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Efficacy of hypnotherapy compared to cognitive behavioural therapy for mild to moderate depression – study protocol of a randomized controlled rater-blind trial (WIKI-D)

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Abstract

Introduction: Even if there is a substantial amount of studies providing evidence for efficacy of psychological treatment for mild to moderate depression, only up to 50% of participants respond to treatment, even in gold standard treatments as cognitive behavioural therapy (CBT) and interpersonal therapy (IPT). New approaches as the 'third wave' psychotherapies provided promising results but there is a lack of studies concerning the comparison with evidence-based treatments. This study has the goal to compare the efficacy of clinical hypnotherapy (HT) with gold standard psychotherapy (CBT) in mild to moderate Major Depressive Episodes.

Methods and analysis: The present study consists of a monocentric two-armed randomized-controlled rater-blind (non-inferiority) clinical trial. A total of 160 participants with mild to moderate Major Depression Episode will be randomized to 20 sessions psychotherapy for 24 weeks either with Cognitive Behavioural Therapy (CBT) or Hypnotherapy (HT). We expected that the mean percentage improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score will not be inferior in HT compared to CBT (non-inferiority-hypothesis).

Further outcome parameters include number of participants in response after end of treatment and one year after end of treatment as well as quality of life, treatment expectations and hypnotic susceptibility before and after end of treatment.

Ethics and dissemination: The study protocol and the documents for the written clarification were approved by the Ethics Committee of the University Hospital Tuebingen (061/2015B02). Results of this trial will be submitted for publication in peer-reviewed journals, and will be presented at national and international conferences.

Registration details: Trial Registration Number: NCT02375308 (clinicaltrials.gov)

Keywords: Depression, Cognitive Behavioural Therapy, Hypnotherapy, Psychotherapy

Strengths and limitations of this study:

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- This is the first clinical trial following the GCP Guidelines concerning hypnotherapy for depression
- The external risk-adapted monitoring, external data management and biometry, as well as the assessment of safety via (serious) adverse events will further enhance the quality of the trial
- The therapists and patients could not be blinded in the current trial, whereas the raters of the follow-up assessments were blind concerning the treatment condition

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Introduction

The national S3 guideline and the international guidelines on treatment of unipolar depression [1, 2, 3] recommend psychotherapy alternatively with a psychopharmacological treatment for mild to moderate unipolar depressive episodes. Monotherapy with cognitive behavioural therapy (CBT) as well as interpersonal therapy (IPT) are the most evidenced approaches.

Current literature supports, that for mild and moderate forms of depressive disorder, psychotherapeutic approaches are in the short term similarly effective as pharmacotherapeutic therapies and even evince a higher long-term efficacy, especially in prevention of relapses [e.g. 4]. The success rates of CBT and IPT, however, only reach about 50% [e.g. 5]. The much-needed increase of successful treatment approaches for unipolar disorders could be achieved by a modification of the existing therapies or by an increasing variety of treatment offers. So far approaches of the so-called 'third wave' of CBT such as schema therapy [6, 7] emotion-focused therapy [8], and CBASP [9] have received increasing attention. Furthermore, approaches mainly shaped from East Asian influences such as the mindfulness-oriented (cognitive) therapy (MBCT) and the acceptance- and commitment oriented therapy (ACT) become more and more popular [10, 11]. Some of these modern approaches are regarded as synthesis of psychodynamic and CBT-oriented procedures with special consideration of early life experiences and correcting emotional experiences (e. g. CBASP resp. schema therapy). The evidence base for the third wave of CBT is, however, low; only minor differences between the third wave of the CBT and other psychological procedures exist or evidence for differences between the third wave and standard approaches is lacking [12].

In this regard hypnotherapy (HT) could be a promising add-on of treatment methods. Nowadays hypnotherapy is understood as resource-oriented approach which is supposed to reinforce the intrinsic value, to initiate self-help and to support the patient in his/her individual problem solving strategies [13]. Beside formal trance induction, also techniques such as utilisation, indirect procedures for instance via the representative technique or working with

time perception, play an important role [13]. To date, only few randomised controlled studies on efficacy of hypnotherapeutic methods, especially for the treatment of depression, are available [14, 15, 16]. Additionally, the cognitive hypnotherapy was investigated among patients with anxiety disorders [17]. Research on the efficacy of HT in addition to CBT also shows additive effects of hypnotherapy [18]. However, further proofs on the efficacy, especially for the treatment of depression compared to cognitive behavioural therapy, are lacking.

Objectives

The present study aims at conducting a first efficacy validation of HT compared to another psychotherapeutic approach, for which the comparison with CBT is chosen and which was recommended in with the highest evidence in the actual treatment guidelines [1, 2, 3].

This study targets to examine the efficacy of HT compared to an evidence-based standard treatment (CBT) for mild to moderate major depression episode.

The following primary hypothesis is to be tested:

1) Regarding reduction of the depressive symptomatic, HT is not inferior to CBT after the end of treatment (mean percentage symptom reduction in the clinician-administered rating Montgomery-Asperg Depression Rating Scale, MADRS).

Additionally, the following secondary target parameters are examined exploratively:

2) A non-superiority of one of both approaches related to a further symptom reduction in MADRS, but also Quick Inventory of Depressive Symptoms - Clinician Rating ($QIDS_{C16}$) and Patient Health Questionnaire – depression scale (PHQ-9) over the follow-up period, up to 12 months after end of treatment.
3) Rate of patients with a response in both treatment conditions at the end of treatment and in the course of the follow-up will be analysed (assessed via clinical results: MADRS, $QIDS_{C16}$, each response defined as symptom reduction >/= 50%).

4) Rate of weeks in remission and rate of patients with relapses in the period of 52 weeks after end of therapy in both treatment conditions will be analysed (assessed via Longitudinal Interval Follow-up Evaluation for DSM-IV, LIFE).

5) Variables predicting response for treatment success will be analysed. The following aspects are regarded as predictors for a response:

   - Personality-related features: sociodemographic variables such as gender, age, family status, further hypnotic susceptibility, expectations concerning treatment, perceived self-efficacy, behavioural activation, working alliance between patient and therapist, early response in the first 6 weeks of treatment
   - Disorder-related features: Number of previous episodes, severity of actual episode, global functional level at inclusion in the study, comorbidities.

Methods and Analysis

Study design

The clinical study is based on a 4 x 2 mixed factors design with the factors measuring time (4 measuring times: prior to (t1) and after end of treatment (t2) as well as 6 (t3) and 12 months (t4) after end of treatment for the follow-up period) and treatment condition (CBT vs. HT). Half of the participants are randomised respectively to HT and CBT.

Sample

Patients with Major Depressive Disorder (MDD) with an actual mild to moderate episode according to the Diagnostic and statistical manual of mental disorders - fifth edition (DSM-5 [19]) are included in the study (assessed via Structured Clinical Interview for DSM-IV Axis I, SCID-I [20], adapted for DSM-5).

