

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057672
Article Type:	Protocol
Date Submitted by the Author:	27-Sep-2021
Complete List of Authors:	Elsaesser, Moritz; University of Freiburg, Department of Psychiatry and Psychotherapy, University Medical Center – University of Freiburg, Faculty of Medicine Herpertz, Sabine; Heidelberg University, Department of General Psychiatry Piosczyk, Hannah; University of Freiburg, Department of Psychiatry and Psychotherapy, University Medical Center – University of Freiburg, Faculty of Medicine Jenkner, Carolin ; Universitätsklinikum Freiburg, Clinical Trials Unit Hautzinger, Martin; Eberhard Karls University of Tübingen, Department of Psychology, Clinical Psychology, and Psychotherapy Schramm, Elisabeth; University of Freiburg, Department of Psychiatry and Psychotherapy
Keywords:	Depression & mood disorders < PSYCHIATRY, PSYCHIATRY, Adult psychiatry < PSYCHIATRY

SCHOLARONE™
Manuscripts

1
2
3 1 **Modular-Based Psychotherapy (MoBa) versus Cognitive**
4
5 2 **Behavioural Therapy (CBT) for patients with comorbid depression**
6
7 3 **and a history of childhood maltreatment: Study protocol for a**
8
9 4 **randomised controlled feasibility trial**
10
11 5
12

13 6 Moritz Elsaesser¹, Sabine Herpertz², Hannah Piosczyk¹, Carolin Jenkner³, Martin
14 7 Hautzinger⁴ & Elisabeth Schramm^{1*}
15 8

17 9 ¹ Department of Psychiatry and Psychotherapy, University Medical Center –
18 10 University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

20 11 ² Department of General Psychiatry, Center for Psychosocial Medicine, Medical
21 12 Faculty, Heidelberg University, Heidelberg, Germany

23 13 ³ Clinical Trials Unit, Faculty of Medicine, University Medical Center, University of
24 14 Freiburg, Freiburg, Germany

26 15 ⁴ Department of Psychology, Clinical Psychology, and Psychotherapy, Eberhard
27 16 Karls University of Tübingen, Tübingen, Germany
28 17

30 18
31
32 19 Word count: 3999
33
34 20
35 21
36 22
37 23
38 24
39 25
40 26
41 27
42 28
43 29
44 30
45 31
46 32
47 33
48 34
49 35
50
51
52
53
54
55
56
57
58
59
60

55 30 *Correspondence:

56 31 Prof. Dr. Elisabeth Schramm

57 32 Department of Psychiatry and Psychotherapy

58 33 University Medical Center – University of Freiburg, Hauptstraße 5

59 34 DE–79104 Freiburg (Germany)

60 35 ✉ elisabeth.schramm@uniklinik-freiburg.de

36 **Abstract**

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

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

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

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

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

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

69 **Abstract Summary**

70 ***Strengths and limitations of this study***

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

83 Introduction

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

96 *Childhood maltreatment*

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

1
2
3 110 higher in depressed patients with early trauma compared to those without [16]. Taken together,
4
5 111 study results indicate that interpersonal trauma exposure complicates the treatment of
6
7 112 depression and reduces the impact of traditional cognitive therapy or treatments such as
8
9 113 psychoeducation, TAU, or pharmacotherapy [24]. However, some approaches like
10
11 114 Mindfulness Based Cognitive Therapy (MBCT) [25] or the Cognitive Behavioral Analysis
12
13 115 System of Psychotherapy (CBASP) [26-28] show promising results in the subgroup of
14
15 116 depressed patients with CM.

17 18 19 117 ***Impact of childhood maltreatment on social and emotional functioning***

20
21 118 A growing body of evidence links interpersonal trauma in both youth and adults to difficulties
22
23 119 in social and emotional functioning [24]. Among other sequelae, CM usually results in marked
24
25 120 avoidance behaviour [9] with negative social consequences and in concomitant retardation of
26
27 121 emotional maturational growth [28,29]. These deficits are also expressed in terms of social
28
29 122 threat hyperresponsivity (i.e. being highly sensitive to social rejection and anxiously expecting,
30
31 123 readily perceiving, and overreacting to it) [30-33], social stress and avoidance behaviour
32
33 124 [34,35], lack of empathy and theory-of-mind [36-38] and emotional dysregulation [39,40].
34
35 125 These emotional and social dysfunctions are mediated in common brain circuits for emotion
36
37 126 and salience regulation, fear, and mentalising, suggesting that abnormalities in these
38
39 127 functional pathways may be induced by CM [41,42]. Despite these severe consequences of
40
41 128 CM and their important implications for treatment, disorder-specific approaches for depression
42
43 129 such as CBT or IPT do not specifically address the role of CM and the affected dimensions of
44
45 130 functioning.

46 47 48 49 131 ***Personalised Treatments***

50
51 132 This calls for personalised treatments that target both comorbidities as well as underlying
52
53 133 mechanisms and factors, which are central to the development and maintenance of
54
55 134 psychological disorders. One of the challenges in the development of personalised approaches
56
57 135 is to select treatment modules for targeted dysfunctions and to determine whether and in which
58
59 136 sequence to combine them with standard treatment. In daily practice, it is left to the clinical

1
2
3 137 judgement and expertise of the therapist to address the patient's individual needs and
4
5 138 comorbidities by adding various therapeutic strategies to the disorder-specific interventions.
6
7 139 However, this choice of add-on strategies is not backed up by empirical evidence and thus
8
9 140 hardly conveyable to usual clinical practice in a systematic way [43]. Driven by these concerns,
10
11 141 there has been growing consensus that a novel approach is needed in the way we classify,
12
13 142 formulate, treat, and prevent depression and other mental disorders [44,45]. Insel and Cuthbert
14
15 143 [46] postulated the concept of Research Domain Criteria (RDoC) to move "toward a new
16
17 144 classification system" of studying and validating transdiagnostic, dimensional constructs since
18
19 145 psychiatric diagnosis seem to be no longer optimal as long as they remain restricted to
20
21 146 symptoms and signs. The transdiagnostic procedure focuses on identifying the common and
22
23 147 core maladaptive temperamental, cognitive, emotional, interpersonal and behavioural
24
25 148 characteristics that underpin a broad array of diagnostic presentations [47] and addresses
26
27 149 them via specific modules in treatment [48]. In this sense, a modular-based psychotherapy
28
29 150 provides a structured approach of tailoring treatments to fit patient needs by allowing greater
30
31 151 flexibility to consider interindividual differences and comorbidity [49,50]. The modules, as sets
32
33 152 of independent but combinable functional units, focus on common transdiagnostic dysfunctions
34
35 153 and offer skills to improve e.g. emotion regulation, social competence, empathy, or self-
36
37 154 motivation. There is only one study [51] in which emotion regulation skills were successfully
38
39 155 added to CBT in depressed patients that had sufficient statistical power to detect a clinically
40
41 156 significant effect.
42
43
44
45

46 157 ***Modular-Based Psychotherapy (MoBa)***

47
48 158 Empirical support for the effectiveness of modular approaches following decision flowcharts is
49
50 159 emerging lately [50,52]. For instance, Weisz and colleagues [49] conducted a large
51
52 160 randomized controlled trial (RCT) in which a Modular Approach to Therapy for Children with
53
54 161 Anxiety, Depression, Trauma, or Conduct Problems (MATCH) outperformed standard manual
55
56 162 treatment as well as care as usual (CAU). The superiority of MATCH was found to be sustained
57
58 163 in a two-year follow-up [53] and was replicated in a more recent trial [54]. Another example of
59
60 164 a modular approach to psychotherapy is Behavioural Interventions for Anxiety in Children with

1
2
3 165 Autism (BIACA) [55]. By using a modular format and including an algorithm to guide the
4
5 166 selection of modules, it offers a treatment approach for several anxiety disorders and
6
7 167 obsessive-compulsive disorder for youths on the autism spectrum. BIACA was superior to
8
9 168 waitlist and CAU in several RCTs (e.g. [56]). In adults, a still ongoing RCT [57] assesses the
10
11 169 feasibility of a modular transdiagnostic intervention for mood, stressor-related and anxiety
12
13 170 disorders (HARMONIC trial) in preparation for a later-stage trial. This represents early signs of
14
15 171 a significant paradigm shift away from single-diagnosis approaches towards dimensional,
16
17 172 transdiagnostic, and modular-based conceptualizations [58,46].

18
19
20 173 The here proposed rationale for a modular-based psychotherapy (MoBa) for depressed
21
22 174 patients with comorbidity and a history of CM is two-fold: First, to include patients regularly
23
24 175 seen in clinical practice showing a) more often comorbid and heterogeneous complaints than
25
26 176 the samples usually included in RCTs and b) a limited treatment response to standard disorder-
27
28 177 specific approaches. Second, tailoring the treatment to the specific characteristics and needs
29
30 178 of patients with CM and comorbid depression can ensure that the psychotherapeutic process
31
32 179 is responsive and may reach better treatment results. The MoBa intervention aims at
33
34 180 interpersonal and emotional maturation by overcoming social threat hypersensitivity and
35
36 181 interpersonal avoidance patterns and improving poor mentalization as well as poor emotion
37
38 182 regulation capacities. The rationale is supported by previous trials with empirically supported
39
40 183 treatments such as CBASP for chronic depression [59-62], MBCT for depression prevention
41
42 184 and treatment [63-66], and Mentalization-Based Therapy (MBT) [67] for borderline personality
43
44 185 disorder [68,69]. In the here used design, MoBa complements standard CBT with modules
45
46 186 compiling specific elements from CBASP, MBCT, and MBT focusing on three disturbed
47
48 187 systems (Figure 1). Those systems are part of the RDoC model and have been shown to be
49
50 188 critically related to CM:

- 51
52
53
54 189 I) the negative valence system (acute, potential, and sustained threat): social threat
55
56 190 response and avoidance behaviour [34,9];
57
58 191 II) the system of social processes: perception and understanding of self and others
59
60 192 (understanding mental states), social communication, attachment [70,37,38];

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

194 **[FIGURE 1]**

195 **Objectives**

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

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

207 **Methods and analysis**

208 **Study design**

209 The bicentric study will be conducted at the Department of Psychiatry and Psychotherapy,
210 University Medical Center Freiburg, Germany, and the Department of General Psychiatry,
211 University Medical Center Heidelberg, Germany. It is a parallel-arm RCT (N=70) comparing
212 MoBa with CBT in 20 individual sessions over 16 weeks of treatment (twice weekly in weeks
213 1-4, then once per week in weeks 5-16). Participants will be assessed at screening, baseline,
214 post-treatment and follow-up (six months after end of treatment).

215 **Study population and recruitment**

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

218

1
2
3 219 Inclusion criteria:
4

- 5 220 1. Age eligibility: 18-65 years.
6
7 221 2. Episodic or persistent MDD or MDD superimposed on Dysthymia (“Double
8
9 222 Depression”) as the primary diagnosis (according to the SCID-5) [74].
10
11 223 3. A score of > 18 on the Hamilton Rating Scale for Depression (HRSD-24) [75].
12
13 224 4. History of CM: at least moderate to severe in one or more of the five CTQ-categories
14
15 225 (emotional neglect, emotional abuse, physical neglect, physical abuse, sexual abuse)
16
17 226 [15].
18
19 227 5. Any psychiatric comorbidity according to the SCID-5 except for those described in the
20
21 228 exclusion criteria below.
22
23 229 6. Exceeding the ‘cut-off’ value of at least one of the following measures (module
24
25 230 questionnaires): 1) Rejection Sensitivity Questionnaire (RSQ, [76]) ≥ 9.88 , 2)
26
27 231 Interpersonal Reactivity Index (IRI, [77]) < 45, or 3) Difficulties in Emotion Regulation
28
29 232 Scale-16 (DERS-16, [78]) ≥ 55.73 .
30
31 233 7. Written informed consent.

32
33
34 234 Exclusion criteria:
35

- 36 235 1. Acute risk of suicide.
37
38 236 2. Other current psychiatric disorders as primary diagnosis.
39
40 237 3. Comorbid schizophrenia, bipolar I disorder, organic disorder or substance dependence
41
42 238 fulfilling criteria within the last 6 months.
43
44 239 4. Antisocial or borderline personality disorder (BPD). For BPD, up to three traits are
45
46 240 allowed.
47
48 241 5. Severe cognitive impairment.
49
50 242 6. Serious medical condition (interfering with participation in regular sessions).
51
52 243 7. Other ongoing psychotherapy or psychotropic medication except antidepressant (e.g.
53
54 244 selective serotonin reuptake inhibitor (SSRI) / serotonin–norepinephrine reuptake
55
56 245 inhibitor (SNRI)) and/or sleep-inducing treatment at baseline if stable for at least three
57
58
59
60

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

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

[FIGURE 2]

254 **Sample size**

255 Due to the exploratory nature of the design and the lack of comparable studies, no formal
256 sample size calculation is possible. One of the major aims of this trial is to generate pilot data
257 for a subsequent sample size calculation for a confirmatory study. With reference to Billingham
258 et al. [79] a medium sample size of 30 patients per group in pilot trials seems to be reasonable
259 for the generation of pilot data for such estimation. That results in a total of 60 patients. Non-
260 compliance and/or dropout of patients after randomization are assumed to be at most 14%.
261 Therefore, 70 patients have to be randomized to observe the desired number of compliant
262 patients, split in two groups for each of the two participating centres (FR=35, HD=35; Figure
263 2).

264 **Outcomes**

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

267 **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.

268

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

271

[FIGURE 3]

272

273 **Adherence**

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

286 **Experimental intervention: Modular-Based Psychotherapy**

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

291 **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
<p>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 “<i>Significant Other History</i>” (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 “<i>transference hypothesis</i>” 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 “<i>hot spot situations</i>”, applying the structured “<i>Interpersonal Discrimination Exercise</i>”. 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 overcome 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 <i>Kiesler’s circumplex model</i> [92] enables the patient to recognize the consequences of his/her own behaviour on other persons and to develop empathy (“reading</p>		

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.

292 **Selection of modules**

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

1
2
3 301 the upper 16% [81,78]. The problem(s) thus identified is/are assigned as the target for one,
4
5 302 two or three of the modules (figure 3) according to the systematic treatment algorithm (figure
6
7 303 4).

9 304 **[FIGURE 4]**

11
12 305 ***Application of modules (time distribution)***

13
14 306 The modules are not simply added as separate components, but rather integrated into the
15
16 307 therapeutic process and course as add-on to the standard CBT procedure. Consequently, the
17
18 308 amount of time spent with single CBT-techniques (e.g. cognitive restructuring) will be reduced
19
20 309 with increasing number of modules and the procedure will be condensed to behavioural
21
22 310 activation (e.g. identifying and promoting pleasant activities) as the most effective component
23
24 311 of CBT [98]. Depending on the selected number of modules, approximately one third of the
25
26 312 time will be spent with basic CBT procedures and two thirds of the time with the application of
27
28 313 modules. Therapists will document the time, which is spent with CBT procedures or with single
29
30 314 modules, after each session.

31
32
33
34 315 ***Control intervention: CBT***

35
36 316 CBT will be delivered according to the German standard manual by Hautzinger [99]. The main
37
38 317 CBT elements are 1. establishing therapeutic relationship, 2. psychoeducation, 3. behaviour
39
40 318 activation, 4. cognitive restructuring, and 5. maintenance and relapse prevention. CBT has
41
42 319 been shown to be efficacious in depressed patients in prior clinical trials [100,101], but not
43
44 320 specifically in this subgroup of depressed and comorbid patients exposed to CM.

45
46
47
48 321 ***Randomisation***

49
50 322 The randomisation code will be generated by the Clinical Trials Unit Freiburg (CTU) using the
51
52 323 following procedure to ensure that treatment assignment is unbiased and concealed from
53
54 324 patients and investigator staff. Randomisation will be performed, stratified by site, in blocks of
55
56 325 variable length in a ratio of 1:1. The block lengths will be documented separately and will not
57
58 326 be disclosed to the sites. The randomisation code will be produced by validated programs

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

329 **Blinding**

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

336 **Data Management and Monitoring**

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

347 **Statistical Analysis**

348 Before the start of the final analysis, a detailed statistical analysis plan will be prepared. This
349 will be completed during the 'blind review' of the data, at the latest. The primary efficacy
350 analysis will be performed according to the intention-to-treat (ITT) principle and will therefore
351 be based on the full analysis set including all randomized patients. Patients are analysed as
352 randomised regardless of any protocol deviations. This analysis corresponds to the analysis
353 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

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

383 ***Consent to participate***

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

391 ***Safety/harms***

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

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

1
2
3 408 e) Withdrawal of the informed consent
4

5 409 If the study principal investigator or the co-principal investigator have serious ethical concerns
6
7 410 because of the performance at one of the sites or severe safety concerns become apparent to
8
9 411 the independent experts, the whole trial will be discontinued.
10

11
12 412 ***Trial Status***
13

14 413 Official study begin was in May 2020. The first patient was included in December 2020. Within
15
16 414 the first months of recruiting, there were no difficulties regarding the recruitment and inclusion
17
18 415 of eligible patients, or the implementation of the MoBa and CBT treatments. Due to the ongoing
19
20 416 COVID-19 pandemic, all in person contacts (assessments as well as psychotherapy sessions)
21
22 417 are done while wearing appropriate face masks (surgical or FFP2) according to the national
23
24 418 guidelines and the respective guidelines of the University Medical Centers in Freiburg and
25
26 419 Heidelberg. The end of treatment is expected for July 2022 and data collection aims to be
27
28 420 completed in March 2023.
29
30

31
32 421 **Discussion**
33

34
35 422 Most evidence-based treatment protocols are single-disorder-specific manuals disregarding
36
37 423 common comorbidities and transdiagnostic clinical phenomena as sequelae of early trauma
38
39 424 and childhood adversities. This leaves a mismatch between the available disorder-specific
40
41 425 manuals and the clinical reality. Many clinicians consider the use of evidence-based manuals
42
43 426 as challenging or even inadequate for their daily work and report resistances to the
44
45 427 'oversimplified', 'rigid', 'inflexible' or 'flawed' rationales and the 'extensive efforts' needed to
46
47 428 maintain up-to-date knowledge by ongoing training [104]. Even attending evidence-based
48
49 429 workshops has little impact on clinicians' decisions to use evidence-based treatment protocols
50
51 430 in their practice resulting in the well-known underutilization in community settings [105,106]. In
52
53 431 contrast to conventional evidence-based treatment protocols, a modular-based psychotherapy
54
55 432 supports the eclectic approach of most clinicians by providing them with an evidence-based
56
57 433 treatment algorithm to combine and integrate available treatment modules as independent but
58
59 434 combinable sets of functional units systematically. This reduces the perceived challenges of
60

1
2
3 435 using evidence-based approaches by ensuring a high flexibility and goodness-of-fit within a
4
5 436 systematic framework for personalised treatments. By optimally tailoring module selection and
6
7 437 application to the specific needs of each patient, MoBa has great potential to improve the
8
9 438 currently unsatisfying results of psychotherapeutic treatments in research and clinical practice
10
11 439 as a bridge between disorder-specific and personalised approaches.

