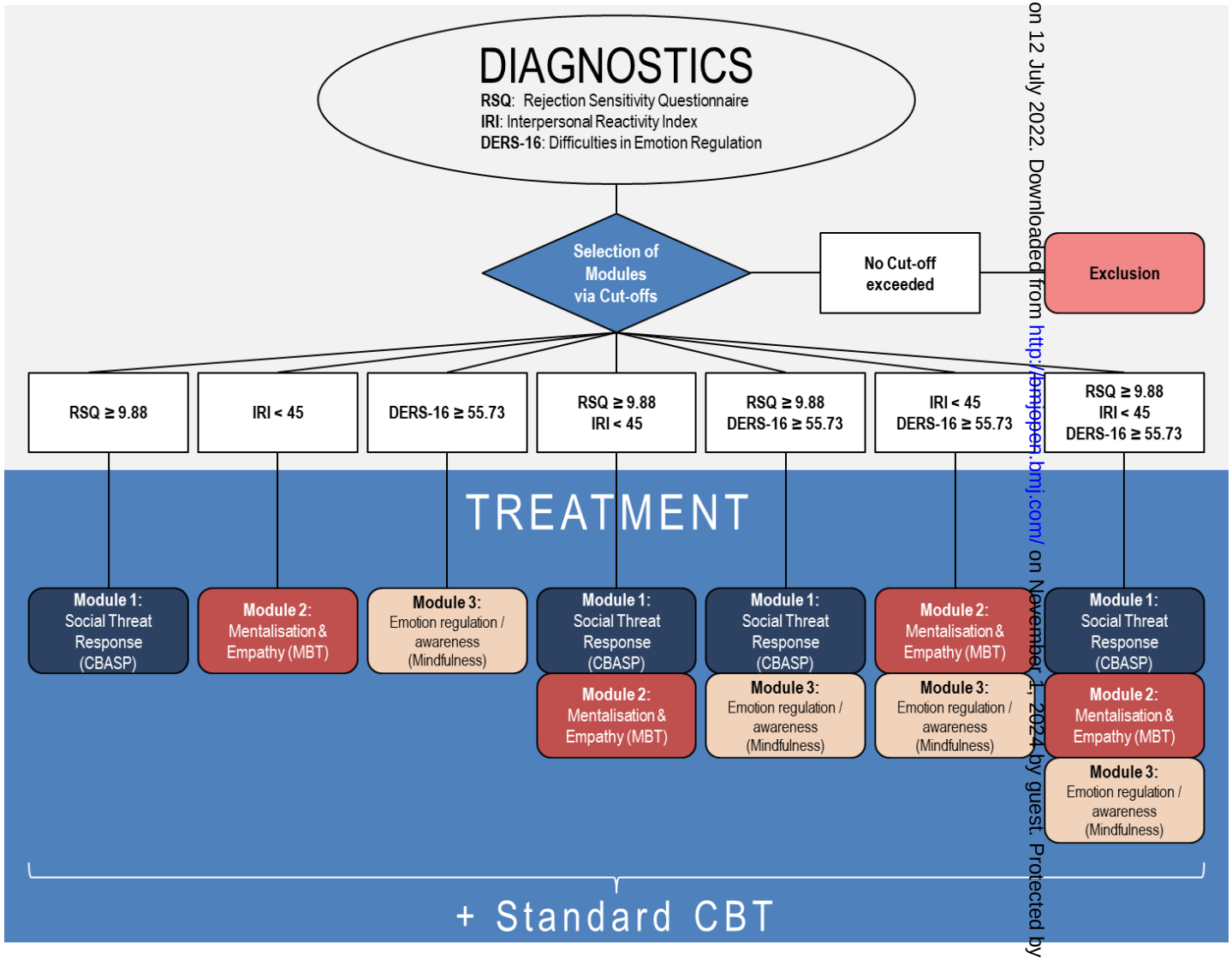


Figure 3. Frequency and scope of trial visits.

		Visits	Pre-screening	Screening	T0 Baseline	*Treatment: MoBa vs. CBT*			T1 Post	T2 Follow-up
		Week(s)	-	-	0	1-4	5-15	16	16	42
THERAPISTS		Sessions per week				2	1	1		
	Questionnaires	Therapeutic Element Checklist				X	X	X		
	Questionnaires	AE / SAE				X	X	X		
	Questionnaires	PHQ-9				X	X	X		
	Questionnaires	WAI-P / WAI-T						X		
RATERS	Interview	telephone screening	(X)							
	Interview	SCID-5 (CV/PD)		X						
	Interview	HRSD-24		X	(X)				X	X
	Interview	SOFAS			X				X	X
	Interview	AE / SAE			(X)				X	X
	Questionnaires	CTQ		X						
	Questionnaires	RSQ		X					X	X
	Questionnaires	IRI		X					X	X
	Questionnaires	DERS-16		X					X	X
	Questionnaires	MZQ			X				X	X
	Questionnaires	BDI-II			X				X	X
	Questionnaires	BAI			X				X	X
	Questionnaires	WHOQoL-BREF			X				X	X
	Questionnaires	PHQ-9			X				X	X
	Questionnaires	ECR-RD8			X				X	X
	Questionnaires	SBC			X				X	X

Figure 4: Decision Tree Algorithm for Modular-Based Psychotherapy.



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

Section/item	Item No	Description	p.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	19-20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	19-20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19-20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-8
	6b	Explanation for choice of comparators	4-8
Objectives	7	Specific objectives or hypotheses	8

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-16
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17-18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15/17-18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16-17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16/19
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	17/19
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

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