Patients will be recruited starting in 2015 via the depression outpatient clinic of the University Hospital for Psychiatry and Psychotherapy and via a network of referring institutions (licensed psychiatrists, psychotherapists, university outpatient clinics, psychotherapeutic education institutes, self-help groups, general practitioners, psychiatric hospitals) from the region Tuebingen, Reutlingen, Rottenburg and if applicable, Stuttgart, via flyers and newspaper articles as well as circular emails via the university and university hospital distributor. Interested individuals were informed about the study in a personal interview. Following written consent, interested individuals were invited for participation in the study after assessment of the following inclusion and exclusion criteria:

Inclusion criteria

- Written informed consent
- Patient fulfils criteria for a mild to moderate depressive disorder according to DSM-5
- 18 – 70 years of age
- Sufficient knowledge of the German language in order to participate in the study
- Sufficient temporal resources for weekly therapy sessions

- In cases of existing anti-depressive medication: stable medication since three months without planned changes during therapy period.

Exclusion criteria

- Lifetime diagnosis of a bipolar disorder or psychotic disorder
- Diagnosis of chronic MDD (duration >/= 2 years)
- Severe Major Depressive Episode (MDE) according to SCID-I resp. MADRS >/= 35 or $QIDS_{C16}$ >/= 16
- remission of actual episode since 4 weeks or longer
- depression with psychotic characteristics acc. to SCID-I
- acute suicidality (intended action, concrete plans or intermittent pronounced suicidal ideation)
- Severe cognitive impairments (in cases of suspicion checked via Mini-Mental StateTest, MMST < 26)
- other severe mental disorders to be treated: dominant panic disorder, severe personality disorder of borderline type with self-injury, active alcohol or drug dependence, actual posttraumatic stress disorder, anorexia nervosa via SCID-I
- Somatic disorder impeding participation in regular psychotherapy sessions
- Outpatient psychotherapy during the last 12 months.

Sample size and power calculation

Primary target size is defined as percentage reduction of the depressive symptomatic (MADRS) between baseline and end of treatment. The following assumptions were made on the basis of the available data: assumed percentage improvement in the MADRS of 50% (standard derivation of 32.9 points, on the basis of the results for the efficacy of CBT, see [5] page 500 (table 2) and half a standard derivation (16.4) as non-inferiority range. A confidence interval of 95% at a randomisation proportion of 1:1 and an alpha-level of 5% are

taken as basis. Under these conditions one-sided t-test at a sample size of n=70 in each group 80% power for refusal of zero hypothesis, that HT therapy is inferior to CBT.

Assuming a drop-out rate from the population of maximal 12.5%, a total of 160 patients with current mild to moderate MDE should be randomised to reach at least a number of 140 assessable patients.

Sample size definition was conducted with Query version 7.0.

Interventions

The two single outpatient treatments include 20 sessions at 50 minutes each during a period of 20 weeks (max. 24 weeks).

The treatment is based on respective manuals of both therapy methods. The manual for the CBT is guided by already well-established CBT approaches [21] and was named “activating cognitive depression therapy (ACDT)”. The manual for the hypnotherapy is based on materials of [22] and was named “hypnotherapeutic depression therapy (HDT)”.

Overall, respectively four therapists with adequate qualification (education in behavioural therapy resp. hypnotherapy and at least 3 years of professional experience) and training of the manual (1 – 2 days) are assigned to each method (CBT resp. HDT) with each 20 patients within the scope of the study. Therapy sessions will be recorded with the agreement of the patient. Therapists’ adherence to the manual is tested for each patient by an adherence test of randomly chosen sessions (tape recording) as well as by regular (monthly) supervisions. Additionally, therapists have to record which contents of the according manuals ACDT or HDT were performed.

ACDT (Cognitive behavioural therapy - activating cognitive depression therapy)

The ACDT consists of techniques already well-established and well examined in depression research such psychoeducation, behavioural activation, cognitive restructuring techniques, problem solving skills, and interpersonal skills. Additionally, homework and exercises will be

performed, daily routine structure is reviewed with the goal to reduce depressive symptoms and to build up skills which enable individuals concerned to proceed with their disorder independently. Additional elements can also be applied from working with ruminative thoughts, sleeping problems, and progressive muscle relaxation.

HDT (Hypnotherapeutic depression therapy)

The modules of the HDT promote the hypnotic activation and reinforcement of own resources and use relevant positive and negative experiences from the biography and the development of adequate solution approaches. Additional elements can also be applied from working with ruminative thoughts and sleeping problems. The therapy procedure can be adjusted to the individual needs.

Assessments

For an overview of the assessments for each assessment time point, see Table 1.

Primary endpoint

Montgomery–Åsberg Depression Rating Scale (MADRS). As primary endpoint of the study, the manifestation of the depressive symptomatic is assessed via MADRS [23] at t1, t2, t3, and t4.

Secondary endpoints

Quick Inventory of Depressive Symptoms – Clinician Rating (QIDSC16 [24]), for the assessment of the depressive symptoms at t1, t2, t3, and t4.

Patient Health Questionnaire – depression scale (PHQ-9). Manifestation of depressive symptomatic assessed with the self-evaluation PHQ-9 [25] at t1, t2, t3, and t4 and weekly (max. 24 weeks) during the therapy period.

Longitudinal Interval Follow-up Evaluation for DSM-IV (LIFE). Time point and duration of remission and possible relapses after treatment as well as to follow-up points, were assessed via LIFE interview [26] to t2, t3, and t4, each over a period of 6 months retrospectively. Additionally, the LIFE assesses if and which therapeutic measures were used in the meantime (e. g. inpatient-treatment, medication).

WHO Quality of Life (WHOQOL-BREF, [27]) assesses patients' quality of life concerning physical health, psychological health, social relationships, and environment with 26 items at t1 and t2.

WHO Disability Assessment Schedule (WHODAS). The WHODAS [28] measures the global functional level with 12 items at t1 und t2.

Response Styles Questionnaire (RSQ [29, 30]) for the assessment of coping and rumination at t1 und t2.

Behavioural Activation for Depression Scale (BADS, [31]) for the assessment of behavioural activation at t1 und t2.

General Self-efficacy Scale (GSES, [32]) measures self-efficacy with ten items at t1 und t2.

Questions to specific **therapy expectations at** t1 and to contentment at t2.

Harvard Harvard Group Scale of Hypnotic Susceptibility (HGSHS). Presently the HGSHS [33] is the most common scale for the assessment of suggestibility. A German validation is available including standardised audio recording, which can be presented to each participant. The HGSHS is applied at t1 and t2.

Working Alliance Inventory - short and revised form (WAI-SR, [34]). Once in treatment week six: assessment of the therapeutic alliance between therapist and patient for both perspectives, resulting in a therapist and a patient version.

Study procedure

After written informed consent an initial test for depressive symptoms, screening for personality disorders and assessment of sociodemographic statements are carried out via questionnaires. Then baseline assessment diagnostics are performed (clinical interviews and questionnaires). This includes extensive diagnostics for the final examination of the inclusion and exclusion criteria (especially current MDE and actual severity of depression) by trained diagnosticians (baseline, t1, for an overview, see Figure 1 and Table 1). The SCID-I [20], adapted for DSM-5, is applied for the examination of inclusion and exclusion criteria and for the assessment of possible comorbid disorders. The diagnostics of personality disorders with SCID-II [35] is only applied for related indications via Assessment of DSM-IV Personality Disorders (ADP-IV) for screening of personality disorders [36]. In case of suspected cognitive impairment/dementia the Mini-Mental State Test (MMST) will be applied [37] with a MMST score 25 or below leads to exclusion.