14 15 440 **Declarations**

17 18 441 ***Availability of data and materials***

19
20 442 The datasets used and/or analysed during the current study are available from the
21
22 443 corresponding author on reasonable request.

23 24 444 ***Patient and public involvement***

25
26 445 Neither patients nor public were systematically involved in designing this study. Feedback is
27
28 446 constantly collected from participants on their experience of participating and implemented in
29
30 447 conducting this trial. The main results will be disseminated to trial participants and systematic
31
32 448 patient and public involvement in the development of a subsequent multicentre confirmatory
33
34 449 trial will be implemented.

35 36 450 ***Competing interests***

37
38
39 451 The authors declare the following competing interests: ME received minor book royalties. SH
40
41 452 received minor royalties for books with chapters on modular psychotherapy. HP and CJ declare
42
43 453 no competing interests. MH received book royalties from several publishers. ES received book
44
45 454 royalties and honoraria for workshops and presentations relating to Interpersonal
46
47 455 Psychotherapy and CBASP.

48 49 456 ***Funding***

50
51
52 457 The clinical trial is financially supported by the German Research Foundation (Deutsche
53
54 458 Forschungsgemeinschaft, DFG; GZ: SCHR 443/16-1). The funders do not control the final
55
56 459 decision regarding any of aspects of the trial: design, conduct, data analysis and interpretation,
57
58 460 manuscript writing, and dissemination of trial results.

461 **Authors contributions**

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

466 **Acknowledgements**

467 We would like to thank Prof. Fritz Hohagen, Prof. Klaus Lieb and Prof. Matthias Backenstraß
468 for their contributions as independent experts, as well as Dr. Thomas Fangmeier for his
469 valuable assistance in determining the module cut-offs for the initial grant. Furthermore, we
470 are grateful for the participation of Dr. Anne Külz and Prof. Svenja Taubner for their ongoing
471 supervision and therapist trainings as experts of their fields in MBCT and MBT.

472 **References**

- 473 1. Beck AT. *Cognitive Therapy of Depression*. Guilford Press; 1979.
- 474 2. Klerman GL, Weissman MM, Rounsaville BJ, Chevron E. *Interpersonal Psychotherapy of*
475 *Depression*. Basic Books; 1984.
- 476 3. Cuijpers P, Karyotaki E, Ciharova M, Miguel C, Noma H, Furukawa TA. The effects of
477 psychotherapies for depression on response, remission, reliable change, and deterioration: A
478 meta-analysis. *Acta Psychiatrica Scandinavica*. 2021. doi:[10.1111/acps.13335](https://doi.org/10.1111/acps.13335)
- 479 4. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression
480 (TRD)? A systematic review of current randomized trials. *European*
481 *Neuropsychopharmacology*. 2007;17(11):696-707. doi:[10.1016/j.euroneuro.2007.03.009](https://doi.org/10.1016/j.euroneuro.2007.03.009)
- 482 5. Holtzheimer PE, Mayberg HS. Stuck in a rut: Rethinking depression and its treatment. *Trends in*
483 *Neurosciences*. 2011;34(1):1-9. doi:[10.1016/j.tins.2010.10.004](https://doi.org/10.1016/j.tins.2010.10.004)
- 484 6. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and
485 Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey
486 Replication. *Archives of General Psychiatry*. 2005;62(6):593-602.
487 doi:[10.1001/archpsyc.62.6.593](https://doi.org/10.1001/archpsyc.62.6.593)
- 488 7. Lamers F, Oppen P van, Comijs HC, et al. Comorbidity Patterns of Anxiety and Depressive
489 Disorders in a Large Cohort Study: The Netherlands Study of Depression and Anxiety
490 (NESDA). *J Clin Psychiatry*. 2011;72(3):0-0. doi:[10.4088/JCP.10m06176blu](https://doi.org/10.4088/JCP.10m06176blu)
- 491 8. Roca M, Gili M, Garcia-Garcia M, et al. Prevalence and comorbidity of common mental disorders
492 in primary care. *Journal of Affective Disorders*. 2009;119(1):52-58. doi:[10.1016/j.jad.2009.03.014](https://doi.org/10.1016/j.jad.2009.03.014)
- 493 9. Klein JP, Roniger A, Schweiger U, Späth C, Brodbeck J. The Association of Childhood Trauma
494 and Personality Disorders With Chronic Depression: A Cross-Sectional Study in Depressed
495 Outpatients. *J Clin Psychiatry*. 2015;76(6):0-0. doi:[10.4088/JCP.14m09158](https://doi.org/10.4088/JCP.14m09158)
- 496 10. Papakostas GI, Fava M. Predictors, moderators, and mediators (correlates) of treatment outcome
497 in major depressive disorder. *Dialogues Clin Neurosci*. 2008;10(4):439-451.
498 doi:[10.31887/DCNS.2008.10.4/gipapakostas](https://doi.org/10.31887/DCNS.2008.10.4/gipapakostas)
- 499 11. Souery D, Oswald P, Massat I, et al. Clinical Factors Associated With Treatment Resistance in
500 Major Depressive Disorder: Results From a European Multicenter Study. *J Clin Psychiatry*.
501 2007;68(7):0-0.
- 502 12. Goddard E, Wingrove J, Moran P. The impact of comorbid personality difficulties on response to
503 IAPT treatment for depression and anxiety. *Behavior Research and Therapy*. 2015;73:1-7.
504 doi:[10.1016/j.brat.2015.07.006](https://doi.org/10.1016/j.brat.2015.07.006)

13. Agosti V. Predictors of remission from chronic depression: A prospective study in a nationally representative sample. *Comprehensive Psychiatry*. 2014;55(3):463-467. doi:[10.1016/j.comppsy.2013.09.016](https://doi.org/10.1016/j.comppsy.2013.09.016)
14. Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. *Psychological Medicine*. 2011;41(1):151-162. doi:[10.1017/S0033291710000553](https://doi.org/10.1017/S0033291710000553)
15. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*. 2003;27(2):169-190. doi:[10.1016/S0145-2134\(02\)00541-0](https://doi.org/10.1016/S0145-2134(02)00541-0)
16. Nelson J, Klumppendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: Meta-analysis. *The British Journal of Psychiatry*. 2017;210(2):96-104. doi:[10.1192/bjp.bp.115.180752](https://doi.org/10.1192/bjp.bp.115.180752)
17. Struck N, Krug A, Yuksel D, et al. Childhood maltreatment and adult mental disorders – the prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Research*. 2020;293:113398. doi:[10.1016/j.psychres.2020.113398](https://doi.org/10.1016/j.psychres.2020.113398)
18. Wiersma JE, Hovens JGFM, Oppen P van, Giltay EJ, Schaik DJF van, Penninx BWJH. The Importance of Childhood Trauma and Childhood Life Events for Chronicity of Depression in Adults. *J Clin Psychiatry*. 2009;70(7):0-0. doi:[10.4088/JCP.08m04521](https://doi.org/10.4088/JCP.08m04521)
19. Humphreys KL, LeMoult J, Wear JG, Piersiak HA, Lee A, Gotlib IH. Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire. *Child Abuse & Neglect*. 2020;102:104361. doi:[10.1016/j.chiabu.2020.104361](https://doi.org/10.1016/j.chiabu.2020.104361)
20. Infurna MR, Reichl C, Parzer P, Schimmenti A, Bifulco A, Kaess M. Associations between depression and specific childhood experiences of abuse and neglect: A meta-analysis. *Journal of Affective Disorders*. 2016;190:47-55. doi:[10.1016/j.jad.2015.09.006](https://doi.org/10.1016/j.jad.2015.09.006)
21. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: A meta-analysis of published literature. *Childhood trauma and adult depression*. *European Psychiatry*. 2015;30(6):665-680. doi:[10.1016/j.eurpsy.2015.04.007](https://doi.org/10.1016/j.eurpsy.2015.04.007)
22. Bausch P, Fangmeier T, Meister R, et al. The Impact of Childhood Maltreatment on Long-Term Outcomes in Disorder-Specific vs. Nonspecific Psychotherapy for Chronic Depression. *Journal of Affective Disorders*. 2020;272:152-157. doi:[10.1016/j.jad.2020.03.164](https://doi.org/10.1016/j.jad.2020.03.164)
23. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry*. 2013;170(10):1114-1133. doi:[10.1176/appi.ajp.2013.12070957](https://doi.org/10.1176/appi.ajp.2013.12070957)
24. Shirk SR, DePrince AP, Crisostomo PS, Labus J. Cognitive behavioral therapy for depressed adolescents exposed to interpersonal trauma: An initial effectiveness trial. *Psychotherapy*. 2014;51(1):167-179. doi:[10.1037/a0034845](https://doi.org/10.1037/a0034845)
25. Williams JMG, Crane C, Barnhofer T, et al. Mindfulness-based cognitive therapy for preventing relapse in recurrent depression: A randomized dismantling trial. *Journal of Consulting and Clinical Psychology*. 2014;82(2):275-286. doi:[10.1037/a0035036](https://doi.org/10.1037/a0035036)
26. Nemeroff CB, Heim CM, Thase ME, et al. Differential Responses to Psychotherapy Versus Pharmacotherapy in Patients With Chronic Forms of Major Depression and Childhood Trauma. *FOC*. 2005;3(1):131-135. doi:[10.1176/foc.3.1.131](https://doi.org/10.1176/foc.3.1.131)
27. Klein JP, Erkens N, Schweiger U, et al. Does Childhood Maltreatment Moderate the Effect of the Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy in Persistent Depressive Disorder? *PPS*. 2018;87(1):46-48. doi:[10.1159/000484412](https://doi.org/10.1159/000484412)
28. McCullough JP. *Treatment for Chronic Depression. Cognitive Behavioral Analysis System of Psychotherapy*. Guilford Press; 2000.
29. McCullough J, Schramm E, Penberthy JK. *CBASP as a Distinctive Treatment for Persistent Depressive Disorder: Distinctive Features*. Routledge; 2015.
30. Bertsch K, Krauch M, Stopfer K, Haeussler K, Herpertz SC, Gamer M. Interpersonal Threat Sensitivity in Borderline Personality Disorder: An Eye-Tracking Study. *Journal of Personality Disorders*. 2017;31(5):647-670. doi:[10.1521/pedi_2017_31_273](https://doi.org/10.1521/pedi_2017_31_273)
31. Chu DA, Bryant RA, Gatt JM, Harris AWF. Failure to differentiate between threat-related and positive emotion cues in healthy adults with childhood interpersonal or adult trauma. *Journal of Psychiatric Research*. 2016;78:31-41. doi:[10.1016/j.jpsychires.2016.03.006](https://doi.org/10.1016/j.jpsychires.2016.03.006)
32. Herpertz SC, Bertsch K. The social-cognitive basis of personality disorders. *Current Opinion in Psychiatry*. 2014;27(1):73-77. doi:[10.1097/YCO.0000000000000026](https://doi.org/10.1097/YCO.0000000000000026)
33. Bertsch K, Gamer M, Schmidt B, et al. Oxytocin and Reduction of Social Threat Hypersensitivity in Women With Borderline Personality Disorder. *AJP*. 2013;170(10):1169-1177. doi:[10.1176/appi.ajp.2013.13020263](https://doi.org/10.1176/appi.ajp.2013.13020263)

- 1
2
3 565 34. Shapero BG, Black SK, Liu RT, et al. Stressful Life Events and Depression Symptoms: The Effect
4 566 of Childhood Emotional Abuse on Stress Reactivity. *Journal of Clinical Psychology*.
5 567 2014;70(3):209-223. doi:[10.1002/jclp.22011](https://doi.org/10.1002/jclp.22011)
6 568 35. Erhardt A, Spoomaker VI. Translational Approaches to Anxiety: Focus on Genetics, Fear
7 569 Extinction and Brain Imaging. *Curr Psychiatry Rep*. 2013;15(12):417. doi:[10.1007/s11920-013-](https://doi.org/10.1007/s11920-013-0417-9)
8 570 [0417-9](https://doi.org/10.1007/s11920-013-0417-9)
9 571 36. Schnell K, Herpertz SC. Emotion Regulation and Social Cognition as Functional Targets of
10 572 Mechanism-Based Psychotherapy in Major Depression With Comorbid Personality Pathology.
11 573 *Journal of Personality Disorders*. 2018;32(Supplement):12-35.
12 574 doi:[10.1521/pedi.2018.32.suppl.12](https://doi.org/10.1521/pedi.2018.32.suppl.12)
13 575 37. Schnell K, Bluschke S, Konradt B, Walter H. Functional relations of empathy and mentalizing: An
14 576 fMRI study on the neural basis of cognitive empathy. *NeuroImage*. 2011;54(2):1743-1754.
15 577 doi:[10.1016/j.neuroimage.2010.08.024](https://doi.org/10.1016/j.neuroimage.2010.08.024)
16 578 38. Mattern M, Walter H, Hentze C, et al. Behavioral Evidence for an Impairment of Affective Theory
17 579 of Mind Capabilities in Chronic Depression. *PSP*. 2015;48(4):240-250. doi:[10.1159/000430450](https://doi.org/10.1159/000430450)
18 580 39. Weissman DG, Bitran D, Miller AB, Schaefer JD, Sheridan MA, McLaughlin KA. Difficulties with
19 581 emotion regulation as a transdiagnostic mechanism linking child maltreatment with the
20 582 emergence of psychopathology. *Development and Psychopathology*. 2019;31(3):899-915.
21 583 doi:[10.1017/S0954579419000348](https://doi.org/10.1017/S0954579419000348)
22 584 40. Cloitre M, Stovall-McClough C, Zorbas P, Charuvastra A. Attachment organization, emotion
23 585 regulation, and expectations of support in a clinical sample of women with childhood abuse
24 586 histories. *Journal of Traumatic Stress*. 2008;21(3):282-289. doi:[10.1002/jts.20339](https://doi.org/10.1002/jts.20339)
25 587 41. Lippard ETC, Nemeroff CB. The Devastating Clinical Consequences of Child Abuse and Neglect:
26 588 Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders. *AJP*.
27 589 2020;177(1):20-36. doi:[10.1176/appi.ajp.2019.19010020](https://doi.org/10.1176/appi.ajp.2019.19010020)
28 590 42. Bock J, Wainstock T, Braun K, Segal M. Stress In Utero: Prenatal Programming of Brain Plasticity
29 591 and Cognition. *Biological Psychiatry*. 2015;78(5):315-326. doi:[10.1016/j.biopsych.2015.02.036](https://doi.org/10.1016/j.biopsych.2015.02.036)
30 592 43. Fonagy P, Luyten P. Fidelity vs. flexibility in the implementation of psychotherapies: Time to move
31 593 on. *World Psychiatry*. 2019;18(3):270-271. doi:[10.1002/wps.20657](https://doi.org/10.1002/wps.20657)
32 594 44. Barlow DH, Bullis JR, Comer JS, Ametaj AA. Evidence-Based Psychological Treatments: An
33 595 Update and a Way Forward. *Annual Review of Clinical Psychology*. 2013;9(1):1-27.
34 596 doi:[10.1146/annurev-clinpsy-050212-185629](https://doi.org/10.1146/annurev-clinpsy-050212-185629)
35 597 45. Lyon AR, Lau AS, McCauley E, Vander Stoep A, Chorpita BF. A case for modular design:
36 598 Implications for implementing evidence-based interventions with culturally diverse youth.
37 599 *Professional Psychology: Research and Practice*. 2014;45(1):57-66. doi:[10.1037/a0035301](https://doi.org/10.1037/a0035301)
38 600 46. Insel TR, Cuthbert BN. Brain disorders? Precisely. *Science*. 2015;348(6234):499-500.
39 601 doi:[10.1126/science.aab2358](https://doi.org/10.1126/science.aab2358)
40 602 47. Harvey AG, Watkins E, Mansell W. *Cognitive Behavioral Processes Across Psychological*
41 603 *Disorders: A Transdiagnostic Approach to Research and Treatment*. Oxford University Press;
42 604 2004.
43 605 48. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. *Behavior*
44 606 *Therapy*. 2004;35(2):205-230. doi:[10.1016/S0005-7894\(04\)80036-4](https://doi.org/10.1016/S0005-7894(04)80036-4)
45 607 49. Weisz JR, Chorpita BF, Palinkas LA, et al. Testing Standard and Modular Designs for
46 608 Psychotherapy Treating Depression, Anxiety, and Conduct Problems in Youth: A Randomized
47 609 Effectiveness Trial. *Archives of General Psychiatry*. 2012;69(3):274-282.
48 610 doi:[10.1001/archgenpsychiatry.2011.147](https://doi.org/10.1001/archgenpsychiatry.2011.147)
49 611 50. Ng MY, Weisz JR. Annual Research Review: Building a science of personalised intervention for
50 612 youth mental health. *Journal of Child Psychology and Psychiatry*. 2016;57(3):216-236.
51 613 doi:[10.1111/jcpp.12470](https://doi.org/10.1111/jcpp.12470)
52 614 51. Berking M, Ebert D, Cuijpers P, Hofmann SG. Emotion Regulation Skills Training Enhances the
53 615 Efficacy of Inpatient Cognitive Behavioral Therapy for Major Depressive Disorder: A
54 616 Randomized Controlled Trial. *PPS*. 2013;82(4):234-245. doi:[10.1159/000348448](https://doi.org/10.1159/000348448)
55 617 52. Cuijpers P, Ebert DD, Acarturk C, Andersson G, Cristea IA. Personalised Psychotherapy for Adult
56 618 Depression: A Meta-Analytic Review. *Behavior Therapy*. 2016;47(6):966-980.
57 619 doi:[10.1016/j.beth.2016.04.007](https://doi.org/10.1016/j.beth.2016.04.007)
58 620 53. Chorpita BF, Weisz JR, Daleiden EL, et al. Long-term outcomes for the Child STEPs randomized
59 621 effectiveness trial: A comparison of modular and standard treatment designs with usual care.
60 622 *Journal of Consulting and Clinical Psychology*. 2013;81(6):999-1009. doi:[10.1037/a0034200](https://doi.org/10.1037/a0034200)
61 623 54. Chorpita BF, Daleiden EL, Park AL, et al. Child STEPs in California: A cluster randomized
62 624 effectiveness trial comparing modular treatment with community implemented treatment for
63 625 youth with anxiety, depression, conduct problems, or traumatic stress. *Journal of Consulting*
64 626 *and Clinical Psychology*. 2017;85(1):13-25. doi:[10.1037/ccp000133](https://doi.org/10.1037/ccp000133)

- 1
2
3 627 55. Wood JJ, Drahota A, Sze K, Har K, Chiu A, Langer DA. Cognitive behavioral therapy for anxiety in
4 628 children with autism spectrum disorders: A randomized, controlled trial. *Journal of Child*
5 629 *Psychology and Psychiatry*. 2009;50(3):224-234. doi:[10.1111/j.1469-7610.2008.01948.x](https://doi.org/10.1111/j.1469-7610.2008.01948.x)
6 630 56. Storch EA, Arnold EB, Lewin AB, et al. The Effect of Cognitive-Behavioral Therapy Versus
7 631 Treatment as Usual for Anxiety in Children With Autism Spectrum Disorders: A Randomized,
8 632 Controlled Trial. *Journal of the American Academy of Child & Adolescent Psychiatry*.
9 633 2013;52(2):132-142.e2. doi:[10.1016/j.jaac.2012.11.007](https://doi.org/10.1016/j.jaac.2012.11.007)
10 634 57. Black M, Hitchcock C, Bevan A, et al. The HARMONIC trial: Study protocol for a randomised
11 635 controlled feasibility trial of Shaping Healthy Minds—a modular transdiagnostic intervention for
12 636 mood, stressor-related and anxiety disorders in adults. *BMJ Open*. 2018;8(8):e024546.
13 637 doi:[10.1136/bmjopen-2018-024546](https://doi.org/10.1136/bmjopen-2018-024546)
14 638 58. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health
15 639 problems: Current status and future directions. *Journal of Consulting and Clinical Psychology*.
16 640 2020;217;88(3):179. doi:[10.1037/ccp0000482](https://doi.org/10.1037/ccp0000482)
17 641 59. Negt P, Brakemeier E-L, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic
18 642 depression with cognitive behavioral analysis system of psychotherapy: A systematic review
19 643 and meta-analysis of randomized-controlled clinical trials. *Brain and Behavior*.
20 644 2016;6(8):e00486. doi:[10.1002/brb3.486](https://doi.org/10.1002/brb3.486)
21 645 60. Keller MB, McCullough JP, Klein DN, et al. A Comparison of Nefazodone, the Cognitive
22 646 Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of
23 647 Chronic Depression. *New England Journal of Medicine*. 2000;342(20):1462-1470.
24 648 doi:[10.1056/NEJM200005183422001](https://doi.org/10.1056/NEJM200005183422001)
25 649 61. Schramm E, Kriston L, Zobel I, et al. Effect of Disorder-Specific vs Nonspecific Psychotherapy for
26 650 Chronic Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2017;74(3):233-242.
27 651 doi:[10.1001/jamapsychiatry.2016.3880](https://doi.org/10.1001/jamapsychiatry.2016.3880)
28 652 62. Schramm E, Kriston L, Elsaesser M, et al. Two-Year Follow-Up after Treatment with the
29 653 Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy for
30 654 Early-Onset Chronic Depression. *PPS*. 2019;88(3):154-164. doi:[10.1159/000500189](https://doi.org/10.1159/000500189)
31 655 63. McCartney M, Nevitt S, Lloyd A, Hill R, White R, Duarte R. Mindfulness-based cognitive therapy
32 656 for prevention and time to depressive relapse: Systematic review and network meta-analysis.
33 657 *Acta Psychiatrica Scandinavica*. 2021;143(1):6-21. doi:[10.1111/acps.13242](https://doi.org/10.1111/acps.13242)
34 658 64. Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Kearney DJ, Simpson TL. Mindfulness-based
35 659 cognitive therapy for the treatment of current depressive symptoms: A meta-analysis.
36 660 *Cognitive Behavior Therapy*. 2019;48(6):445-462. doi:[10.1080/16506073.2018.1556330](https://doi.org/10.1080/16506073.2018.1556330)
37 661 65. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in
38 662 recurrent major depressive disorder: A systematic review and meta-analysis. *Clinical*
39 663 *Psychology Review*. 2011;31(6):1032-1040. doi:[10.1016/j.cpr.2011.05.002](https://doi.org/10.1016/j.cpr.2011.05.002)
40 664 66. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based
41 665 cognitive therapy compared with maintenance antidepressant treatment in the prevention of
42 666 depressive relapse or recurrence (PREVENT): A randomised controlled trial. *The Lancet*.
43 667 2015;386(9988):63-73. doi:[10.1016/S0140-6736\(14\)62222-4](https://doi.org/10.1016/S0140-6736(14)62222-4)
44 668 67. Bateman AW, Fonagy P. *Handbook of Mentalizing in Mental Health Practice*. American
45 669 Psychiatric Publishing, Inc.; 2012.
46 670 68. Malda-Castillo J, Browne C, Perez-Algorta G. Mentalization-based treatment and its evidence-
47 671 base status: A systematic literature review. *Psychology and Psychotherapy: Theory, Research*
48 672 *and Practice*. 2019;92(4):465-498. doi:[10.1111/papt.12195](https://doi.org/10.1111/papt.12195)
49 673 69. Bateman A, Fonagy P. Randomized Controlled Trial of Outpatient Mentalization-Based Treatment
50 674 Versus Structured Clinical Management for Borderline Personality Disorder. *AJP*.
51 675 2009;166(12):1355-1364. doi:[10.1176/appi.ajp.2009.09040539](https://doi.org/10.1176/appi.ajp.2009.09040539)
52 676 70. Zilberstein K. Neurocognitive considerations in the treatment of attachment and complex trauma in
53 677 children. *Clin Child Psychol Psychiatry*. 2014;19(3):336-354. doi:[10.1177/1359104513486998](https://doi.org/10.1177/1359104513486998)
54 678 71. Hofmann M, Fehlinger T, Stenzel N, Rief W. The Relationship Between Skill Deficits and
55 679 Disability—A Transdiagnostic Study. *Journal of Clinical Psychology*. 2015;71(4):413-421.
56 680 doi:[10.1002/jclp.22156](https://doi.org/10.1002/jclp.22156)
57 681 72. Fehlinger T, Stumpfenhorst M, Stenzel N, Rief W. Emotion regulation is the essential skill for
58 682 improving depressive symptoms. *Journal of Affective Disorders*. 2013;144(1):116-122.
59 683 doi:[10.1016/j.jad.2012.06.015](https://doi.org/10.1016/j.jad.2012.06.015)
60 684 73. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: A synthetic
61 685 review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*.
62 686 2012;1251:E1-24. doi:[10.1111/j.1749-6632.2012.06751.x](https://doi.org/10.1111/j.1749-6632.2012.06751.x)
63 687 74. Beesdo-Baum K, Zaudig M, Wittchen H-U. *Strukturiertes Klinisches Interview Für DSM-5 [The*
64 688 *Structured Clinical Interview for DSM-5-Clinician Version] (SCID-5-CV)*. Hogrefe; 2019.

- 1
2
3 689 75. Hamilton M. Development of a Rating Scale for Primary Depressive Illness. *British Journal of*
4 690 *Social and Clinical Psychology*. 1967;6(4):278-296. doi:[10.1111/j.2044-8260.1967.tb00530.x](https://doi.org/10.1111/j.2044-8260.1967.tb00530.x)
5 691 76. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. *Journal of*
6 692 *Personality and Social Psychology*. 1996;70(6):1327-1343. doi:[10.1037/0022-3514.70.6.1327](https://doi.org/10.1037/0022-3514.70.6.1327)
7 693 77. Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional
8 694 approach. *Journal of Personality and Social Psychology*. 1983;44(1):113-126.
9 695 doi:[10.1037/0022-3514.44.1.113](https://doi.org/10.1037/0022-3514.44.1.113)
10 696 78. Bjureberg J, Ljótsson B, Tull MT, et al. Development and Validation of a Brief Version of the
11 697 Difficulties in Emotion Regulation Scale: The DERS-16. *J Psychopathol Behav Assess*.
12 698 2016;38(2):284-296. doi:[10.1007/s10862-015-9514-x](https://doi.org/10.1007/s10862-015-9514-x)
13 699 79. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials
14 700 being undertaken in the United Kingdom registered in the United Kingdom Clinical Research
15 701 Network database. *BMC Med Res Methodol*. 2013;13(1):104. doi:[10.1186/1471-2288-13-104](https://doi.org/10.1186/1471-2288-13-104)
16 702 80. Munder T, Wilmers F, Leonhart R, Linster HW, Barth J. Working Alliance Inventory-Short Revised
17 703 (WAI-SR): Psychometric properties in outpatients and inpatients. *Clinical Psychology &*
18 704 *Psychotherapy*. 2010;17(3):231-239. doi:[10.1002/cpp.658](https://doi.org/10.1002/cpp.658)
19 705 81. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline
20 706 personality disorder. *Clinical Psychology & Psychotherapy*. 2011;18(4):275-283.
21 707 doi:[10.1002/cpp.705](https://doi.org/10.1002/cpp.705)
22 708 82. Paulus C. Der Saarbrücker Persönlichkeitsfragebogen zur Messung von Empathie (SPF-IRI).
23 709 Published 2006. [http://bildungswissenschaften.uni-](http://bildungswissenschaften.uni-saarland.de/personal/paulus/homepage/empathie.html)
24 710 [saarland.de/personal/paulus/homepage/empathie.html](http://bildungswissenschaften.uni-saarland.de/personal/paulus/homepage/empathie.html)
25 711 83. Hausberg MC, Schulz H, Piegler T, et al. Is a self-rated instrument appropriate to assess
26 712 mentalization in patients with mental disorders? Development and first validation of the
27 713 Mentalization Questionnaire (MZQ). *Psychotherapy Research*. 2012;22(6):699-709.
28 714 doi:[10.1080/10503307.2012.709325](https://doi.org/10.1080/10503307.2012.709325)
29 715 84. Gratz KL, Roemer L. Multidimensional Assessment of Emotion Regulation and Dysregulation:
30 716 Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation
31 717 Scale. *Journal of Psychopathology and Behavioral Assessment*. 2004;26(1):41-54.
32 718 doi:[10.1023/B:JOBA.0000007455.08539.94](https://doi.org/10.1023/B:JOBA.0000007455.08539.94)
33 719 85. Goldman HH, Skodol AE, Lave TR. Revising Axis V for DSM-IV: A Review of Measures of Social
34 720 Functioning. Published online September 1, 1992. Accessed July 27, 2021.
35 721 <https://papers.ssrn.com/abstract=2143992>
36 722 86. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF Quality of Life
37 723 Assessment. *Psychological Medicine*. 1998;28(3):551-558. doi:[10.1017/S0033291798006667](https://doi.org/10.1017/S0033291798006667)
38 724 87. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. Psychological
39 725 Cooperation; 1996.
40 726 88. Beck AT, Steer RA. *Beck Anxiety Inventory Manual*. Psychological Cooperation; 1993.
41 727 89. Ehrenthal JC, Dinger U, Lamla A, Funken B, Schauenburg H. Evaluation der deutschsprachigen
42 728 Version des Bindungsfragebogens „Experiences in Close Relationships – Revised” (ECR-RD).
43 729 *Psychother Psychosom Med Psychol*. 2009;59(6):215-223. doi:[10.1055/s-2008-1067425](https://doi.org/10.1055/s-2008-1067425)
44 730 90. Price CJ, Thompson EA. Measuring Dimensions of Body Connection: Body Awareness and Bodily
45 731 Dissociation. *The Journal of Alternative and Complementary Medicine*. 2007;13(9):945-953.
46 732 doi:[10.1089/acm.2007.0537](https://doi.org/10.1089/acm.2007.0537)
47 733 91. Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure.
48 734 *Psychiatric Annals*. 2002;32(9):509-515. doi:[10.3928/0048-5713-20020901-06](https://doi.org/10.3928/0048-5713-20020901-06)
49 735 92. Kiesler DJ. The 1982 Interpersonal Circle: A taxonomy for complementarity in human transactions.
50 736 *Psychological Review*. 1983;90(3):185-214. doi:[10.1037/0033-295X.90.3.185](https://doi.org/10.1037/0033-295X.90.3.185)
51 737 93. Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How Does Mindfulness
52 738 Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural
53 739 Perspective. *Perspect Psychol Sci*. 2011;6(6):537-559. doi:[10.1177/1745691611419671](https://doi.org/10.1177/1745691611419671)
54 740 94. Arch JJ, Craske MG. Mechanisms of mindfulness: Emotion regulation following a focused
55 741 breathing induction. *Behavior Research and Therapy*. 2006;44(12):1849-1858.
56 742 doi:[10.1016/j.brat.2005.12.007](https://doi.org/10.1016/j.brat.2005.12.007)
57 743 95. Geschwind N, Peeters F, Drukker M, van Os J, Wichers M. Mindfulness training increases
58 744 momentary positive emotions and reward experience in adults vulnerable to depression: A
59 745 randomized controlled trial. *Journal of Consulting and Clinical Psychology*. 2011;79(5):618-
60 746 628. doi:[10.1037/a0024595](https://doi.org/10.1037/a0024595)
747 96. Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: A comprehensive meta-
748 analysis. *Clinical Psychology Review*. 2013;33(6):763-771. doi:[10.1016/j.cpr.2013.05.005](https://doi.org/10.1016/j.cpr.2013.05.005)

- 1
2
3 749 97. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in Brain and Immune Function
4 750 Produced by Mindfulness Meditation. *Psychosomatic Medicine*. 2003;65(4):564–570.
5 751 doi:[10.1097/01.PSY.0000077505.67574.E3](https://doi.org/10.1097/01.PSY.0000077505.67574.E3)
6 752 98. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive
7 753 therapy, and antidepressant medication in the acute treatment of adults with major depression.
8 754 *Journal of Consulting and Clinical Psychology*. 2006;74(4):658-670. doi:[10.1037/0022-](https://doi.org/10.1037/0022-006X.74.4.658)
9 755 [006X.74.4.658](https://doi.org/10.1037/0022-006X.74.4.658)
10 756 99. Hautzinger M. *Kognitive Verhaltenstherapie Bei Depressionen*. 7. Auflage. Beltz Psychologie
11 757 Verlags Union; 2013.
12 758 100. Cuijpers P. Four decades of outcome research on psychotherapies for adult depression: An
13 759 overview of a series of meta-analyses. *Canadian Psychology/Psychologie*
14 760 *canadienne*. 2017;58(1):7-19. doi:[10.1037/cap0000096](https://doi.org/10.1037/cap0000096)
15 761 101. Barth J, Munder T, Gerger H, et al. Comparative Efficacy of Seven Psychotherapeutic
16 762 Interventions for Patients with Depression: A Network Meta-Analysis. *FOC*.
17 763 2016;14(2):229-243. doi:[10.1176/appi.focus.140201](https://doi.org/10.1176/appi.focus.140201)
18 764 102. Linden M, Strauß B. *Risiken und Nebenwirkungen von Psychotherapie: Erfassung,*
19 765 *Bewältigung, Risikovermeidung*. 1st ed. MWV Medizinisch Wissenschaftliche
20 766 Verlagsgesellschaft; 2012.
21 767 103. Hoffmann SO, Rudolf G, Strauß B. Unerwünschte und schädliche Wirkungen von
22 768 Psychotherapie. *Psychotherapeut*. 2008;53(1):4-16. doi:[10.1007/s00278-007-0578-2](https://doi.org/10.1007/s00278-007-0578-2)
23 769 104. Cook SC, Schwartz AC, Kaslow NJ. Evidence-Based Psychotherapy: Advantages and
24 770 Challenges. *Neurotherapeutics*. 2017;14(3):537-545. doi:[10.1007/s13311-017-0549-4](https://doi.org/10.1007/s13311-017-0549-4)
25 771 105. Herschell AD, Kolko DJ, Baumann BL, Davis AC. The role of therapist training in the
26 772 implementation of psychosocial treatments: A review and critique with
27 773 recommendations. *Clinical Psychology Review*. 2010;30(4):448-466.
28 774 doi:[10.1016/j.cpr.2010.02.005](https://doi.org/10.1016/j.cpr.2010.02.005)
29 775 106. Ecker AH, O'Leary K, Fletcher TL, et al. Training and supporting mental health providers to
30 776 implement evidence-based psychotherapies in frontline practice. *Translational*
31 777 *Behavioral Medicine*. 2021;(ibab084). doi:[10.1093/tbm/ibab084](https://doi.org/10.1093/tbm/ibab084)
32 778

779 Figure and Table Legends

33
34
35 780 **Figure 1:** Overview of the targeted RDoC domains and their corresponding objectives,
36 781 assessments and modules. A detailed description of the modules is given below.

37
38 782 **Figure 2:** Trial design and flow of patients.