If the first treatment session is scheduled more than 3 weeks after the date of baseline assessment, the depressive symptomatic will be re-assessed via MADRS and QIDS.

A computerized random algorithm using nQuery 7.0 was used to generate the random allocation of the participants to one of the two study groups 1: HDT; group 2, CBT). A randomization procedure was established by electronic interaction between the study centre and the data centre. The allocation of patients is blinded to the diagnosticians who make the outcome assessments. Both approaches have the same number and duration of sessions, in all conditions 20 50-minute outpatient sessions are performed during a period of maximum 24 weeks. Furthermore, single sessions can be summarised to 4 double sessions maximum. The approaches differ especially concerning the application of different behavioural therapy approaches (e. g. behaviour activation, cognitive restructuring, establish social competence)

resp. hypnotherapeutic techniques (e. g. time progression, working with trance and metaphors, representative technique, reframing). After the end of therapy (t2) and 6 (t3) and 12 months (t4) later, patients will be followed-up concerning their symptomatic by blind diagnosticians acc. to the study condition. After the follow-up to t4, participation in the study is concluded for patients, see figure 1.

If patients withdraw their participation in the study, this will be classified as discontinuation. The patient decides, if already assessed data can be included in the evaluation or not.

Treatment participation is considered as completed per protocol (CPP), if the patient attended at least 80% of sessions (this corresponds to 16 for a total of 20 planned sessions). For the implementation of the 20 sessions, a total of max. 24 weeks (6 months) is provided. This period can be exceeded up to 4 weeks in cases of impending loss of patients (less than 80% of sessions). Possible intermissions due to hospitalisation or other reasons have to be recorded (protocol violation). If a patient starts another inpatient, day-care or outpatient psychotherapeutic treatment or an inpatient crisis intervention takes longer than 14 days, study therapy is discontinued. The patient is then considered as therapy dropout but is further questioned to the follow-ups on a regular basis. For all randomised patients, all planned follow-ups should be carried out (Intention to treat, ITT), irrespectively of the fact if treatment was concluded acc. to the protocol. Study therapists should not continue any contact to study patients during the follow-up period of 12 months after end of therapy.

Statistical Analysis

Analysis of primary endpoint

Primary endpoint of the study is the comparison of HDT and ACDT regarding mean percentage modification of symptoms (MADRS) between baseline value t1 and value after end of therapy (t2). Mean modification (%) has to be estimated for both treatment arms (incl. 95% confidence intervals).

Evaluation collective

Modified intent-to-treat analysis is applied.

The per-protocol-population is a partial quantity of the ITT. Excluded are patients with one of the following protocol violations:

- Randomisation despite violation of inclusion and exclusion criteria
- error at assignment to randomised therapy group
- usage of other psychotherapy according to patient's statement
- negative compliance (participation in less than 16 session)
- lost to follow-up (non-appearance to last follow-up session after 12 months)
- missing data concerning depressive symptoms (MADRS) after therapy (t2).

The statistical evaluation is carried out after conclusion of data assessment at t4 (data base conclusion) for the last randomised patient.

The following hypotheses are tested on a one-site significance level of 5%:

H_0: μAKDT- μHDT ≥ 16.4%

H_1: μHDT – μAKDT < 16.4%

whereas μ stands for mean percentage change of MADRS between baseline score (t1) and the score after end of therapy (t2) in each therapy group.

This is calculated by estimating the difference of the mean percentage change scores of both therapy groups incl. an one-sided 95% confidence interval. HDT is regarded as non-inferior compared to ACDT, if the range of this confidence interval is smaller than the allowed non-inferiority level of 16.4%. The range of 16.4% for non-inferiority was chosen on the basis of the available data.

Primary analysis is performed acc. to PP population, which statistically represents the conservative approach for the analysis of non-inferiority. An additional analysis on the basis

of the ITT population serves as sensitivity analysis to estimate the robustness of the primary analysis.

External data management and biometry

Data will be entered in a database (www.koordobas.de). All available data will be entered twice independently of each other in the database, will be checked for errors, consistency and completeness, before being applied to the statistical analyses.

Statistical analysis will be performed with SAS (version 9.2) and SPSS (version 22).

Methods for the assessment of safety

In order to guarantee participants' safety, adverse events (AEs) and serious adverse events, SAEs) are assessed in the study according to the GCP regulations.

In addition to commonly used SAEs such as death and hospitalisation, also expressed suicidal intentions and a two-week or longer lasting deterioration of the symptomatic, are encoded in the study as SAEs

The occurrence of new symptoms of another mental disorder or changes in the social or professional environment, are defined as AEs.

In cases of occurring crises or suicidality the PI will be informed and if necessary, appropriate interventions will be discussed together with the patient and therapist (e.g. hospitalization).

Monitoring

To grant the quality assurance, external risk-adapted monitoring of the study will be conducted by the Centre for Clinical Trials (ZKS) in Tuebingen. The monitoring includes control of informed consent documents and the documentation of inclusion and exclusion criteria as well as primary endpoints (MADRS t1 and t2). Additionally, the compliance of the study implementation is monitored and the documentation of the AEs and SAEs is controlled.

Quality assurance

All procedures related to implementation, evaluation and documentation of the study, described in the present study protocol, are used to ensure, that all persons involved in the study, act in compliance with Good Clinical Practice (GCP) and the current Declaration of Helsinki. The study protocol was approved by the local Ethics Committee of the University Hospital Tuebingen (061/2015BO1).

Ethics approval

Implementation, evaluation and documentation of the study are carried out in accordance with the Good Clinical Practice (GCP) and the Declaration of Helsinki.

The study protocol and the documents for the written clarification were approved by the Ethics Committee of the University Hospital Tuebingen (061/2015B02).

Availability of data and material

The datasets analysed during the current study are available by making a reasonable request to the corresponding author.

All participants approved data assessment, data retention and data evaluation of the data assessed in the scope of the study in encoded pseudonymised form. Additionally, participants agreed to the storage of the data for 10 years in the archive of the University Hospital.

Dissemination

Results of this trial will be submitted for publication in peer-reviewed journals, and will be presented at national and international conferences. The trials is registered within clinicaltrials.gov with the Trial Registration Number: NCT02375308.

Discussion

The present randomised-controlled study compares the efficacy of HT with the standard treatment CBT in individuals with mild to moderate depressive episodes. It is one of the first studies which systematically examine HT as monotherapy for the treatment of depression in an evidence-based study design. The techniques of hypnotherapy are already integrated in other therapy approaches for quite some time, but so far scientific evidence for the efficacy was lacking. For this purpose, this study aims at making a contribution for further evidence. Furthermore, there are certain efforts during the last couple of years to extend and improve actually existing therapy concepts in the scope of third wave therapy approaches. Techniques such as acceptance-based approaches and working with patient's resources were already described in the first developments of the HT.