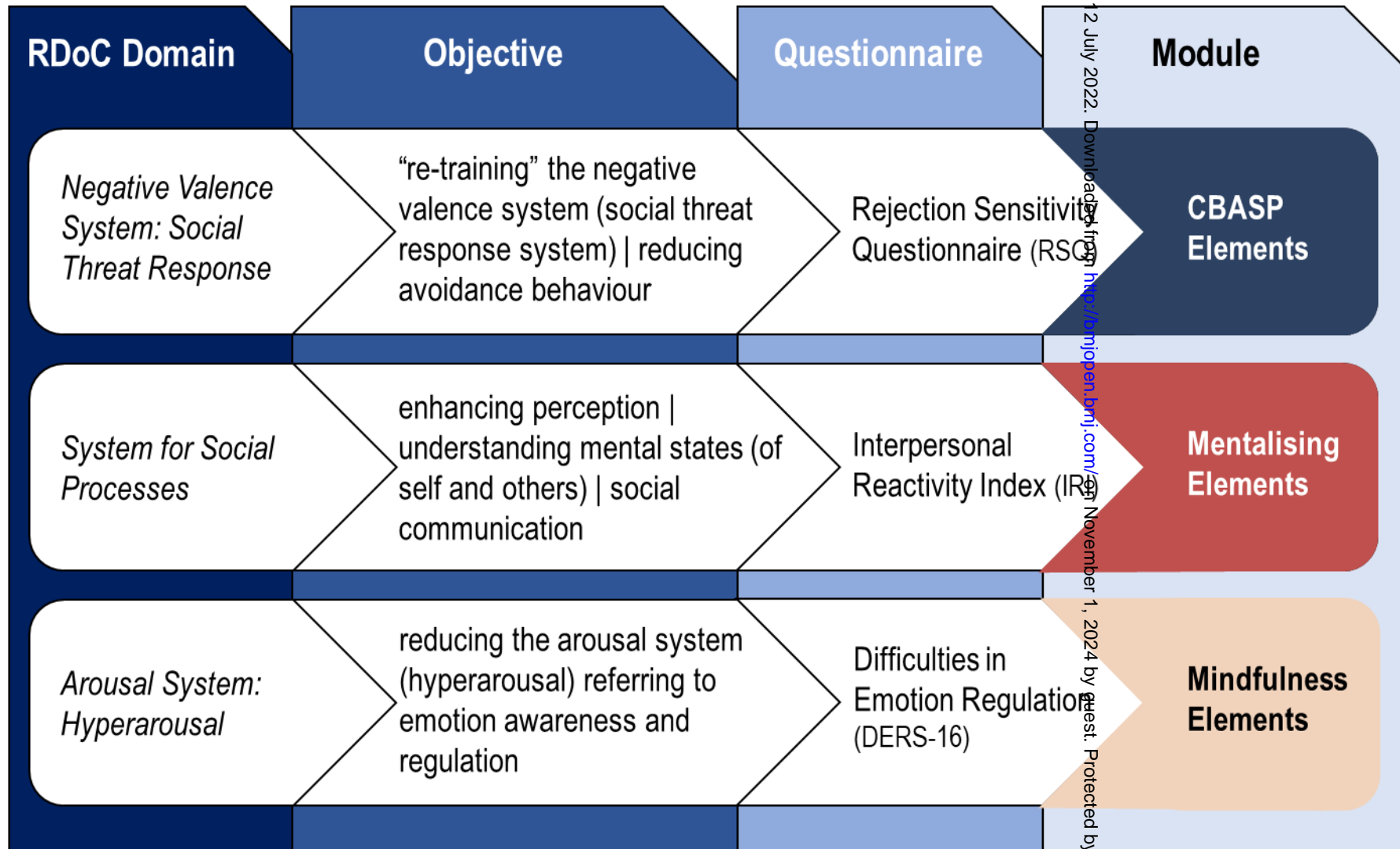
39
40 783 **Table 1:** Primary and Secondary Endpoints and corresponding measures.

41
42 784 **Figure 3.** Frequency and scope of trial visits.

43
44 785 **Figure 4:** Decision Tree Algorithm for Modular-Based Psychotherapy.

45
46 786 **Table 2:** Content and implementation of modules.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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



bmjopen-2021-05-7172 on 12 July 2022. Downloaded from <http://bmjopen.bmj.com/> on November 1, 2024 by guest. Protected by copyright.

Figure 2: Trial design and flow of patients.

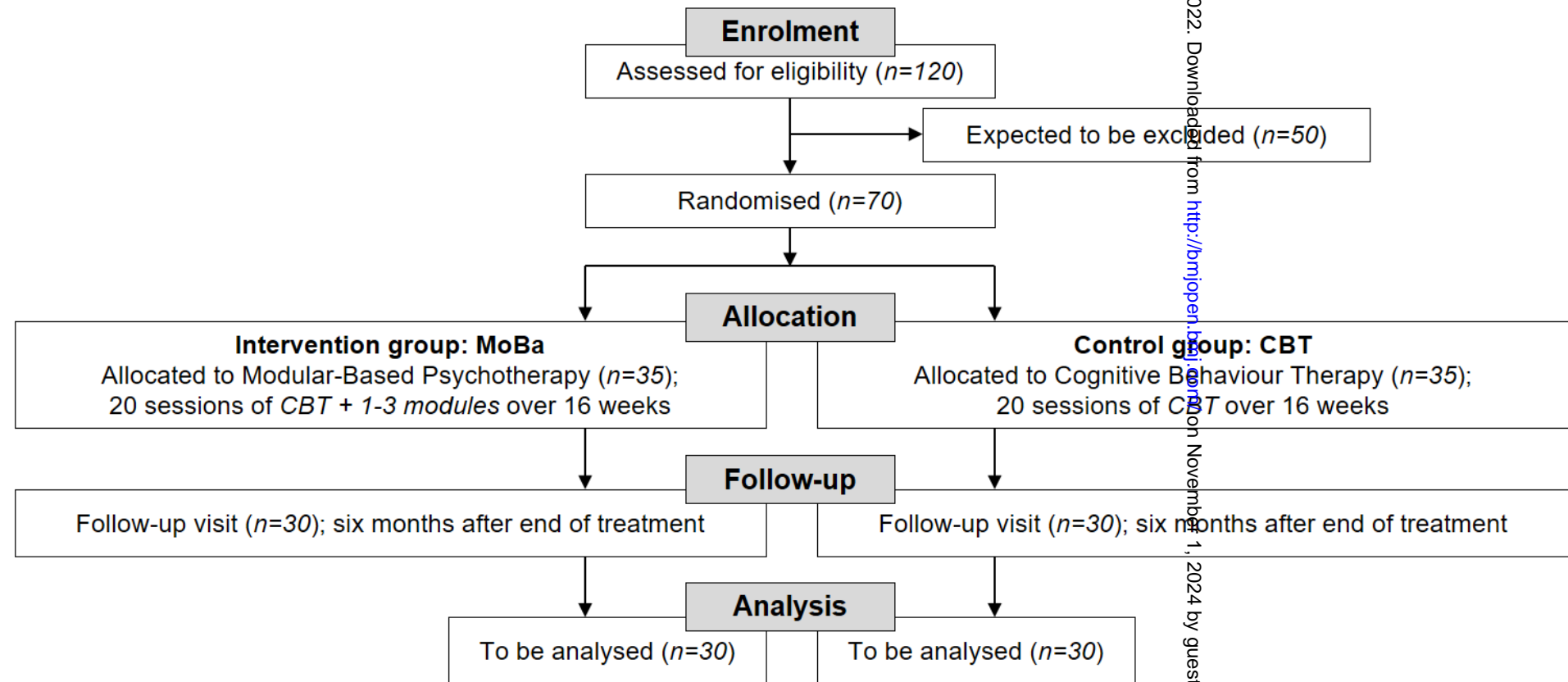
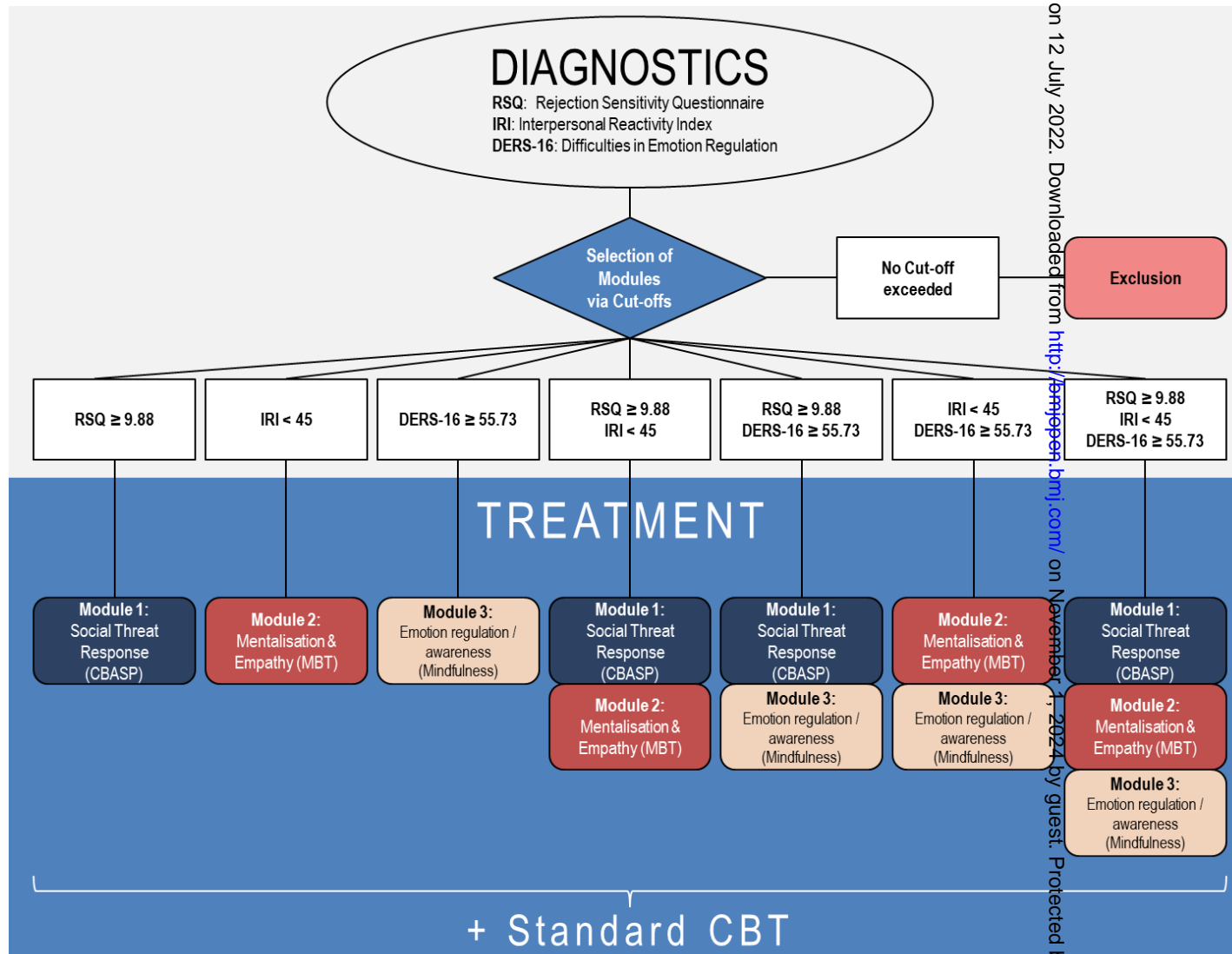


Figure 3. Frequency and scope of trial visits.

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		
		AE / SAE				X	X	X		
		PHQ-9				X	X	X		
		WAI-P / WAI-T						X		
RATERS	Interview	telephone screening	(X)							
		SCID-5 (CV/PD)		X						
		HRSD-24		X	(X)				X	X
		SOFAS			X				X	X
		AE / SAE			(X)				X	X
	Questionnaires	CTQ		X						
		RSQ		X					X	X
		IRI		X					X	X
		DERS-16		X					X	X
		MZQ			X				X	X
		BDI-II			X				X	X
		BAI			X				X	X
		WHOQoL-BREF			X				X	X
		PHQ-9			X				X	X
		ECR-RD8			X				X	X
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

1				
2	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
3				
4				
5				
6				
7				
8	Methods: Participants, interventions, and outcomes			
9				
10	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
11				
12				
13				
14				
15	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
16				
17				
18				
19				
20				
21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
22				
23				
24				
25				
26		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
27				
28				
29				
30				
31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
32				
33				
34				
35				
36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
37				
38				
39	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
40				
41				
42				
43				
44				
45				
46				
47				
48	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
49				
50				
51				
52				
53				
54	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
55				
56				
57				
58				
59				
60				

1				
2	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
3				
4				
5	Methods: Assignment of interventions (for controlled trials)			
6	Allocation:			
7				
8				
9	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
10				
11				
12				
13				
14				
15				
16				
17				
18	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
19				
20				
21				
22				
23				
24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
25				
26				
27				
28				
29	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
30				
31				
32				
33		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
34				
35				
36				
37	Methods: Data collection, management, and analysis			
38				
39	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
40				
41				
42				
43				
44				
45				
46				
47				
48				
49		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
50				
51				
52				
53				
54	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
55				
56				
57				
58				
59				
60				

1				
2	Statistical	20a	Statistical methods for analysing primary and secondary	
3	methods		outcomes. Reference to where other details of the statistical	15-16
4			analysis plan can be found, if not in the protocol	
5				
6		20b	Methods for any additional analyses (eg, subgroup and	
7			adjusted analyses)	15-16
8				
9		20c	Definition of analysis population relating to protocol non-	
10			adherence (eg, as randomised analysis), and any statistical	15-16
11			methods to handle missing data (eg, multiple imputation)	
12				
13				

Methods: Monitoring

14				
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC);	
17			summary of its role and reporting structure; statement of	
18			whether it is independent from the sponsor and competing	15
19			interests; and reference to where further details about its	
20			charter can be found, if not in the protocol. Alternatively, an	
21			explanation of why a DMC is not needed	
22				
23				
24		21b	Description of any interim analyses and stopping	
25			guidelines, including who will have access to these interim	15-16
26			results and make the final decision to terminate the trial	
27				
28	Harms	22	Plans for collecting, assessing, reporting, and managing	
29			solicited and spontaneously reported adverse events and	17-18
30			other unintended effects of trial interventions or trial conduct	
31				
32				
33	Auditing	23	Frequency and procedures for auditing trial conduct, if any,	15/17
34			and whether the process will be independent from	-18
35			investigators and the sponsor	
36				
37				

Ethics and dissemination

38				
39				
40	Research ethics	24	Plans for seeking research ethics committee/institutional	16-17
41	approval		review board (REC/IRB) approval	
42				
43	Protocol	25	Plans for communicating important protocol modifications	
44	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	n.a.
45			relevant parties (eg, investigators, REC/IRBs, trial	
46			participants, trial registries, journals, regulators)	
47				
48	Consent or	26a	Who will obtain informed consent or assent from potential	
49	assent		trial participants or authorised surrogates, and how (see	17
50			Item 32)	
51				
52				
53		26b	Additional consent provisions for collection and use of	
54			participant data and biological specimens in ancillary	n.a.
55			studies, if applicable	
56				
57				
58				
59				
60				

1				
2	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
3				
4				
5				
6				
7	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
8				
9				
10	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
11				
12				
13				
14				
15	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.
16				
17				
18				
19	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
20				
21				
22				
23				
24				
25				
26				
27		31b	Authorship eligibility guidelines and any intended use of professional writers	20
28				
29				
30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
31				
32				
33	Appendices			
34				
35	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	17/19
36				
37				
38				
39				
40	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.
41				
42				
43				
44				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057672.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Feb-2022
Complete List of Authors:	Elsaesser, Moritz; University of Freiburg, Department of Psychiatry and Psychotherapy, University Medical Center – University of Freiburg, Faculty of Medicine Herpertz, Sabine; Heidelberg University, Department of General Psychiatry Piosczyk, Hannah; University of Freiburg, Department of Psychiatry and Psychotherapy, University Medical Center – University of Freiburg, Faculty of Medicine Jenkner, Carolin ; Universitätsklinikum Freiburg, Clinical Trials Unit Hautzinger, Martin; Eberhard Karls University of Tübingen, Department of Psychology, Clinical Psychology, and Psychotherapy Schramm, Elisabeth; University of Freiburg, Department of Psychiatry and Psychotherapy
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Depression & mood disorders < PSYCHIATRY, PSYCHIATRY, Adult psychiatry < PSYCHIATRY

SCHOLARONE™
Manuscripts

1
2
3 1 **Modular-Based Psychotherapy (MoBa) versus Cognitive**
4
5 2 **Behavioural Therapy (CBT) for patients with comorbid depression**
6
7 3 **and a history of childhood maltreatment: Study protocol for a**
8
9 4 **randomised controlled feasibility trial**
10
11 5
12

13 6 Moritz Elsaesser¹, Sabine Herpertz², Hannah Piosczyk¹, Carolin Jenkner³, Martin
14 7 Hautzinger⁴ & Elisabeth Schramm^{1*}
15 8

17 9 ¹ Department of Psychiatry and Psychotherapy, University Medical Centre –
18 10 University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

20 11 ² Department of General Psychiatry, Centre for Psychosocial Medicine, Medical
21 12 Faculty, Heidelberg University, Heidelberg, Germany

23 13 ³ Clinical Trials Unit, Faculty of Medicine, University Medical Centre, University of
24 14 Freiburg, Freiburg, Germany

26 15 ⁴ Department of Psychology, Clinical Psychology, and Psychotherapy, Eberhard
27 16 Karls University of Tübingen, Tübingen, Germany
28 17

30 18
31 19
32 20
33 21
34 22
35 23
36 24
37 25
38 26
39 27
40 28
41 29
42 30
43 31
44 32
45 33
46 34
47 35
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Word count: 3999

*Correspondence:

Prof Dr Elisabeth Schramm

Department of Psychiatry and Psychotherapy

University Medical Centre – University of Freiburg, Hauptstraße 5

DE–79104 Freiburg (Germany)

✉ elisabeth.schramm@uniklinik-freiburg.de

36 **Abstract**

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

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

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

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

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

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

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

70 **Abstract Summary**

71 ***Strengths and limitations of this study***

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

84 Introduction

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

97 *Childhood maltreatment*

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

1
2
3 111 higher in depressed patients with early trauma compared to those without [16]. Taken together,
4
5 112 study results indicate that interpersonal trauma exposure complicates the treatment of
6
7 113 depression and reduces the impact of traditional cognitive therapy or treatments such as
8
9 114 psychoeducation, TAU, or pharmacotherapy [24]. However, some approaches like
10
11 115 Mindfulness Based Cognitive Therapy (MBCT) [25] or the Cognitive Behavioral Analysis
12
13 116 System of Psychotherapy (CBASP) [26-28] show promising results in the subgroup of
14
15 117 depressed patients with CM.

18 118 ***Impact of childhood maltreatment on social and emotional functioning***

19 119 A growing body of evidence links interpersonal trauma in both youth and adults to difficulties
20
21 120 in social and emotional functioning [24]. Among other sequelae, CM usually results in marked
22
23 121 avoidance behaviour [9] with negative social consequences and in concomitant retardation of
24
25 122 emotional maturational growth [28,29]. These deficits are also expressed in terms of social
26
27 123 threat hyperresponsivity (i.e. being highly sensitive to social rejection and anxiously expecting,
28
29 124 readily perceiving, and overreacting to it) [30-33], social stress and avoidance behaviour
30
31 125 [34,35], lack of empathy and theory-of-mind [36-38] and emotional dysregulation [39,40].
32
33 126 These emotional and social dysfunctions are mediated in common brain circuits for emotion
34
35 127 and salience regulation, fear, and mentalising, suggesting that abnormalities in these
36
37 128 functional pathways may be induced by CM [41,42]. Despite these severe consequences of
38
39 129 CM and their important implications for treatment, disorder-specific approaches for depression
40
41 130 such as CBT or IPT do not specifically address the role of CM and the affected dimensions of
42
43 131 functioning.

48 132 ***Personalised Treatments***

49 133 This calls for personalised treatments that target both comorbidities as well as underlying
50
51 134 mechanisms and factors, which are central to the development and maintenance of
52
53 135 psychological disorders. One of the challenges in the development of personalised approaches
54
55 136 is to select treatment modules for targeted dysfunctions and to determine whether and in which
56
57 137 sequence to combine them with standard treatment. In daily practice, it is left to the clinical

1
2
3 138 judgement and expertise of the therapist to address the patient's individual needs and
4
5 139 comorbidities by adding various therapeutic strategies to the disorder-specific interventions.
6
7 140 However, this choice of add-on strategies is not backed up by empirical evidence and thus
8
9 141 hardly conveyable to usual clinical practice in a systematic way [43]. Driven by these concerns,
10
11 142 there has been growing consensus that a novel approach is needed in the way we classify,
12
13 143 formulate, treat, and prevent depression and other mental disorders [44,45]. Insel and Cuthbert
14
15 144 [46] postulated the concept of Research Domain Criteria (RDoC) to move "toward a new
16
17 145 classification system" of studying and validating transdiagnostic, dimensional constructs since
18
19 146 psychiatric diagnosis seem to be no longer optimal as long as they remain restricted to
20
21 147 symptoms and signs. The transdiagnostic procedure focuses on identifying the common and
22
23 148 core maladaptive temperamental, cognitive, emotional, interpersonal and behavioural
24
25 149 characteristics that underpin a broad array of diagnostic presentations [47] and addresses
26
27 150 them via specific modules in treatment [48]. In this sense, a modular-based psychotherapy
28
29 151 provides a structured approach of tailoring treatments to fit patient needs by allowing greater
30
31 152 flexibility to consider interindividual differences and comorbidity [49,50]. The modules, as sets
32
33 153 of independent but combinable functional units, focus on common transdiagnostic dysfunctions
34
35 154 and offer skills to improve e.g. emotion regulation, social competence, empathy, or self-
36
37 155 motivation. There is only one study [51] in which emotion regulation skills were successfully
38
39 156 added to CBT in depressed patients that had sufficient statistical power to detect a clinically
40
41 157 significant effect.
42
43
44
45

46 ***Modular-Based Psychotherapy (MoBa)***

47
48 159 Empirical support for the effectiveness of modular approaches following decision flowcharts is
49
50 160 emerging lately [50,52]. For instance, Weisz and colleagues [49] conducted a large
51
52 161 randomized controlled trial (RCT) in which a Modular Approach to Therapy for Children with
53
54 162 Anxiety, Depression, Trauma, or Conduct Problems (MATCH) outperformed standard manual
55
56 163 treatment as well as care as usual (CAU). The superiority of MATCH was found to be sustained
57
58 164 in a two-year follow-up [53] and was replicated in a more recent trial [54]. Another example of
59
60 165 a modular approach to psychotherapy is Behavioural Interventions for Anxiety in Children with

1
2
3 166 Autism (BIACA) [55]. By using a modular format and including an algorithm to guide the
4
5 167 selection of modules, it offers a treatment approach for several anxiety disorders and
6
7 168 obsessive-compulsive disorder for youths on the autism spectrum. BIACA was superior to
8
9 169 waitlist and CAU in several RCTs (e.g. [56]). In adults, a recent RCT [57] assessed the
10
11 170 feasibility and efficacy of a modular transdiagnostic intervention for mood, stressor-related and
12
13 171 anxiety disorders (HARMONIC trial) in preparation for a later-stage trial. The modular
14
15 172 transdiagnostic intervention demonstrated superiority with moderate effect sizes compared to
16
17 173 psychological treatment-as-usual [58]. This represents early signs of a significant paradigm
18
19 174 shift away from single-diagnosis approaches towards dimensional, transdiagnostic, and
20
21 175 modular-based conceptualizations [59,46].

22
23
24 176 The here proposed rationale for a modular-based psychotherapy (MoBa) for depressed
25
26 177 patients with comorbidity and a history of CM is two-fold: First, to include patients regularly
27
28 178 seen in clinical practice showing a) more often comorbid and heterogeneous complaints than
29
30 179 the samples usually included in RCTs and b) a limited treatment response to standard disorder-
31
32 180 specific approaches. Second, tailoring the treatment to the specific characteristics and needs
33
34 181 of patients with CM and comorbid depression can ensure that the psychotherapeutic process
35
36 182 is responsive and may reach better treatment results. The MoBa intervention aims at
37
38 183 interpersonal and emotional maturation by overcoming social threat hypersensitivity and
39
40 184 interpersonal avoidance patterns and improving poor mentalisation as well as poor emotion
41
42 185 regulation capacities. The rationale is supported by previous trials with empirically supported
43
44 186 treatments such as CBASP for chronic depression [60-63], MBCT for depression prevention
45
46 187 and treatment [64-67], and Mentalization-Based Therapy (MBT) [68] for borderline personality
47
48 188 disorder [69,70]. In the here used design, MoBa complements standard CBT with modules
49
50 189 compiling specific elements from CBASP, MBCT, and MBT focusing on three disturbed
51
52 190 systems (Figure 1). Those systems are part of the RDoC model and have been shown to be
53
54 191 critically related to CM:

55
56
57
58 192 I) the negative valence system (acute, potential, and sustained threat): social threat
59
60 193 response and avoidance behaviour [34,9];

- 1
2
3 194 II) the system of social processes: perception and understanding of self and others
4
5 195 (understanding mental states), social communication, attachment [71,37,38];
6
7 196 III) the arousal system: emotion awareness and arousal regulation [40,72-74].
8

9
10 **[FIGURE 1]**
11

12
13 **Objectives**
14

15 199 This pilot study has a number of objectives appropriate to its status as a feasibility study:

- 16
17 200 1. Providing initial evidence for the efficacy of MoBa (reduction of clinician-rated
18
19 201 depressive symptoms) as well as generating pilot data for the power calculation in
20
21 202 terms of effect and sample size for a subsequent multicentre confirmatory trial.
22
23 203 2. Investigating the planned study design regarding the feasibility of recruitment, feasibility
24
25 204 of applying cut-off values of self-reported deficits to select the modules, acceptability of
26
27 205 the program to therapists and patients as well as patient ratings of 'usefulness' (both
28
29 206 overall and in terms of individual modules). A crucial goal is to refine the algorithm for
30
31 207 the selection of modules based on questionnaires.
32
33 208 3. Explore potential moderators of the primary outcome (in a hypothesis-generating
34
35 209 exercise and to help refine the intervention).
36
37
38

39 **Methods and analysis**
40
41

42 **Study design**
43

44 212 The bicentric study will be conducted at the Department of Psychiatry and Psychotherapy,
45
46 213 University Medical Centre Freiburg, Germany, and the Department of General Psychiatry,
47
48 214 University Medical Centre Heidelberg, Germany. It is a parallel-arm RCT (N=70) comparing
49
50 215 MoBa with CBT in 20 individual sessions over 16 weeks of treatment (twice weekly in weeks
51
52 216 1-4, then once per week in weeks 5-16). Participants will be assessed at screening, baseline,
53
54 217 post-treatment and follow-up (six months after end of treatment).
55
56
57

58 **Study population and recruitment**
59
60

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

221

222 Inclusion criteria:

- 223 1. Age eligibility: 18-65 years.
- 224 2. Episodic or persistent MDD or MDD superimposed on Dysthymia (“Double
225 Depression”) as the primary diagnosis (according to the SCID-5) [75].
- 226 3. A score of > 18 on the Hamilton Rating Scale for Depression (HRSD-24) [76].
- 227 4. History of CM: at least moderate to severe in one or more of the five CTQ-categories
228 (emotional neglect, emotional abuse, physical neglect, physical abuse, sexual abuse)
229 [15].
- 230 5. At least one psychiatric comorbidity or more according to the SCID-5 (except for those
231 described in the exclusion criteria below).
- 232 6. Exceeding the ‘cut-off’ value of at least one of the following measures (module
233 questionnaires): 1) Rejection Sensitivity Questionnaire (RSQ, [77]) ≥ 9.88 , 2)
234 Interpersonal Reactivity Index (IRI, [78]) < 45, or 3) Difficulties in Emotion Regulation
235 Scale-16 (DERS-16, [79]) ≥ 55.73 .
- 236 7. Written informed consent.

237 Exclusion criteria:

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

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

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

257 **[FIGURE 2]**

258 **Sample size**

259 Due to the exploratory nature of the design and the lack of comparable studies, no formal
 260 sample size calculation is possible. One of the major aims of this trial is to generate pilot data
 261 for a subsequent sample size calculation for a confirmatory study. With reference to Billingham
 262 et al. [80] a medium sample size of 30 patients per group in pilot trials seems to be reasonable
 263 for the generation of pilot data for such estimation. That results in a total of 60 patients. Non-
 264 compliance and/or dropout of patients after randomization are assumed to be at most 14%.
 265 Therefore, 70 patients have to be randomized to observe the desired number of compliant
 266 patients, split in two groups for each of the two participating centres (FR=35, HD=35; Figure
 267 2).

268 **Outcomes**

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

271 **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.

Modular-Based Psychotherapy (MoBa) vs. CBT

11

	(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.

272

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

275 **[FIGURE 3]**

276 ***Adherence***

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

289 ***Experimental intervention: Modular-Based Psychotherapy***

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

294 **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
<p>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 “<i>Significant Other History</i>” (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 “<i>transference hypothesis</i>” is formulated stating the patient’s most relevant interpersonal expectation/fear regarding the therapist-patient</p>		

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.

295 **Selection of modules**

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

1
2
3 301 and regulation). The corresponding modular interventions will be applied if the cut-off value in
4
5 302 one or more of these measures is exceeded. Since no a priori values are established, the cut-
6
7 303 offs used here are defined as one standard deviation above the general population mean, i.e.
8
9 304 the upper 16% [82,79]. The problem(s) thus identified is/are assigned as the target for one,
10
11 305 two or three of the modules (figure 3) according to the systematic treatment algorithm (figure
12
13 306 4).

15 307 [FIGURE 4]

16 308 Treatment modules are selected according to the evidence-based treatment algorithm on the
17
18 309 basis of the self-rated module-specific questionnaires. However, the selection of specific
19
20 310 treatment strategies or techniques *within* a specific module (e.g. BA or cognitive restructuring
21
22 311 in CBT, use of Kiesler's circumplex model or interpersonal discrimination exercise in CBASP)
23
24 312 and the sequence of treatment strategies or techniques *between* modules are based on the
25
26 313 clinical judgement and expertise of the therapist and the supervisors, since there is no reliable
27
28 314 evidence to implement a data-driven decision algorithm for sequencing yet. The individual case
29
30 315 conceptualizations are formulated in consultation with the supervisors who regularly check on
31
32 316 the weekly intraindividual PHQ-9 courses and the utilisation of treatment techniques within
33
34 317 each session according to the Therapy Elements Checklist (TEC) and the video recordings.

35 318 ***Application of modules (time distribution)***

36 319 The modules are not simply added as separate components, but rather integrated into the
37
38 320 therapeutic process and course as add-on to the standard CBT procedure as basis for both
39
40 321 interventions. Consequently, the amount of time spent with single CBT-techniques (e.g.
41
42 322 cognitive restructuring) will be reduced with increasing number of modules and the procedure
43
44 323 will be condensed to behavioural activation (e.g. identifying and promoting pleasant activities)
45
46 324 as the most effective component of CBT [99]. Depending on the selected number of modules,
47
48 325 approximately one third of the time will be spent with basic CBT procedures and two thirds of
49
50 326 the time with the application of modules. Therapists will document the time, which is spent with
51
52 327 CBT procedures or with single modules, after each session.
53
54
55
56
57
58
59
60

1
2
3 328 **Control intervention: CBT**

4
5 329 CBT will be delivered according to the German standard manual by Hautzinger [100]. The main
6
7 330 CBT elements are 1. establishing therapeutic relationship, 2. psychoeducation, 3. behaviour
8
9 331 activation, 4. cognitive restructuring, and 5. maintenance and relapse prevention. CBT has
10
11 332 been shown to be efficacious in depressed patients in prior clinical trials [101,102], but not
12
13 333 specifically in this subgroup of depressed and comorbid patients exposed to CM.

14
15
16 334 **Randomisation**

17
18 335 The randomisation code will be generated by the Clinical Trials Unit Freiburg (CTU) using the
19
20 336 following procedure to ensure that treatment assignment is unbiased and concealed from
21
22 337 patients and investigator staff. Randomisation will be performed, stratified by site, in blocks of
23
24 338 variable length in a ratio of 1:1. The block lengths will be documented separately and will not
25
26 339 be disclosed to the sites. The randomisation code will be produced by validated programs
27
28 340 based on the Statistical Analysis System (SAS). This dataset is included in Redcap so that
29
30 341 patients can be randomised directly in the eCRF.

31
32
33
34 342 **Blinding**

35
36 343 All clinical ratings will be completed by trained and independent raters blinded to treatment
37
38 344 assignment. Each of the sites implements procedures to mask a patient treatment assignment
39
40 345 from the person who will evaluate the results of the clinical ratings through the following: 1)
41
42 346 locating the raters at a separate physical location, and 2) reminding the patients at each visit
43
44 347 not to mention anything that might reveal their treatment condition to the independent
45
46 348 evaluator.

47
48
49
50 349 **Data Management and Monitoring**

51
52 350 Study data will be entered in pseudonymised form in a study database by authorized and
53
54 351 trained members of the study team via electronic case report forms (eCRF). The data
55
56 352 management will be performed with REDCap™ Version 9, a fully web based remote data entry
57
58 353 system based on web forms, which is developed and maintained by the REDCap Consortium
59
60 354 (redcap@vanderbilt.edu). This system uses built-in security features to prevent unauthorized

1
2
3 355 access to patient data, including an encrypted transport protocol for data transmission from
4
5 356 the participating sites to the study database. An audit trail provides a history of the data
6
7 357 entered, changed, or deleted, indicating the processor and date. Monitoring is performed by
8
9 358 CTU. Risk-based monitoring will be done according to ICH-GCP E6 (R2) and standard
10
11 359 operating procedures (SOP) to ensure patient's safety and integrity of clinical trial data.

14 360 **Statistical Analysis**

16 361 Before the start of the final analysis, a detailed statistical analysis plan will be prepared. This
17
18 362 will be completed during the 'blind review' of the data, at the latest. The primary efficacy
19
20 363 analysis will be performed according to the intention-to-treat (ITT) principle and will therefore
21
22 364 be based on the full analysis set (FAS) including all randomized patients. Patients are analysed
23
24 365 as randomised regardless of any protocol deviations. This analysis corresponds to the analysis
25
26 366 of the treatment policy estimand. The effects of CBT and MoBa with respect to the HRSD-24
27
28 367 score after 16 weeks of treatment (primary endpoint) will be estimated within a linear
29
30 368 regression model, and the two-sided 95% confidence interval will be calculated for the
31
32 369 treatment effect. The model will include treatment and study centre as independent variables,
33
34 370 as well as baseline HRSD-24 score. A conservative assumption of the effect size anticipated
35
36 371 for the subsequent confirmative trial will be derived from these analyses by a combination of
37
38 372 clinical and statistical judgement. Secondary endpoints will be analysed descriptively in a
39
40 373 similar fashion as the primary outcome in the FAS, using regression models as appropriate for
41
42 374 the respective type of data. Treatment effects will be calculated with two-sided 95% confidence
43
44 375 intervals. All secondary analyses are exploratory and are interpreted in a descriptive fashion.
45
46 376 The safety analysis includes calculation and comparison of frequencies and rates of serious
47
48 377 adverse events. Furthermore, statistical methods are used to assess the quality of data and
49
50 378 the homogeneity of intervention groups. Data should be collected regardless of the patients'
51
52 379 adherence to the protocol, especially on the clinical outcome, to obtain the best approximation
53
54 380 to the full analysis set. Data should also be collected on other therapies received post dropout.
55
56 381 Patients with missing follow-up will be excluded. As the only available measurement of the
57
58 382 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

1
2
3 410 screened for at every assessment or therapy session. AEs have to be reported to the principal
4
5 411 investigators (ES, SH) and SAEs to the independent experts. In addition, on-site data
6
7 412 monitoring will be regularly conducted by a clinical monitor from CTU to ensure patients' safety
8
9 413 and integrity of the clinical data in adherence to the study protocol, as well as to check data
10
11 414 quality and accuracy. Individual trial participation will be stopped if one of the following
12
13 415 discontinuation criteria occurs:

- 14
15 416 a) Active suicidality
16
17 417 b) The physical health of the patient is at risk according to clinical judgment
18
19 418 c) Occurrence of an AE/SAE with therapeutic implications incompatible with the study
20
21 419 d) Newly occurring exclusion criteria (demanding further procedures not compatible with
22
23 420 the continuation of the study participation)
24
25 421 e) Withdrawal of the informed consent

26
27 422 If the study principal investigator or the co-principal investigator have serious ethical concerns
28
29 423 because of the performance at one of the sites or severe safety concerns become apparent to
30
31 424 the independent experts, the whole trial will be discontinued.
32
33
34

35 425 ***Trial Status***

36
37 426 Official study begin was in May 2020. The first patient was included in December 2020. Within
38
39 427 the first months of recruiting, there were no difficulties regarding the recruitment and inclusion
40
41 428 of eligible patients, or the implementation of the MoBa and CBT treatments. Due to the ongoing
42
43 429 COVID-19 pandemic, all in person contacts (assessments as well as psychotherapy sessions)
44
45 430 are done while wearing appropriate face masks (surgical or FFP2) according to the national
46
47 431 guidelines and the respective guidelines of the University Medical Centres in Freiburg and
48
49 432 Heidelberg. The end of treatment is expected for August 2022 and data collection aims to be
50
51 433 completed in April 2023.
52
53
54

55 434 **Discussion**

56
57 435 Most evidence-based treatment protocols are single-disorder-specific manuals disregarding
58
59 436 common comorbidities and transdiagnostic clinical phenomena as sequelae of early trauma
60

1
2
3 437 and childhood adversities. This leaves a mismatch between the available disorder-specific
4
5 438 manuals and the clinical reality. Many clinicians consider the use of evidence-based manuals
6
7 439 as challenging or even inadequate for their daily work and report resistances to the
8
9 440 'oversimplified', 'rigid', 'inflexible' or 'flawed' rationales and the 'extensive efforts' needed to
10
11 441 maintain up-to-date knowledge by ongoing training [105]. Even attending evidence-based
12
13 442 workshops has little impact on clinicians' decisions to use evidence-based treatment protocols
14
15 443 in their practice resulting in the well-known underutilization in community settings [106,107]. In
16
17 444 contrast to conventional evidence-based treatment protocols, a modular-based psychotherapy
18
19 445 supports the eclectic approach of most clinicians by providing them with an evidence-based
20
21 446 treatment algorithm to combine and integrate available treatment modules as independent but
22
23 447 combinable sets of functional units systematically. This reduces the perceived challenges of
24
25 448 using evidence-based approaches by ensuring a high flexibility and goodness-of-fit within a
26
27 449 systematic framework for personalised treatments. By optimally tailoring module selection and
28
29 450 application to the specific needs of each patient, MoBa has great potential to improve the
30
31 451 currently unsatisfying results of psychotherapeutic treatments in research and clinical practice
32
33 452 as a bridge between disorder-specific and personalised approaches. Due to the limited sample
34
35 453 size of this feasibility study, statistical analyses will be limited exclusively to comparisons of
36
37 454 MoBa versus CBT, since tests between different modules within the MoBa intervention arm
38
39 455 are not sufficiently powered. While the modules are selected based on our evidence-based
40
41 456 algorithm, the selection of specific treatment strategies or techniques *within* a specific module
42
43 457 and the sequencing *between* modules are based on individual case conceptualisations, since
44
45 458 there is no reliable evidence to implement a data-driven decision algorithm for sequencing yet.
46
47
48
49

50 459 **Declarations**

51 52 53 54 460 ***Availability of data and materials***

55
56 461 The datasets used and/or analysed during the current study are available from the
57
58 462 corresponding author on reasonable request.
59
60

463 ***Patient and public involvement***

1
2
3 464 Neither patients nor public were systematically involved in designing this study. Feedback is
4
5 465 constantly collected from participants on their experience of participating and implemented in
6
7 466 conducting this trial. The main results will be disseminated to trial participants and systematic
8
9 467 patient and public involvement in the development of a subsequent multicentre confirmatory
10
11 468 trial will be implemented.