A special strength of the present study is the highly methodical quality. Beside the systematic assessment and documentation of AEs and SAEs, an external database and independent monitoring of the data quality are additionally applied for this study according to the GCP regulations of pharmacotherapy research.

Additionally, further parameters such as expectations concerning therapy, but also different clinical and psychosocial parameters are assessed in the scope of the present study, which allows for further analyses, such as subgroup analyses and an analysis of the responders in both therapy concepts. Furthermore, with the LIFE interview the manifestation of the depressive symptoms over the complete study period for each patient such as depression-free weeks, the time of remission, but also relapses can be evaluated. The assessment of weekly depressive symptoms scores with the PHQ-9 during the treatment period allows for a closer examination of the early change patterns and their correlation with the treatment outcome.

Overall, the present study makes a contribution to the significance of hypnotherapy in the treatment of depression. Additionally, this study can also provide results, to what extent highly methodological standards can also be implemented in psychotherapy studies.

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List of abbreviations

ACDT: Activating Cognitive Depression Therapy; ACT: Acceptance and Commitment Therapy; ADP-IV: Assessment of DSM-IV Personality Disorders; AE: adverse event; AMG: Germans medicines Law; ANOVA: analysis of variance; BADS: Behavioural Activation for Depression Scale; CBASP: Cognitive Behavioural Analysis System of Psychotherapy; CPP: Completers per protocol; DSM: Diagnostic and Statistical Manual of Mental Disorders ; GCP: Good Clinical Practice; GSES: General Self-efficacy Scale; HDT: Hypnotherapeutic Depression Therapy; HGSHS: Harvard Harvard Group Scale of Hypnotic Susceptibility; HT: Hypnotherapy ; IPT: Interpersonal Psychotherapy; ITT: Intention to treat; CBT: Cognitive behavioural therapy; LIFE: Longitudinal Interval Follow-up Evaluation for DSM-IV; MADRS: Montgomery–Åsberg Depression Rating Scale; MBCT: Mindfulness-based Cognitive Therapy; MDD: Major Depressive Disorder; MEG: Milton Erickson Gesellschaft; MMST: Mini-Mental State Test; PHQ-9: Patient Health Questionnaire; QIDS: Quick Inventory of Depressive Symptoms; RSQ: Response Styles Questionnaire; SAE: severe adverse event; SCID: Structured Clinical Interview for DSM-IV; WAI: Working Alliance Inventory; WHO: World Health Organisation; WHODAS: WHO Disability Assessment Schedule; WHOQOL: WHO Quality of Life; ZKS: Centre for Clinical Trials.

Author's contributions

AB wrote the first version of this study protocol when submitted to the MEG. CS was involved in the process of application for a grant. CM was involved with the statistical analyses section of the study protocol. KF finalised the study protocol for submission to the ethic committee and was involved in the selection of the assessments for the secondary aims of the study. All authors read and approved the final manuscript.

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Competing interests

Not applicable.

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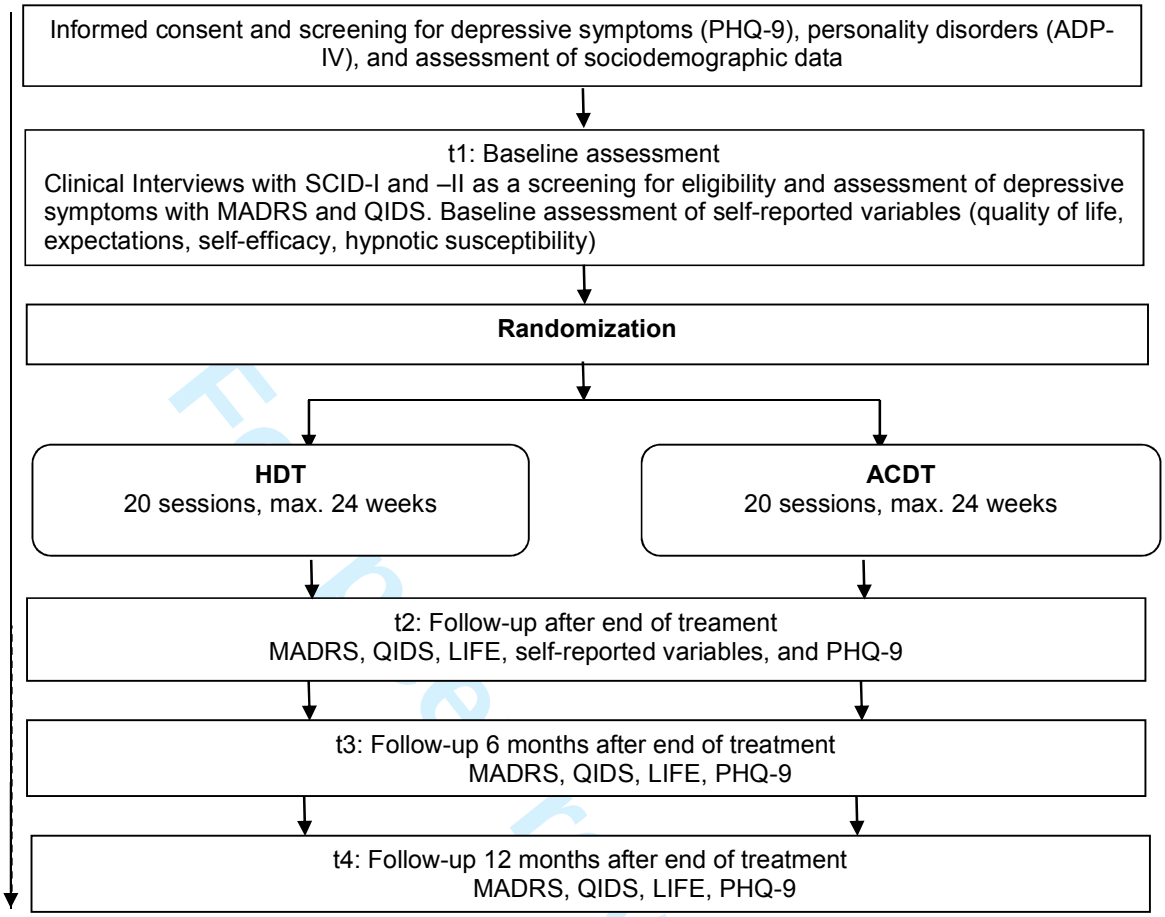

Figure 1.

Study flow chart.