14 469 **Competing interests**

16 470 The authors declare the following competing interests: ME received minor book royalties. SH
17
18 471 received minor royalties for books with chapters on modular psychotherapy. HP and CJ declare
19
20 472 no competing interests. MH received book royalties from several publishers. ES received book
21
22 473 royalties and honoraria for workshops and presentations relating to Interpersonal
23
24 474 Psychotherapy and CBASP.

28 475 **Funding**

30 476 The clinical trial is financially supported by the German Research Foundation (Deutsche
31
32 477 Forschungsgemeinschaft, DFG; GZ: SCHR 443/16-1). The funders do not control the final
33
34 478 decision regarding any of aspects of the trial: design, conduct, data analysis and interpretation,
35
36 479 manuscript writing, and dissemination of trial results.

40 480 **Authors contributions**

42 481 ME, ES and SH were the main contributors in drafting this manuscript. ES and SH were the
43
44 482 main contributors in designing this study with support by ME. CJ provided expertise on data
45
46 483 monitoring, data management and statistical analyses. HP and MH provided important
47
48 484 feedback on all manuscript versions. All authors approved the final version.

51 485 **Acknowledgements**

53 486 The article processing charge was funded by the Baden-Wuerttemberg Ministry of Science,
54
55 487 Research and Art and the University of Freiburg in the funding programme Open Access
56
57 488 Publishing. We would like to thank Prof Fritz Hohagen, Prof Klaus Lieb and Prof Matthias
58
59 489 Backenstraß for their contributions as independent experts, as well as Dr Thomas Fangmeier

490 for his valuable assistance in determining the module cut-offs for the initial grant. Furthermore,
 491 we are grateful for the participation of Dr Anne Külz and Prof Svenja Taubner for their ongoing
 492 supervision and therapist trainings as experts of their fields in MBCT and MBT.

493 References

- 494 1. Beck AT. *Cognitive Therapy of Depression*. Guilford Press; 1979.
- 495 2. Klerman GL, Weissman MM, Rounsaville BJ, Chevron E. *Interpersonal Psychotherapy of*
 496 *Depression*. Basic Books; 1984.
- 497 3. Cuijpers P, Karyotaki E, Ciharova M, Miguel C, Noma H, Furukawa TA. The effects of
 498 psychotherapies for depression on response, remission, reliable change, and deterioration: A
 499 meta-analysis. *Acta Psychiatrica Scandinavica*. 2021. doi:[10.1111/acps.13335](https://doi.org/10.1111/acps.13335)
- 500 4. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression
 501 (TRD)? A systematic review of current randomized trials. *European*
 502 *Neuropsychopharmacology*. 2007;17(11):696-707. doi:[10.1016/j.euroneuro.2007.03.009](https://doi.org/10.1016/j.euroneuro.2007.03.009)
- 503 5. Holtzheimer PE, Mayberg HS. Stuck in a rut: Rethinking depression and its treatment. *Trends in*
 504 *Neurosciences*. 2011;34(1):1-9. doi:[10.1016/j.tins.2010.10.004](https://doi.org/10.1016/j.tins.2010.10.004)
- 505 6. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and
 506 Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey
 507 Replication. *Archives of General Psychiatry*. 2005;62(6):593-602.
 508 doi:[10.1001/archpsyc.62.6.593](https://doi.org/10.1001/archpsyc.62.6.593)
- 509 7. Lamers F, Oppen P van, Comijs HC, et al. Comorbidity Patterns of Anxiety and Depressive
 510 Disorders in a Large Cohort Study: The Netherlands Study of Depression and Anxiety
 511 (NESDA). *J Clin Psychiatry*. 2011;72(3):0-0. doi:[10.4088/JCP.10m06176blu](https://doi.org/10.4088/JCP.10m06176blu)
- 512 8. Roca M, Gili M, Garcia-Garcia M, et al. Prevalence and comorbidity of common mental disorders
 513 in primary care. *Journal of Affective Disorders*. 2009;119(1):52-58. doi:[10.1016/j.jad.2009.03.014](https://doi.org/10.1016/j.jad.2009.03.014)
- 514 9. Klein JP, Roniger A, Schweiger U, Späth C, Brodbeck J. The Association of Childhood Trauma
 515 and Personality Disorders With Chronic Depression: A Cross-Sectional Study in Depressed
 516 Outpatients. *J Clin Psychiatry*. 2015;76(6):0-0. doi:[10.4088/JCP.14m09158](https://doi.org/10.4088/JCP.14m09158)
- 517 10. Papakostas GI, Fava M. Predictors, moderators, and mediators (correlates) of treatment outcome
 518 in major depressive disorder. *Dialogues Clin Neurosci*. 2008;10(4):439-451.
 519 doi:[10.31887/DCNS.2008.10.4/gipapakostas](https://doi.org/10.31887/DCNS.2008.10.4/gipapakostas)
- 520 11. Souery D, Oswald P, Massat I, et al. Clinical Factors Associated With Treatment Resistance in
 521 Major Depressive Disorder: Results From a European Multicenter Study. *J Clin Psychiatry*.
 522 2007;68(7):0-0.
- 523 12. Goddard E, Wingrove J, Moran P. The impact of comorbid personality difficulties on response to
 524 IAPT treatment for depression and anxiety. *Behavior Research and Therapy*. 2015;73:1-7.
 525 doi:[10.1016/j.brat.2015.07.006](https://doi.org/10.1016/j.brat.2015.07.006)
- 526 13. Agosti V. Predictors of remission from chronic depression: A prospective study in a nationally
 527 representative sample. *Comprehensive Psychiatry*. 2014;55(3):463-467.
 528 doi:[10.1016/j.comppsy.2013.09.016](https://doi.org/10.1016/j.comppsy.2013.09.016)
- 529 14. Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major
 530 depression with interpersonal psychotherapy and SSRI pharmacotherapy. *Psychological*
 531 *Medicine*. 2011;41(1):151-162. doi:[10.1017/S0033291710000553](https://doi.org/10.1017/S0033291710000553)
- 532 15. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening
 533 version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*. 2003;27(2):169-190.
 534 doi:[10.1016/S0145-2134\(02\)00541-0](https://doi.org/10.1016/S0145-2134(02)00541-0)
- 535 16. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of
 536 adult depression: Meta-analysis. *The British Journal of Psychiatry*. 2017;210(2):96-104.
 537 doi:[10.1192/bjp.bp.115.180752](https://doi.org/10.1192/bjp.bp.115.180752)
- 538 17. Struck N, Krug A, Yuksel D, et al. Childhood maltreatment and adult mental disorders – the
 539 prevalence of different types of maltreatment and associations with age of onset and severity
 540 of symptoms. *Psychiatry Research*. 2020;293:113398. doi:[10.1016/j.psychres.2020.113398](https://doi.org/10.1016/j.psychres.2020.113398)
- 541 18. Wiersma JE, Hovens JGFM, Oppen P van, Giltay EJ, Schaik DJF van, Penninx BWJH. The
 542 Importance of Childhood Trauma and Childhood Life Events for Chronicity of Depression in
 543 Adults. *J Clin Psychiatry*. 2009;70(7):0-0. doi:[10.4088/JCP.08m04521](https://doi.org/10.4088/JCP.08m04521)

- 1
2
3 544 19. Humphreys KL, LeMoult J, Wear JG, Piersiak HA, Lee A, Gotlib IH. Child maltreatment and
4 545 depression: A meta-analysis of studies using the Childhood Trauma Questionnaire. *Child*
5 546 *Abuse & Neglect*. 2020;102:104361. doi:[10.1016/j.chiabu.2020.104361](https://doi.org/10.1016/j.chiabu.2020.104361)
- 6 547 20. Infurna MR, Reichl C, Parzer P, Schimmenti A, Bifulco A, Kaess M. Associations between
7 548 depression and specific childhood experiences of abuse and neglect: A meta-analysis. *Journal*
8 549 *of Affective Disorders*. 2016;190:47-55. doi:[10.1016/j.jad.2015.09.006](https://doi.org/10.1016/j.jad.2015.09.006)
- 9 550 21. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: A meta-
10 551 analysis of published literature. Childhood trauma and adult depression. *European Psychiatry*.
11 552 2015;30(6):665-680. doi:[10.1016/j.eurpsy.2015.04.007](https://doi.org/10.1016/j.eurpsy.2015.04.007)
- 12 553 22. Bausch P, Fangmeier T, Meister R, et al. The Impact of Childhood Maltreatment on Long-Term
13 554 Outcomes in Disorder-Specific vs. Nonspecific Psychotherapy for Chronic Depression. *Journal*
14 555 *of Affective Disorders*. 2020;272:152-157. doi:[10.1016/j.jad.2020.03.164](https://doi.org/10.1016/j.jad.2020.03.164)
- 15 556 23. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic
16 557 variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry*.
17 558 2013;170(10):1114-1133. doi:[10.1176/appi.ajp.2013.12070957](https://doi.org/10.1176/appi.ajp.2013.12070957)
- 18 559 24. Shirk SR, DePrince AP, Crisostomo PS, Labus J. Cognitive behavioral therapy for depressed
19 560 adolescents exposed to interpersonal trauma: An initial effectiveness trial. *Psychotherapy*.
20 561 2014;51(1):167-179. doi:[10.1037/a0034845](https://doi.org/10.1037/a0034845)
- 21 562 25. Williams JMG, Crane C, Barnhofer T, et al. Mindfulness-based cognitive therapy for preventing
22 563 relapse in recurrent depression: A randomized dismantling trial. *Journal of Consulting and*
23 564 *Clinical Psychology*. 2014;82(2):275-286. doi:[10.1037/a0035036](https://doi.org/10.1037/a0035036)
- 24 565 26. Nemeroff CB, Heim CM, Thase ME, et al. Differential Responses to Psychotherapy Versus
25 566 Pharmacotherapy in Patients With Chronic Forms of Major Depression and Childhood
26 567 Trauma. *FOC*. 2005;3(1):131-135. doi:[10.1176/foc.3.1.131](https://doi.org/10.1176/foc.3.1.131)
- 27 568 27. Klein JP, Erkens N, Schweiger U, et al. Does Childhood Maltreatment Moderate the Effect of the
28 569 Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy in
29 570 Persistent Depressive Disorder? *PPS*. 2018;87(1):46-48. doi:[10.1159/000484412](https://doi.org/10.1159/000484412)
- 30 571 28. McCullough JP. *Treatment for Chronic Depression. Cognitive Behavioral Analysis System of*
31 572 *Psychotherapy*. Guilford Press; 2000.
- 32 573 29. McCullough J, Schramm E, Penberthy JK. *CBASP as a Distinctive Treatment for Persistent*
33 574 *Depressive Disorder: Distinctive Features*. Routledge; 2015.
- 34 575 30. Bertsch K, Krauch M, Stopfer K, Haeussler K, Herpertz SC, Gamer M. Interpersonal Threat
35 576 Sensitivity in Borderline Personality Disorder: An Eye-Tracking Study. *Journal of Personality*
36 577 *Disorders*. 2017;31(5):647-670. doi:[10.1521/pepi.2017.31.273](https://doi.org/10.1521/pepi.2017.31.273)
- 37 578 31. Chu DA, Bryant RA, Gatt JM, Harris AWF. Failure to differentiate between threat-related and
38 579 positive emotion cues in healthy adults with childhood interpersonal or adult trauma. *Journal of*
39 580 *Psychiatric Research*. 2016;78:31-41. doi:[10.1016/j.jpsychires.2016.03.006](https://doi.org/10.1016/j.jpsychires.2016.03.006)
- 40 581 32. Herpertz SC, Bertsch K. The social-cognitive basis of personality disorders. *Current Opinion in*
41 582 *Psychiatry*. 2014;27(1):73-77. doi:[10.1097/YCO.000000000000026](https://doi.org/10.1097/YCO.000000000000026)
- 42 583 33. Bertsch K, Gamer M, Schmidt B, et al. Oxytocin and Reduction of Social Threat Hypersensitivity in
43 584 Women With Borderline Personality Disorder. *AJP*. 2013;170(10):1169-1177.
44 585 doi:[10.1176/appi.ajp.2013.13020263](https://doi.org/10.1176/appi.ajp.2013.13020263)
- 45 586 34. Shapero BG, Black SK, Liu RT, et al. Stressful Life Events and Depression Symptoms: The Effect
46 587 of Childhood Emotional Abuse on Stress Reactivity. *Journal of Clinical Psychology*.
47 588 2014;70(3):209-223. doi:[10.1002/jclp.22011](https://doi.org/10.1002/jclp.22011)
- 48 589 35. Erhardt A, Spoomaker VI. Translational Approaches to Anxiety: Focus on Genetics, Fear
49 590 Extinction and Brain Imaging. *Curr Psychiatry Rep*. 2013;15(12):417. doi:[10.1007/s11920-013-0417-9](https://doi.org/10.1007/s11920-013-0417-9)
- 50 591 36. Schnell K, Herpertz SC. Emotion Regulation and Social Cognition as Functional Targets of
51 592 Mechanism-Based Psychotherapy in Major Depression With Comorbid Personality Pathology.
52 593 *Journal of Personality Disorders*. 2018;32(Supplement):12-35.
53 594 doi:[10.1521/pepi.2018.32.suppl.12](https://doi.org/10.1521/pepi.2018.32.suppl.12)
- 54 595 37. Schnell K, Bluschke S, Konradt B, Walter H. Functional relations of empathy and mentalizing: An
55 596 fMRI study on the neural basis of cognitive empathy. *NeuroImage*. 2011;54(2):1743-1754.
56 597 doi:[10.1016/j.neuroimage.2010.08.024](https://doi.org/10.1016/j.neuroimage.2010.08.024)
- 57 598 38. Mattern M, Walter H, Hentze C, et al. Behavioral Evidence for an Impairment of Affective Theory
58 599 of Mind Capabilities in Chronic Depression. *PSP*. 2015;48(4):240-250. doi:[10.1159/000430450](https://doi.org/10.1159/000430450)
- 59 600 39. Weissman DG, Bitran D, Miller AB, Schaefer JD, Sheridan MA, McLaughlin KA. Difficulties with
60 601 emotion regulation as a transdiagnostic mechanism linking child maltreatment with the
602 602 emergence of psychopathology. *Development and Psychopathology*. 2019;31(3):899-915.
603 603 doi:[10.1017/S0954579419000348](https://doi.org/10.1017/S0954579419000348)
- 604 604