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Table 1

Assessments

Variables	t1: Baseline assessment	Treatment period (24 weeks)	t2: end of treatment 6 months	Follow-up t3 (12 months)	Follow-up t4 (18 months)
Clinician-administered assessments					
SCID-I	X	-	-	-	-
SCID-II	X	-	-	-	-
MADRS	X	-	X	X	X
QIDS	X	-	X	X	X
LIFE	-	-	X	X	X
Self-report measures					
Sociodemographic data	X	-	-	-	-
ADP-IV	X	-	-	-	-
PHQ-9	X	X weekly	X	X	X
WHOQOL-BREF	X	-	X	-	-
WHODAS	X	-	X	-	-
RSQ	X	-	X	-	-
BADS	X	-	X	-	-
GSES	X	-	X	-	-
Expectations regarding treatment/ contentment with treatment	X	-	X	-	-
HGSHS	X	-	X	-	-
WAI-P	-	X*	-	-	-
WAI-T	-	X*	-	-	-

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Records during treatment					
Records concerning techniques applied by therapists	-	weekly	-	-	-

SCID = Structured Clinical Interview for DSM-IV; MADRS = Montgomery Asperg Depression Scale; QIDS = Quick Inventory of Depressive Symptomatology; LIFE = Longitudinal Interval Follow-Up Evaluation; ADP-IV = Assessment of DSM-IV Personality Disorders Questionnaire; PHQ-9 = Patient Health Questionnaire; WHOQOL-BREF = World Health Organization Quality of Life Instruments-BREF; WHODAS = World Health Organization Disability Assessment Schedule; RSQ = Response Styles Questionnaire; BADS = Behavioral Activation for Depression Scale; GSES = General Self-efficacy Scale; HGSHS = Harvard Group Scale of Hypnotic Susceptibility; WAI-P = Working Alliance Inventory – patient perspective; WAI-T = Working Alliance Inventory – therapist perspective.

* only applied in session .6

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-6
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	8-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	12
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	12

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	12
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13-14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	2 and 16
Protocol	24	Where the full trial protocol can be accessed, if available	16
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Efficacy of hypnotherapy compared to cognitive behavioural therapy for mild to moderate depression – study protocol of a randomised controlled rater-blind trial (WIKI-D)

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Efficacy of hypnotherapy compared to cognitive behavioural therapy for mild to moderate depression – study protocol of a randomised controlled rater-blind trial (WIKI-D)

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Protocol Version 5 (23/11/2015)

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Running head: Efficacy of hypnotherapy compared to CBT therapy for depression

Abstract

Introduction: Despite a substantial number of studies providing evidence for the efficacy of psychological treatment for mild to moderate depression, maximally only 50% of participants respond to treatment, even when using gold standard treatments such as cognitive behavioural therapy (CBT) and interpersonal therapy (IPT). New approaches such as the 'third wave' psychotherapies have provided promising results, however studies concerning the comparison with evidence-based treatments are lacking. This study aims to compare the efficacy of clinical hypnotherapy (HT) with gold standard psychotherapy (CBT) in the treatment of mild to moderate Major Depressive Episodes.

Methods and analysis: The present study comprises a monocentric, two-armed, randomised-controlled, rater-blind (non-inferiority) clinical trial. A total of 160 participants with mild to moderate Major Depression Episode will be randomly assigned to either Cognitive Behavioural Therapy (CBT) or Hypnotherapy (HT) involving 20 sessions psychotherapy over a period of 24 weeks. We predict that the average improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score will not be inferior in HT compared to CBT (non-inferiority-hypothesis).

Further outcome parameters will include the number of participants responding to treatment following the completion of treatment and one year after. Additionally, quality of life, treatment expectations, and hypnotic susceptibility before and after end of treatment will be assessed.

Ethics and dissemination: The study protocol and the documents for the informed consent have been approved by the Ethics Committee of the University Hospital Tuebingen (061/2015B02). The results of this trial will be submitted for publication in peer-reviewed journals, and will be presented at national and international conferences.

Registration details: Trial Registration Number: NCT02375308 (clinicaltrials.gov)

Keywords: Depression, Cognitive Behavioural Therapy, Hypnotherapy, Psychotherapy

Strengths and limitations of this study:

Running head: Efficacy of hypnotherapy compared to CBT therapy for depression

- This is the first clinical trial following the GCP Guidelines concerning hypnotherapy for depression
- The external risk-adapted monitoring, external data management and biometry, as well as the assessment of safety due to (serious) adverse events will further enhance the quality of the trial
- The therapists and patients will not be blind to the treatment condition in the current trial, however the raters of the follow-up assessments will be blind

Introduction

The national S3 guideline and the international guidelines for the treatment of unipolar depression [1, 2, 3] recommend psychotherapy alternatively with psychopharmacological treatment for mild to moderate major depressive episodes. Monotherapy with cognitive behavioural therapy (CBT), as well as interpersonal therapy (IPT), are the most evident treatments. For mild and moderate forms of major depressive disorder, psychotherapy is as effective as pharmacotherapy and even shows a higher long-term efficacy, especially for the prevention of relapses [e.g. 4]. For chronic major depression with a duration of two years or longer, as well as for severe unipolar episodes, long-term psychotherapy is needed and yet the evidence concerning psychotherapy is ambiguous [3]. Regarding the years lived with disability (YLD) as assessed by the WHO, mental disorders are the first cause for chronic conditions in the population of Europe. In Europe, unipolar depressive disorder is the first and leading reason for chronic condition, leading alone 11% of all YLD [5]. The response rates to CBT and IPT even for mild to moderate depressive episodes, however, only achieve approximately 50% [e.g. 6]. Thus, improvements in the efficacy of treatment for unipolar disorders are greatly needed. This could be achieved by modification of the existing therapies or by an increase in the variety of treatments. To date, interventions of the so-called 'third wave' of CBT such as schema therapy [7,8], emotion-focused therapy [9], and CBASP [10] have received increasing attention. Furthermore, some therapies influenced by East Asian culture such as mindfulness-oriented (cognitive) therapy (MBCT) and acceptance- and commitment oriented therapy (ACT) are becoming more and more popular [11, 12]. Other new interventions are regarded as a synthesis of psychodynamic and CBT-oriented techniques with special consideration of early life experiences (i. e. CBASP resp. schema therapy). Evidence for the 'third wave' of CBT is growing, while at the same time trials comparing 'third wave' interventions with the gold-standard CBT or IPT are lacking [13]. Beyond the therapies mentioned, hypnotherapy (HT) could provide a promising add-on effect to these treatment methods. Clinical hypnotherapy according to Milton H. Erickson is understood as a resource-oriented approach which aims to enhance self-efficacy and to

support the patient in regard to his/her individual problem solving strategies [14]. In addition to formal trance induction, techniques such as the utilisation of the symptoms and resources of the client, indirect techniques as the use of metaphors or via the representative technique (e.g. using an animal or landscape or another 'agent' that best represents the current problem), or those working with time perception, also play important roles in hypnotherapy [14]. Thus far, few randomised controlled trials on the efficacy of hypnotherapy, especially for the treatment of depression, have been conducted [15, 16, 17]. Additionally, 'cognitive hypnotherapy' as described in a previous study for patients with depression [e.g. 15] was also investigated among patients with anxiety disorders [18]. Research on the efficacy of HT in addition to CBT confirms additive effects of hypnotherapy [19]. However, further support concerning the efficacy of HT compared to CBT especially for the treatment of depression is missing.

Objectives

The present study aims to be the first randomised-controlled trial to evaluate the efficacy of HT compared to an evidence-based gold-standard treatment (i.e. CBT) for mild to moderate major depression episode. According to the actual treatment guidelines, CBT is recommended with the highest evidence of successful outcomes [1, 2, 3].