- 1
2
3 605 40. Cloitre M, Stovall-McClough C, Zorbas P, Charuvastra A. Attachment organization, emotion
4 606 regulation, and expectations of support in a clinical sample of women with childhood abuse
5 607 histories. *Journal of Traumatic Stress*. 2008;21(3):282-289. doi:[10.1002/jts.20339](https://doi.org/10.1002/jts.20339)
6 608 41. Lippard ETC, Nemeroff CB. The Devastating Clinical Consequences of Child Abuse and Neglect:
7 609 Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders. *AJP*.
8 610 2020;177(1):20-36. doi:[10.1176/appi.ajp.2019.19010020](https://doi.org/10.1176/appi.ajp.2019.19010020)
9 611 42. Bock J, Wainstock T, Braun K, Segal M. Stress In Utero: Prenatal Programming of Brain Plasticity
10 612 and Cognition. *Biological Psychiatry*. 2015;78(5):315-326. doi:[10.1016/j.biopsych.2015.02.036](https://doi.org/10.1016/j.biopsych.2015.02.036)
11 613 43. Fonagy P, Luyten P. Fidelity vs. flexibility in the implementation of psychotherapies: Time to move
12 614 on. *World Psychiatry*. 2019;18(3):270-271. doi:[10.1002/wps.20657](https://doi.org/10.1002/wps.20657)
13 615 44. Barlow DH, Bullis JR, Comer JS, Ametaj AA. Evidence-Based Psychological Treatments: An
14 616 Update and a Way Forward. *Annual Review of Clinical Psychology*. 2013;9(1):1-27.
15 617 doi:[10.1146/annurev-clinpsy-050212-185629](https://doi.org/10.1146/annurev-clinpsy-050212-185629)
16 618 45. Lyon AR, Lau AS, McCauley E, Vander Stoep A, Chorpita BF. A case for modular design:
17 619 Implications for implementing evidence-based interventions with culturally diverse youth.
18 620 *Professional Psychology: Research and Practice*. 2014;45(1):57-66. doi:[10.1037/a0035301](https://doi.org/10.1037/a0035301)
19 621 46. Insel TR, Cuthbert BN. Brain disorders? Precisely. *Science*. 2015;348(6234):499-500.
20 622 doi:[10.1126/science.aab2358](https://doi.org/10.1126/science.aab2358)
21 623 47. Harvey AG, Watkins E, Mansell W. *Cognitive Behavioral Processes Across Psychological*
22 624 *Disorders: A Transdiagnostic Approach to Research and Treatment*. Oxford University Press;
23 625 2004.
24 626 48. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. *Behavior*
25 627 *Therapy*. 2004;35(2):205-230. doi:[10.1016/S0005-7894\(04\)80036-4](https://doi.org/10.1016/S0005-7894(04)80036-4)
26 628 49. Weisz JR, Chorpita BF, Palinkas LA, et al. Testing Standard and Modular Designs for
27 629 Psychotherapy Treating Depression, Anxiety, and Conduct Problems in Youth: A Randomized
28 630 Effectiveness Trial. *Archives of General Psychiatry*. 2012;69(3):274-282.
29 631 doi:[10.1001/archgenpsychiatry.2011.147](https://doi.org/10.1001/archgenpsychiatry.2011.147)
30 632 50. Ng MY, Weisz JR. Annual Research Review: Building a science of personalised intervention for
31 633 youth mental health. *Journal of Child Psychology and Psychiatry*. 2016;57(3):216-236.
32 634 doi:[10.1111/jcpp.12470](https://doi.org/10.1111/jcpp.12470)
33 635 51. Berking M, Ebert D, Cuijpers P, Hofmann SG. Emotion Regulation Skills Training Enhances the
34 636 Efficacy of Inpatient Cognitive Behavioral Therapy for Major Depressive Disorder: A
35 637 Randomized Controlled Trial. *PPS*. 2013;82(4):234-245. doi:[10.1159/000348448](https://doi.org/10.1159/000348448)
36 638 52. Cuijpers P, Ebert DD, Acarturk C, Andersson G, Cristea IA. Personalised Psychotherapy for Adult
37 639 Depression: A Meta-Analytic Review. *Behavior Therapy*. 2016;47(6):966-980.
38 640 doi:[10.1016/j.beth.2016.04.007](https://doi.org/10.1016/j.beth.2016.04.007)
39 641 53. Chorpita BF, Weisz JR, Daleiden EL, et al. Long-term outcomes for the Child STEPs randomized
40 642 effectiveness trial: A comparison of modular and standard treatment designs with usual care.
41 643 *Journal of Consulting and Clinical Psychology*. 2013;81(6):999-1009. doi:[10.1037/a0034200](https://doi.org/10.1037/a0034200)
42 644 54. Chorpita BF, Daleiden EL, Park AL, et al. Child STEPs in California: A cluster randomized
43 645 effectiveness trial comparing modular treatment with community implemented treatment for
44 646 youth with anxiety, depression, conduct problems, or traumatic stress. *Journal of Consulting*
45 647 *and Clinical Psychology*. 2017;85(1):13-25. doi:[10.1037/ccp000133](https://doi.org/10.1037/ccp000133)
46 648 55. Wood JJ, Drahota A, Sze K, Har K, Chiu A, Langer DA. Cognitive behavioral therapy for anxiety in
47 649 children with autism spectrum disorders: A randomized, controlled trial. *Journal of Child*
48 650 *Psychology and Psychiatry*. 2009;50(3):224-234. doi:[10.1111/j.1469-7610.2008.01948.x](https://doi.org/10.1111/j.1469-7610.2008.01948.x)
49 651 56. Storch EA, Arnold EB, Lewin AB, et al. The Effect of Cognitive-Behavioral Therapy Versus
50 652 Treatment as Usual for Anxiety in Children With Autism Spectrum Disorders: A Randomized,
51 653 Controlled Trial. *Journal of the American Academy of Child & Adolescent Psychiatry*.
52 654 2013;52(2):132-142.e2. doi:[10.1016/j.jaac.2012.11.007](https://doi.org/10.1016/j.jaac.2012.11.007)
53 655 57. Black M, Hitchcock C, Bevan A, et al. The HARMONIC trial: Study protocol for a randomised
54 656 controlled feasibility trial of Shaping Healthy Minds—a modular transdiagnostic intervention for
55 657 mood, stressor-related and anxiety disorders in adults. *BMJ Open*. 2018;8(8):e024546.
56 658 doi:[10.1136/bmjopen-2018-024546](https://doi.org/10.1136/bmjopen-2018-024546)
57 659 58. Black M, Johnston D, Elliott R, et al. A randomised controlled feasibility trial (the HARMONIC Trial)
58 660 of a novel modular transdiagnostic intervention—Shaping Healthy Minds—versus
59 661 psychological treatment-as-usual, for clinic-attending adults with comorbid mood, stressor-
60 662 related and anxiety disorders. *mrc-cbu.cam.ac* [Preprint]. February 2, 2022 [cited 2022 Feb 2]
60 663 [https://www.mrc-cbu.cam.ac.uk/wp-content/uploads/2021/05/Black-et-al.-Shaping-Healthy-](https://www.mrc-cbu.cam.ac.uk/wp-content/uploads/2021/05/Black-et-al.-Shaping-Healthy-Minds.pdf)
60 664 [Minds.pdf](https://www.mrc-cbu.cam.ac.uk/wp-content/uploads/2021/05/Black-et-al.-Shaping-Healthy-Minds.pdf).

- 1
2
3 665 59. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health
4 666 problems: Current status and future directions. *Journal of Consulting and Clinical Psychology*.
5 667 2020;217;88(3):179. doi:[10.1037/ccp0000482](https://doi.org/10.1037/ccp0000482)
- 6 668 60. Negt P, Brakemeier E-L, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic
7 669 depression with cognitive behavioral analysis system of psychotherapy: A systematic review
8 670 and meta-analysis of randomized-controlled clinical trials. *Brain and Behavior*.
9 671 2016;6(8):e00486. doi:[10.1002/brb3.486](https://doi.org/10.1002/brb3.486)
- 10 672 61. Keller MB, McCullough JP, Klein DN, et al. A Comparison of Nefazodone, the Cognitive
11 673 Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of
12 674 Chronic Depression. *New England Journal of Medicine*. 2000;342(20):1462-1470.
13 675 doi:[10.1056/NEJM200005183422001](https://doi.org/10.1056/NEJM200005183422001)
- 14 676 62. Schramm E, Kriston L, Zobel I, et al. Effect of Disorder-Specific vs Nonspecific Psychotherapy for
15 677 Chronic Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2017;74(3):233-242.
16 678 doi:[10.1001/jamapsychiatry.2016.3880](https://doi.org/10.1001/jamapsychiatry.2016.3880)
- 17 679 63. Schramm E, Kriston L, Elsaesser M, et al. Two-Year Follow-Up after Treatment with the
18 680 Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy for
19 681 Early-Onset Chronic Depression. *PPS*. 2019;88(3):154-164. doi:[10.1159/000500189](https://doi.org/10.1159/000500189)
- 20 682 64. McCartney M, Nevitt S, Lloyd A, Hill R, White R, Duarte R. Mindfulness-based cognitive therapy
21 683 for prevention and time to depressive relapse: Systematic review and network meta-analysis.
22 684 *Acta Psychiatrica Scandinavica*. 2021;143(1):6-21. doi:[10.1111/acps.13242](https://doi.org/10.1111/acps.13242)
- 23 685 65. Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Kearney DJ, Simpson TL. Mindfulness-based
24 686 cognitive therapy for the treatment of current depressive symptoms: A meta-analysis.
25 687 *Cognitive Behavior Therapy*. 2019;48(6):445-462. doi:[10.1080/16506073.2018.1556330](https://doi.org/10.1080/16506073.2018.1556330)
- 26 688 66. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in
27 689 recurrent major depressive disorder: A systematic review and meta-analysis. *Clinical*
28 690 *Psychology Review*. 2011;31(6):1032-1040. doi:[10.1016/j.cpr.2011.05.002](https://doi.org/10.1016/j.cpr.2011.05.002)
- 29 691 67. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based
30 692 cognitive therapy compared with maintenance antidepressant treatment in the prevention of
31 693 depressive relapse or recurrence (PREVENT): A randomised controlled trial. *The Lancet*.
32 694 2015;386(9988):63-73. doi:[10.1016/S0140-6736\(14\)62222-4](https://doi.org/10.1016/S0140-6736(14)62222-4)
- 33 695 68. Bateman AW, Fonagy P. *Handbook of Mentalizing in Mental Health Practice*. American
34 696 Psychiatric Publishing, Inc.; 2012.
- 35 697 69. Malda-Castillo J, Browne C, Perez-Algorta G. Mentalization-based treatment and its evidence-
36 698 base status: A systematic literature review. *Psychology and Psychotherapy: Theory, Research*
37 699 *and Practice*. 2019;92(4):465-498. doi:[10.1111/papt.12195](https://doi.org/10.1111/papt.12195)
- 38 700 70. Bateman A, Fonagy P. Randomized Controlled Trial of Outpatient Mentalization-Based Treatment
39 701 Versus Structured Clinical Management for Borderline Personality Disorder. *AJP*.
40 702 2009;166(12):1355-1364. doi:[10.1176/appi.ajp.2009.09040539](https://doi.org/10.1176/appi.ajp.2009.09040539)
- 41 703 71. Zilberstein K. Neurocognitive considerations in the treatment of attachment and complex trauma in
42 704 children. *Clin Child Psychol Psychiatry*. 2014;19(3):336-354. doi:[10.1177/1359104513486998](https://doi.org/10.1177/1359104513486998)
- 43 705 72. Hofmann M, Fehlinger T, Stenzel N, Rief W. The Relationship Between Skill Deficits and
44 706 Disability—A Transdiagnostic Study. *Journal of Clinical Psychology*. 2015;71(4):413-421.
45 707 doi:[10.1002/jclp.22156](https://doi.org/10.1002/jclp.22156)
- 46 708 73. Fehlinger T, Stumpfenhorst M, Stenzel N, Rief W. Emotion regulation is the essential skill for
47 709 improving depressive symptoms. *Journal of Affective Disorders*. 2013;144(1):116-122.
48 710 doi:[10.1016/j.jad.2012.06.015](https://doi.org/10.1016/j.jad.2012.06.015)
- 49 711 74. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: A synthetic
50 712 review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*.
51 713 2012;1251:E1-24. doi:[10.1111/j.1749-6632.2012.06751.x](https://doi.org/10.1111/j.1749-6632.2012.06751.x)
- 52 714 75. Beesdo-Baum K, Zaudig M, Wittchen H-U. *Strukturiertes Klinisches Interview Für DSM-5 [The*
53 715 *Structured Clinical Interview for DSM-5-Clinician Version] (SCID-5-CV)*. Hogrefe; 2019.
- 54 716 76. Hamilton M. Development of a Rating Scale for Primary Depressive Illness. *British Journal of*
55 717 *Social and Clinical Psychology*. 1967;6(4):278-296. doi:[10.1111/j.2044-8260.1967.tb00530.x](https://doi.org/10.1111/j.2044-8260.1967.tb00530.x)
- 56 718 77. Downey G, Feldman SI. Implications of rejection sensitivity for intimate relationships. *Journal of*
57 719 *Personality and Social Psychology*. 1996;70(6):1327-1343. doi:[10.1037/0022-3514.70.6.1327](https://doi.org/10.1037/0022-3514.70.6.1327)
- 58 720 78. Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional
59 721 approach. *Journal of Personality and Social Psychology*. 1983;44(1):113-126.
60 722 doi:[10.1037/0022-3514.44.1.113](https://doi.org/10.1037/0022-3514.44.1.113)
- 723 79. Bjureberg J, Ljótsson B, Tull MT, et al. Development and Validation of a Brief Version of the
724 Difficulties in Emotion Regulation Scale: The DERS-16. *J Psychopathol Behav Assess*.
725 2016;38(2):284-296. doi:[10.1007/s10862-015-9514-x](https://doi.org/10.1007/s10862-015-9514-x)

- 1
2
3 726 80. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials
4 727 being undertaken in the United Kingdom registered in the United Kingdom Clinical Research
5 728 Network database. *BMC Med Res Methodol*. 2013;13(1):104. doi:[10.1186/1471-2288-13-104](https://doi.org/10.1186/1471-2288-13-104)
6 729 81. Munder T, Wilmers F, Leonhart R, Linster HW, Barth J. Working Alliance Inventory-Short Revised
7 730 (WAI-SR): Psychometric properties in outpatients and inpatients. *Clinical Psychology &*
8 731 *Psychotherapy*. 2010;17(3):231-239. doi:[10.1002/cpp.658](https://doi.org/10.1002/cpp.658)
9 732 82. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline
10 733 personality disorder. *Clinical Psychology & Psychotherapy*. 2011;18(4):275-283.
11 734 doi:[10.1002/cpp.705](https://doi.org/10.1002/cpp.705)
12 735 83. Paulus C. Der Saarbrücker Persönlichkeitsfragebogen zur Messung von Empathie (SPF-IRI).
13 736 Published 2006. [http://bildungswissenschaften.uni-](http://bildungswissenschaften.uni-saarland.de/personal/paulus/homepage/empathie.html)
14 737 [saarland.de/personal/paulus/homepage/empathie.html](http://bildungswissenschaften.uni-saarland.de/personal/paulus/homepage/empathie.html)
15 738 84. Hausberg MC, Schulz H, Piegler T, et al. Is a self-rated instrument appropriate to assess
16 739 mentalization in patients with mental disorders? Development and first validation of the
17 740 Mentalization Questionnaire (MZQ). *Psychotherapy Research*. 2012;22(6):699-709.
18 741 doi:[10.1080/10503307.2012.709325](https://doi.org/10.1080/10503307.2012.709325)
19 742 85. Gratz KL, Roemer L. Multidimensional Assessment of Emotion Regulation and Dysregulation:
20 743 Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation
21 744 Scale. *Journal of Psychopathology and Behavioral Assessment*. 2004;26(1):41-54.
22 745 doi:[10.1023/B:JOBA.0000007455.08539.94](https://doi.org/10.1023/B:JOBA.0000007455.08539.94)
23 746 86. Goldman HH, Skodol AE, Lave TR. Revising Axis V for DSM-IV: A Review of Measures of Social
24 747 Functioning. Published online September 1, 1992. Accessed July 27, 2021.
25 748 <https://papers.ssrn.com/abstract=2143992>
26 749 87. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF Quality of Life
27 750 Assessment. *Psychological Medicine*. 1998;28(3):551-558. doi:[10.1017/S0033291798006667](https://doi.org/10.1017/S0033291798006667)
28 751 88. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. Psychological
29 752 Corporation; 1996.
30 753 89. Beck AT, Steer RA. *Beck Anxiety Inventory Manual*. Psychological Corporation; 1993.
31 754 90. Ehrenthal JC, Dinger U, Lamla A, Funken B, Schauenburg H. Evaluation der deutschsprachigen
32 755 Version des Bindungsfragebogens „Experiences in Close Relationships – Revised” (ECR-RD).
33 756 *Psychother Psychosom Med Psychol*. 2009;59(6):215-223. doi:[10.1055/s-2008-1067425](https://doi.org/10.1055/s-2008-1067425)
34 757 91. Price CJ, Thompson EA. Measuring Dimensions of Body Connection: Body Awareness and Bodily
35 758 Dissociation. *The Journal of Alternative and Complementary Medicine*. 2007;13(9):945-953.
36 759 doi:[10.1089/acm.2007.0537](https://doi.org/10.1089/acm.2007.0537)
37 760 92. Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure.
38 761 *Psychiatric Annals*. 2002;32(9):509-515. doi:[10.3928/0048-5713-20020901-06](https://doi.org/10.3928/0048-5713-20020901-06)
39 762 93. Kiesler DJ. The 1982 Interpersonal Circle: A taxonomy for complementarity in human transactions.
40 763 *Psychological Review*. 1983;90(3):185-214. doi:[10.1037/0033-295X.90.3.185](https://doi.org/10.1037/0033-295X.90.3.185)
41 764 94. Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How Does Mindfulness
42 765 Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural
43 766 Perspective. *Perspect Psychol Sci*. 2011;6(6):537-559. doi:[10.1177/1745691611419671](https://doi.org/10.1177/1745691611419671)
44 767 95. Arch JJ, Craske MG. Mechanisms of mindfulness: Emotion regulation following a focused
45 768 breathing induction. *Behavior Research and Therapy*. 2006;44(12):1849-1858.
46 769 doi:[10.1016/j.brat.2005.12.007](https://doi.org/10.1016/j.brat.2005.12.007)
47 770 96. Geschwind N, Peeters F, Drukker M, van Os J, Wichers M. Mindfulness training increases
48 771 momentary positive emotions and reward experience in adults vulnerable to depression: A
49 772 randomized controlled trial. *Journal of Consulting and Clinical Psychology*. 2011;79(5):618-
50 773 628. doi:[10.1037/a0024595](https://doi.org/10.1037/a0024595)
51 774 97. Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: A comprehensive meta-
52 775 analysis. *Clinical Psychology Review*. 2013;33(6):763-771. doi:[10.1016/j.cpr.2013.05.005](https://doi.org/10.1016/j.cpr.2013.05.005)
53 776 98. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in Brain and Immune Function
54 777 Produced by Mindfulness Meditation. *Psychosomatic Medicine*. 2003;65(4):564-570.
55 778 doi:[10.1097/01.PSY.0000077505.67574.E3](https://doi.org/10.1097/01.PSY.0000077505.67574.E3)
56 779 99. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive
57 780 therapy, and antidepressant medication in the acute treatment of adults with major depression.
58 781 *Journal of Consulting and Clinical Psychology*. 2006;74(4):658-670. doi:[10.1037/0022-](https://doi.org/10.1037/0022-006X.74.4.658)
59 782 [006X.74.4.658](https://doi.org/10.1037/0022-006X.74.4.658)
60 783 100. Hautzinger M. *Kognitive Verhaltenstherapie Bei Depressionen*. 7. Auflage. Beltz Psychologie
784 Verlags Union; 2013.
785 101. Cuijpers P. Four decades of outcome research on psychotherapies for adult depression: An
786 overview of a series of meta-analyses. *Canadian Psychology/Psychologie*
787 *canadienne*. 2017;58(1):7-19. doi:[10.1037/cap0000096](https://doi.org/10.1037/cap0000096)

- 1
2
3 788 102. Barth J, Munder T, Gerger H, et al. Comparative Efficacy of Seven Psychotherapeutic
4 789 Interventions for Patients with Depression: A Network Meta-Analysis. *FOC*.
5 790 2016;14(2):229-243. doi:[10.1176/appi.focus.140201](https://doi.org/10.1176/appi.focus.140201)
6 791 103. Linden M, Strauß B. *Risiken und Nebenwirkungen von Psychotherapie: Erfassung,*
7 792 *Bewältigung, Risikovermeidung*. 1st ed. MWV Medizinisch Wissenschaftliche
8 793 Verlagsgesellschaft; 2012.
9 794 104. Hoffmann SO, Rudolf G, Strauß B. Unerwünschte und schädliche Wirkungen von
10 795 Psychotherapie. *Psychotherapeut*. 2008;53(1):4-16. doi:[10.1007/s00278-007-0578-2](https://doi.org/10.1007/s00278-007-0578-2)
11 796 105. Cook SC, Schwartz AC, Kaslow NJ. Evidence-Based Psychotherapy: Advantages and
12 797 Challenges. *Neurotherapeutics*. 2017;14(3):537-545. doi:[10.1007/s13311-017-0549-4](https://doi.org/10.1007/s13311-017-0549-4)
13 798 106. Herschell AD, Kolko DJ, Baumann BL, Davis AC. The role of therapist training in the
14 799 implementation of psychosocial treatments: A review and critique with
15 800 recommendations. *Clinical Psychology Review*. 2010;30(4):448-466.
16 801 doi:[10.1016/j.cpr.2010.02.005](https://doi.org/10.1016/j.cpr.2010.02.005)
17 802 107. Ecker AH, O'Leary K, Fletcher TL, et al. Training and supporting mental health providers to
18 803 implement evidence-based psychotherapies in frontline practice. *Translational*
19 804 *Behavioral Medicine*. 2021;(ibab084). doi:[10.1093/tbm/ibab084](https://doi.org/10.1093/tbm/ibab084)
20 805

21 806 **Figure and Table Legends**

22
23
24 807 **Figure 1:** Overview of the targeted RDoC domains and their corresponding objectives,
25 808 assessments and modules. A detailed description of the modules is given below.