The following primary hypothesis will be tested:

1) Regarding reduction of the depressive symptoms, HT will not be inferior to CBT after the end of treatment (mean percentage symptom reduction in the clinician-administered rating Montgomery-Asperg Depression Rating Scale, MADRS).

Additionally, the following secondary target parameters will be examined exploratively:

2) A non-superiority of one of both interventions related to a further symptom reduction in the MADRS, but also in the Quick Inventory of Depressive Symptoms - Clinician Rating

($QIDS_{C16}$) and the Patient Health Questionnaire – depression scale (PHQ-9) over the follow-up period occurring up to twelve months after end of treatment.

3) The response rate of patients in both treatment conditions at the end of treatment and in the follow-up period will be analysed (assessed via the clinical results: MADRS, $QIDS_{C16}$, response defined as symptom reduction >/= 50%).
4) The rate of remission (number of weeks) and of patients with relapses in the twelve months following therapy in both treatment conditions will be analysed (assessed via the Longitudinal Interval Follow-up Evaluation for DSM-IV, LIFE).
5) Variables predicting the treatment response will be analysed. The following variables will be regarded as potential predictors for a response:
    - Sociodemographic variables: Gender, age, family status, further hypnotic susceptibility, expectations concerning treatment, perceived self-efficacy, behavioural activation, working alliance between patient and therapist, early response in the first six weeks of treatment
    - Disorder-related variables: Number of previous episodes, severity of actual episode, global functional level at inclusion in the study, comorbidities.

Running head: Efficacy of hypnotherapy compared to CBT therapy for depression

Methods and Analysis

Study design

The clinical trial will be based on a 4 x 2 mixed factors design with the factors Time (4 time intervals: prior to (t1) and immediately after treatment (t2) as well as six (t3) and twelve months (t4) after treatment for the follow-up period) and Treatment condition (CBT vs. HT). Half of the participants will be randomly assigned to HT and CBT.

Sample

Patients with Major Depressive Disorder (MDD) with an actual mild to moderate episode according to the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5 [20]) will be included in the study (assessed via Structured Clinical Interview for DSM-IV Axis I, SCID-I [21], adapted for DSM-5).

Patients will be recruited starting in 2015 via the depression outpatient clinic of the University Hospital Tuebingen in the Department of Psychiatry and Psychotherapy and via a network of referring institutions (licensed psychiatrists, psychotherapists, university outpatient clinics, institutes for psychotherapy training, self-help groups, general practitioners, psychiatric hospitals) from the region Tuebingen, Reutlingen, Rottenburg and if applicable, Stuttgart, via flyers, newspaper advertisements, and university and university hospital mailing lists. Interested individuals will be informed about the study in written form and undergo a personal interview at the study centre by one of the trained and authorised study coordinators. Following written consent, interested individuals will be invited for participation in the study after assessment of the following inclusion and exclusion criteria:

Inclusion criteria

- Written informed consent
- Patient fulfils criteria for a mild to moderate depressive disorder according to DSM-5
- 18 – 70 years of age
- Sufficient knowledge of the German language in order to participate in the study

- Sufficient availability to participate in weekly therapy sessions
- In cases of existing anti-depressive medication: stable medication since three months without planned changes during the duration of therapy.

Exclusion criteria

- Lifetime diagnosis of a bipolar disorder or psychotic disorder
- Diagnosis of chronic MDD (duration >/= 2 years)
- Severe Major Depressive Episode (MDE) according to SCID-I resp. MADRS >/= 35 or $QIDS_{C16}$ >/= 16
- Remission of actual episode since four weeks or longer
- Depression with psychotic characteristics acc. to SCID-I
- Acute suicidality (intended action, concrete plans or intermittent pronounced suicidal ideation)
- Severe cognitive impairments (in cases of suspicion evaluation via Mini-Mental StateTest, MMST < 26, will be conducted)
- Other severe mental disorders to be treated: dominant panic disorder, severe personality disorder of borderline type with self-injury, active alcohol or drug dependence, actual posttraumatic stress disorder, anorexia nervosa via SCID-I
- Somatic disorder impeding participation in regular psychotherapy sessions
- Outpatient psychotherapy during the last twelve months.

Sample size and power analysis

The primary target size is defined as the percentage reduction of the depressive symptoms (MADRS) between baseline and the end of treatment. The following assumptions are made on the basis of the available data: an assumed improvement in the MADRS of 50% (standard deviation of 32.9 points, on the basis of the results for the efficacy of CBT, see [6] page 500 and half standard deviation (16.4) as the non-inferiority range. A confidence interval of 95% using a randomisation proportion of 1:1 and an alpha-level of 5% will be used. Under these

conditions a one-sided t-test applied to a sample size of n=70 in each group will have 80% statistical power for refusal of the null hypothesis that HT is inferior to CBT.

Assuming a maximal drop-out rate of 12.5%, a total of 160 patients with current mild to moderate MDE should be employed to reach at least a number of 140 assessable patients. The sample size definition was established using Query version 7.0.

Intervention

The two single outpatient treatments include 20 sessions at 50 minutes each during a period of 20 weeks (max. 24 weeks).

The treatment is based on the respective manuals of both therapy methods. The manual for CBT, entitled “Activating Cognitive Depression Therapy (ACDT)” delineates already well-established CBT approaches [22]. The manual for the hypnotherapy is based on established materials [23] and is named “Hypnotherapeutic Depression Therapy (HDT)”.

Overall, four therapists with adequate qualification (education in behavioural therapy or hypnotherapy and at least 3 years of professional experience) each in ACDT and HDT will be trained (1 – 2 days) related to the treatment manuals.. Each therapist (four therapists per treatment condition) will treat 20 patients within the scope of the study. The therapy sessions will be recorded when agreement of the patient is attained. Therapists’ adherence to the manual will be enhanced by regular supervisions on a monthly basis. Adherence to the manual will be tested by a therapist that is not involved in the study procedure. Thus, randomly chosen, digitally recorded sessions will be evaluated regarding treatment adherence based on a list of the relevant techniques of the given treatment manual. Additionally, for each session therapists will be required to document which elements of the manual for ACDT or HDT were conducted.

ACDT (Cognitive behavioural therapy - Activating Cognitive Depression Therapy)

The ACDT consists of techniques already well-established and well examined in depression research such psychoeducation, behavioural activation, cognitive restructuring techniques, problem solving skills, and interpersonal skills. In this treatment condition, homework will be assigned, exercises will be performed, and daily routine structure will be reviewed with the overall goal to reduce depressive symptoms and to build up skills which enable individuals to cope with their disorder independently. Additional elements will also be optionally applied, such as by addressing ruminative thoughts or sleeping problems, and practicing progressive muscle relaxation.

HDT (Hypnotherapeutic Depression Therapy)

The modules of the HDT promote hypnotic activation and reinforcement of one's own resources, the use of relevant positive and negative experiences from the biography, and the development of positive solution imagery. Furthermore, formal trance induction, utilisation techniques, indirect techniques such as the use of metaphors or the representative technique, or work with time progression will be used. Additional elements will be applied as needed, such as by addressing ruminative thoughts and sleeping problems. The therapy can be adjusted according to the individual needs of the patient.

Assessment

For an overview of the evaluations for each assessment time point, see Table 1.

Primary endpoint

Montgomery–Åsberg Depression Rating Scale (MADRS). As the primary endpoint of the study, the manifestation of the depressive symptoms will be assessed via the clinician-rating MADRS [24] at t1, t2, t3, and t4.

Secondary endpoints

Quick Inventory of Depressive Symptoms – Clinician Rating (QIDSC16 [25]), for the

assessment of the depressive symptoms at t1, t2, t3, and t4.

Patient Health Questionnaire – depression module (PHQ-9). Manifestation of depressive symptoms will be assessed using the self-report PHQ-9 [26] at t1, t2, t3, and t4 and weekly (max. 24 weeks) during the therapy period.

Longitudinal Interval Follow-up Evaluation for DSM-IV (LIFE). The time intervals, duration of remission, and possible relapses after the treatment, as well as the follow-up intervals will be assessed via the LIFE interview [27] to t2, t3, and t4, each over a period of six months retrospectively. Additionally, the LIFE will assess whether and which alternative treatments have been used in the meantime (e. g. inpatient-treatment, medication).

WHO Quality of Life (WHOQOL-BREF, [28]) will assess patients' quality of life concerning physical health, psychological health, social relationships, and environment with 26 items at t1 and t2.

WHO Disability Assessment Schedule (WHODAS). The WHODAS [29] will measure the global functional level with 12 items at t1 und t2.

Response Styles Questionnaire (RSQ [30, 31]) for the assessment of coping and rumination at t1 und t2.

Behavioural Activation for Depression Scale (BADS, [32]) for the assessment of behavioural activation at t1 und t2.

General Self-Efficacy Scale (GSES, [33]) will measure self-efficacy using ten items at t1 and t2.

Questions to specific **therapy expectations** at t1 and to contentment at t2 will be included.

Harvard Group Scale of Hypnotic Susceptibility (HGSHS). Presently the HGSHS [34] is the most common scale for the assessment of suggestibility. A German validation is available including a standardised audio recording, which can be presented to each participant. The HGSHS will be applied at t1 and t2.

Working Alliance Inventory - short and revised form (WAI-SR, [35]). Once in treatment during week six there will be assessment of the therapeutic alliance between the therapist and the patient from both perspectives, resulting in a therapist and a patient version. The assessment of the WAI early in therapy was chosen because this is a better predictor for therapy outcome [36, 37].

Study procedure

Following written informed consent, an initial test for depressive symptoms with the PHQ-9, a screening for personality disorders and the assessment of sociodemographic statements will be carried out via questionnaires. The baseline assessment diagnostics will then be performed (clinical interviews and questionnaires). This includes extensive diagnostics for the final examination of the inclusion and exclusion criteria (especially the current MDE and the actual severity of depression) by trained diagnosticians (baseline, t1, for an overview, see Figure 1 and Table 1). The SCID-I [21], adapted for DSM-5, will be applied for the examination of inclusion and exclusion criteria and for the assessment of possible comorbid disorders. The diagnostics of personality disorders with SCID-II [38] will be only applied for related indications via the Assessment of DSM-IV Personality Disorders (ADP-IV) for screening of personality disorders [39]. In the case of suspected cognitive impairment/dementia, the Mini-Mental State Test (MMST) will be applied [40] in which a MMST score of 25 or below will lead to exclusion.

If the first treatment session will be scheduled more than 3 weeks after the date of the baseline assessment, the depressive symptoms will be re-assessed via MADRS and QIDS.

A computerized random algorithm using nQuery 7.0 will be used to generate the random allocation of the participants to one of the two study groups: Group 1: HDT, Group 2: CBT). A randomisation procedure will be established by electronic interaction between the study centre and the data centre. The diagnosticians responsible for conducting the outcome assessments at the follow-ups will be blind to the patient's treatment. Both interventions will have the same number and duration of sessions. In all conditions 20 50-minute outpatient sessions will be performed during a maximum period of 24 weeks. Furthermore, single sessions can maximally be combined to four double sessions. The interventions differ especially concerning the application of different behavioural therapy techniques (e. g. behaviour activation, cognitive restructuring, establishing social competence) or hypnotherapy techniques (e. g. time progression, working with trance and metaphors, representative technique, reframing). After the end of therapy (t2), and six (t3), and twelve months (t4) later, patients will be evaluated in follow-up assessments concerning their symptoms by blind diagnosticians. To ensure the completion of the follow-up assessments, participants will receive reminding emails and up to three phone calls or a postal letter. After the follow-up at t4, participation in the study will be concluded for patients, see Figure 1.

Patients who withdraw their participation from the study will be classified as discontinued. The patient will decide whether or not already assessed data may be included in the evaluation.

Treatment participation will be considered as completed per protocol (CPP), if the patient will have attended at least 80% of sessions (≥ 16 of the 20 planned sessions). For the implementation of the 20 sessions, a maximum of 24 weeks (six months) will be provided. This period can be exceeded up to four weeks in cases of impending loss of patients (those achieving less than 80% participation). Possible intermissions due to hospitalisation or for other reasons will be recorded as protocol violations. If a patient starts another inpatient, day-care or outpatient psychotherapeutic treatment, or if an inpatient crisis intervention takes

longer than 14 days, the study therapy will be discontinued. The patient will then be considered as a therapy dropout, but will undergo follow-up evaluation on a regular basis. For all randomised patients, all planned follow-up intervals should be carried out (Intention to treat, ITT), regardless of whether or not the treatment was concluded according to the protocol. Study therapists are not permitted to maintain contact with the study patients during the follow-up period of twelve months after the end of therapy.

Statistical Analysis

Analysis of primary endpoint

The primary endpoint of the study will be the comparison of HDT and ACDT regarding the mean percentage modification of symptoms (MADRS) between baseline at t1 and after the end of therapy (t2). The mean modification (%) will be estimated for both treatment groups using a 95% confidence interval.

Definition of study population for the analysis

A modified intent-to-treat analysis will be applied.

The per-protocol-population will be a partial quantity of the ITT. Patients with one of the following protocol violations will be excluded:

- Randomised assignment despite violation of the inclusion and exclusion criteria
- Error in the assignment to a randomised therapy group
- Usage of another psychotherapy according to the patient's report
- Negative compliance (participation in less than 16 session)
- Lacking follow-up participation (absence at the last follow-up session after twelve months)
- Missing data concerning depressive symptoms (MADRS) after the end of therapy (t2).

Statistical evaluation will be carried out after conclusion of the data assessment at t4 (data base conclusion) for the last randomly assigned patient.

The following hypotheses will be tested at a one-site significance level of 5%:

H_0: μAKDT- μHDT ≥ 16.4%

H_1: μHDT – μAKDT < 16.4%

μ stands for the mean percentage change of MADRS between the baseline score (t1) and the score at the end of therapy (t2) for each therapy group.

The primary hypothesis will be calculated by estimating the difference of the mean percentage change scores of both therapy groups using a one-sided 95% confidence interval. HDT will be regarded as non-inferior compared to ACDT if the range of the confidence interval is smaller than the allowed non-inferiority level of 16.4%. The range of 16.4% for non-inferiority will be employed for the available data.