26
27 809 **Figure 2:** Trial design and flow of patients.

28
29 810 **Table 1:** Primary and Secondary Endpoints and corresponding measures.

30
31 811 **Figure 3.** Frequency and scope of trial visits.

32
33 812 **Figure 4:** Decision Tree Algorithm for Modular-Based Psychotherapy.

34
35 813 **Table 2:** Content and implementation of modules.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

bmjopen-2021-05-7172 on 12 July 2022. Downloaded from <http://bmjopen.bmj.com/> on November 1, 2024 by guest. Protected by copyright.

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

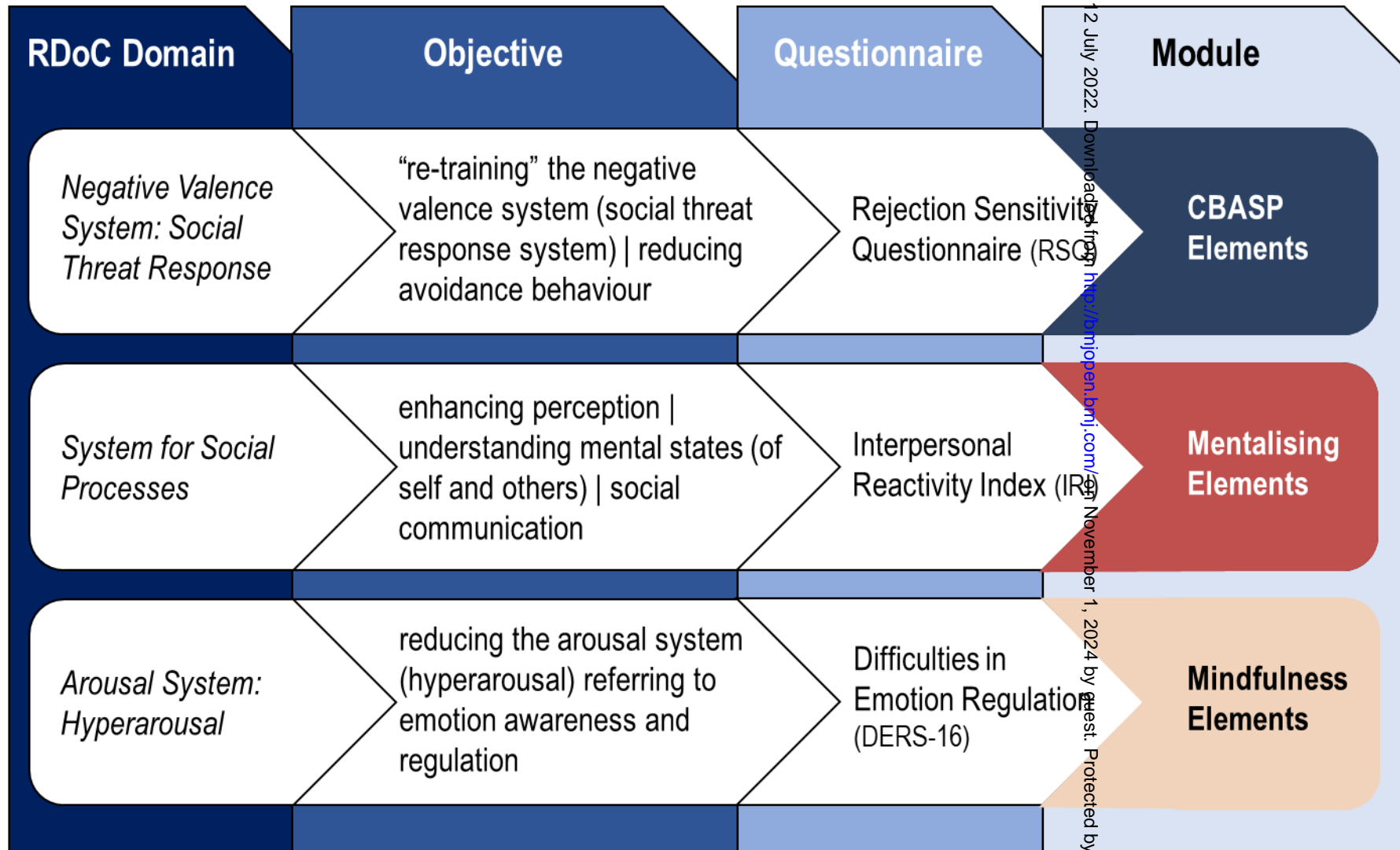
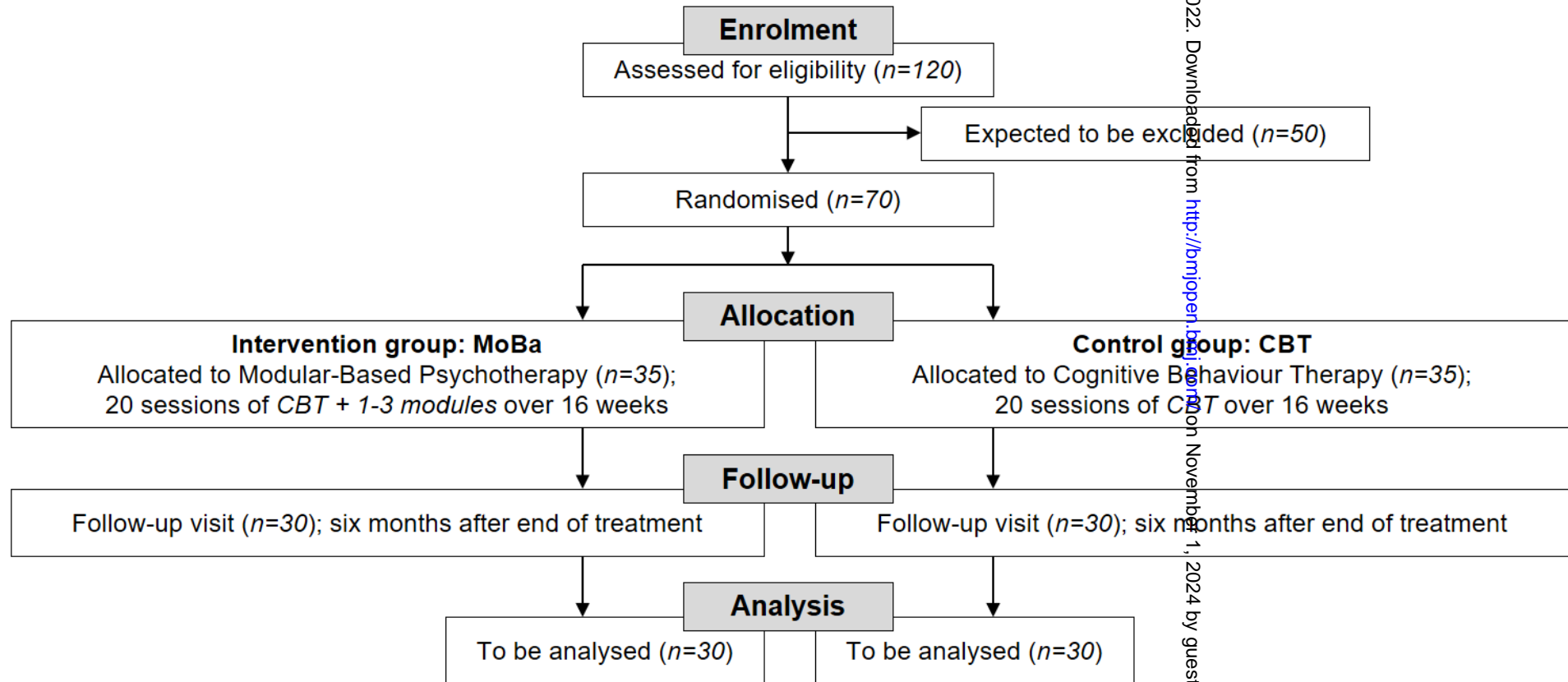


Figure 2: Trial design and flow of patients.

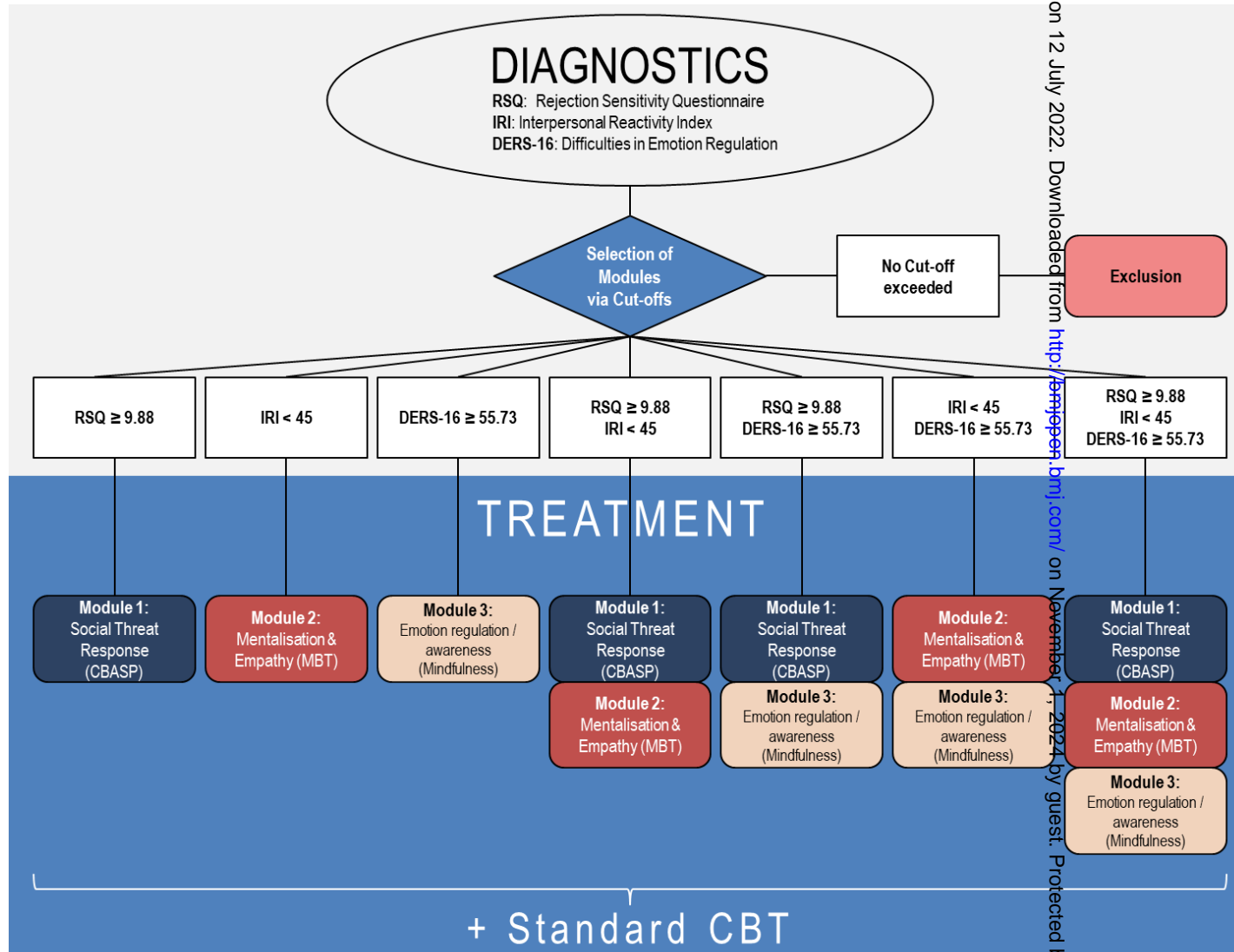


bmjopen-2021-057672 on 12 July 2022. Downloaded from <http://bmjopen.bmj.com/> on November 1, 2024 by guest. Protected by copyright.

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		
		AE / SAE				X	X	X		
		PHQ-9				X	X	X		
		WAI-P / WAI-T						X		
RATERS	Interview	telephone screening	(X)							
		SCID-5 (CV/PD)		X						
		HRSD-24		X	(X)				X	X
		SOFAS			X				X	X
		AE / SAE			(X)				X	X
	Questionnaires	CTQ		X						
		RSQ		X					X	X
		IRI		X					X	X
		DERS-16		X					X	X
		MZQ			X				X	X
		BDI-II			X				X	X
		BAI			X				X	X
		WHOQoL-BREF			X				X	X
		PHQ-9			X				X	X
		ECR-RD8			X				X	X
SBC			X				X	X		

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



bmjopen-2021-057672 on 12 July 2022. Downloaded from <http://bmjopen.bmj.com/> on November 1, 2024 by guest. Protected by copyright.



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

1				
2	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
3				
4				
5				
6				
7				
8	Methods: Participants, interventions, and outcomes			
9				
10	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
11				
12				
13				
14				
15	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
16				
17				
18				
19				
20				
21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
22				
23				
24				
25				
26		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
27				
28				
29				
30				
31				
32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
33				
34				
35				
36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
37				
38				
39	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
40				
41				
42				
43				
44				
45				
46				
47				
48	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
49				
50				
51				
52				
53				
54	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
55				
56				
57				
58				
59				
60				

1				
2	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
3				
4				
5	Methods: Assignment of interventions (for controlled trials)			
6	Allocation:			
7				
8				
9	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
10				
11				
12				
13				
14				
15				
16				
17				
18	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
19				
20				
21				
22				
23				
24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
25				
26				
27				
28				
29	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
30				
31				
32				
33		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
34				
35				
36				
37	Methods: Data collection, management, and analysis			
38				
39	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
40				
41				
42				
43				
44				
45				
46				
47				
48				
49		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
50				
51				
52				
53				
54	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
55				
56				
57				
58				
59				
60				

1				
2	Statistical	20a	Statistical methods for analysing primary and secondary	
3	methods		outcomes. Reference to where other details of the statistical	15-16
4			analysis plan can be found, if not in the protocol	
5				
6		20b	Methods for any additional analyses (eg, subgroup and	
7			adjusted analyses)	15-16
8				
9		20c	Definition of analysis population relating to protocol non-	
10			adherence (eg, as randomised analysis), and any statistical	15-16
11			methods to handle missing data (eg, multiple imputation)	
12				
13				

Methods: Monitoring

14				
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC);	
17			summary of its role and reporting structure; statement of	
18			whether it is independent from the sponsor and competing	15
19			interests; and reference to where further details about its	
20			charter can be found, if not in the protocol. Alternatively, an	
21			explanation of why a DMC is not needed	
22				
23				
24		21b	Description of any interim analyses and stopping	
25			guidelines, including who will have access to these interim	15-16
26			results and make the final decision to terminate the trial	
27				
28	Harms	22	Plans for collecting, assessing, reporting, and managing	
29			solicited and spontaneously reported adverse events and	17-18
30			other unintended effects of trial interventions or trial conduct	
31				
32				
33	Auditing	23	Frequency and procedures for auditing trial conduct, if any,	15/17
34			and whether the process will be independent from	-18
35			investigators and the sponsor	
36				
37				

Ethics and dissemination

38				
39				
40	Research ethics	24	Plans for seeking research ethics committee/institutional	16-17
41	approval		review board (REC/IRB) approval	
42				
43	Protocol	25	Plans for communicating important protocol modifications	
44	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	n.a.
45			relevant parties (eg, investigators, REC/IRBs, trial	
46			participants, trial registries, journals, regulators)	
47				
48	Consent or	26a	Who will obtain informed consent or assent from potential	
49	assent		trial participants or authorised surrogates, and how (see	17
50			Item 32)	
51				
52				
53		26b	Additional consent provisions for collection and use of	
54			participant data and biological specimens in ancillary	n.a.
55			studies, if applicable	
56				
57				
58				
59				
60				

1				
2	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
3				
4				
5				
6				
7	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
8				
9				
10	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
11				
12				
13				
14				
15	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.
16				
17				
18				
19	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
20				
21				
22				
23				
24				
25				
26				
27		31b	Authorship eligibility guidelines and any intended use of professional writers	20
28				
29				
30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
31				
32				
33	Appendices			
34				
35	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	17/19
36				
37				
38				
39				
40	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.
41				
42				
43				
44				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.