The primary analysis will be performed according to PP population, which statistically represents the conservative approach for the analysis of non-inferiority. An additional analysis based on the ITT population will serve as the sensitivity analysis in order to estimate the robustness of the primary analysis.

All secondary outcomes will be evaluated using exploratory data analysis and compared in regard to the PP and the ITT population.

2) The endpoint of the study will be the comparison of HDT and ACDT regarding the mean percentage modification of symptoms as assessed with the MADRS, but also with the QIDSC16 and the PHQ-9 between baseline t1 and after the end of therapy (t2), as well as to the follow-up intervals at six (t3) and twelve months (t4) after the end of treatment. The mean modification (%) will be estimated for both treatment groups (incl. 95% confidence intervals).
3) Response will be defined as a symptom reduction at a rate of >/= 50% in the MADRS/ QIDSC16. Incidence of response from baseline (t1) and the end of treatment (t2) as well as follow-up intervals (t3, t4) will be compared between both

treatment conditions using Cochrane-Mantel-Haenszel tests. The relative risk (HDT vs. AKDT) including a 95% confidence interval will be estimated.

4) The median rates of weeks in remission in the period of twelve months after the end of therapy for both treatment conditions will be analysed using a 95% confidence interval and comparison with a Mann-Whitney-U-test. Concerning the rate of patients with relapses, both treatment conditions will be compared using a Cochrane-Mantel-Haenszel test. The relative risk (HDT vs. AKDT) will be estimated using a 95% confidence interval.
5) A logistic regression analysis with the dummy variable response (1/0) as the outcome and the potential predictors at t1 (WHODAS, WHOQOL, RSQ, BADS, HGSHS, HRV, SWE, WAI, age, gender, number of previous episodes, early response in the first six weeks, severity of actual episode, global functional level at inclusion in the study, and comorbidities) will be calculated based on significant correlations between the potential predictor and the outcome.

External data management and biometry

Data will be entered in a database (www.koordobas.de). All available data will be entered twice in the database and be checked for errors, consistency and completeness before being submected to the statistical analyses.

Statistical analysis will be performed with SAS (Version 9.2) and SPSS (Version 22).

The data monitoring committee is independent from the sponsor and competing interests, from participant recruitment and conduction of the trial. The committee is involved in the establishment of the sample size and power calculation, the management of the database, and the statistical analysis of the primary endpoint.

Methods for the assessment of safety

In order to guarantee the participants' safety, adverse events (AEs) and serious adverse events (SAEs) will be assessed in the study according to GCP regulations.

In addition to commonly used SAEs, such as death and hospitalisation, expressed suicidal intentions and a two-week or longer deterioration of the symptoms, will be encoded in the study as SAEs

The occurrence of new symptoms of another mental disorder, or changes in the social or professional environment, will be defined as AEs.

In cases of crises or suicidality the PI will be informed and, if necessary, the appropriate steps will be discussed together with the patient and therapist (e.g. hospitalization). In case of multiple cases of suicidality in one of the intervention groups or completed suicides, the study will be considered to be stopped based on the reported SAEs.

Monitoring

To establish quality assurance, an external risk-adapted monitoring of the study will be conducted by the Centre for Clinical Trials (ZKS) in Tuebingen. The monitoring will include control of the informed consent documents and of the documentation associated with the inclusion and exclusion criteria and the primary endpoints (MADRS t1 and t2). Additionally, compliance-to the implementation of the study protocol will be monitored and the documentation related to the AEs and SAEs will be controlled. In total three visits are planned, at the beginning, in the middle, and after completion of the trial. This will be independent from investigators and the sponsor.

Quality assurance

All procedures related to the implementation, evaluation, and documentation of this study which are described in the present study protocol will be used to ensure that all persons involved in the study act in compliance with the Good Clinical Practice (GCP) and the current Declaration of Helsinki. The study protocol has already been approved by the local Ethics Committee of the University Hospital Tuebingen (061/2015BO1).

Ethics approval

The implementation, evaluation and documentation of the study will be carried out in accordance with the Good Clinical Practice (GCP) and the Declaration of Helsinki.

The study protocol and the documents for the informed consent were approved by the Ethics Committee of the University Hospital Tuebingen (061/2015B02).

Availability of data and material

The datasets analysed, the informed consent form, and other material used for the current study will be available via request to the corresponding author.

The database will be closed after all data are entered and the last patient has completed or left the trial. The principal investigator, as well as the study centre, will have access to the final dataset only after the database has been closed.

All participants will be obliged to accept that the data assessment, data retention, and data evaluation of the data assessed within the scope of the study will be retained in an encoded form using pseudonyms. Additionally, the participants obliged to agree to the storage of the data for ten years in the archive of the University Hospital.

Dissemination

The results of this trial will be submitted for publication in peer-reviewed journals, and will be presented at national and international conferences. The trial is registered within clinicaltrials.gov with the Trial Registration Number: NCT02375308. For details concerning the registration according to the World Health Organization Trial Registration Data Set, see Table 2.

Roles and responsibilities

The coordinating centre is represented by the affiliation of the first and the last authors. These authors are responsible for the supervision and realisation of the study, in addition to maintaining communication with the sponsor, the external data monitoring committee, and the external monitoring committee, as well as with dissemination of the results. Data will be

obtained and collected at the study centre. The data management team is independent of the data acquisition. For the data monitoring committee, see page 16 (External data management and biometry).

Discussion

The present randomised-controlled study will compare the efficacy of HT with the standard treatment, CBT, in individuals with mild to moderate depressive episodes. It is one of the first studies which will systematically examine HT as monotherapy for the treatment of depression in an evidence-based study design. The techniques of hypnotherapy have already been integrated in other therapy approaches for quite some time, however thus far scientific evidence for the efficacy has been lacking. For this reason, this study aims to contribute further evidence regarding the therapeutic efficacy of hypnotherapy. Furthermore, within the scope of 'third wave' psychotherapy certain efforts have been made during recent years to extend and improve existing therapy concepts. Techniques such as acceptance-based approaches and working with patient's resources have already been described during the early developments related to the HT.

A special strength of the present study is the highly methodological quality of the study protocol. Beyond the systematic assessment and documentation of the AEs and SAEs, an external database and independent monitoring of the data quality will be applied for this study which is in accord to the GCP regulations of pharmacotherapy research.

Additionally, further variables such as expectations about the therapy and various clinical and sociodemographic factors will be assessed within the scope of the present study, which allow for further analyses such as subgroup analyses and an analysis of the responders. Furthermore, the LIFE interview enables for each patient evaluation of the manifestation of depressive symptoms (e.g. depression-free weeks) the time of remission, and relapses during the entire study period. The assessment of weekly depressive symptoms scores with the PHQ-9 during the treatment period will allow for closer examination of the early change patterns and their correlation with the treatment outcome.

Overall, the present study will make a contribution to the significance of hypnotherapy in the treatment of depression. Additionally, this study can also provide results about the extent to which highly methodological standards can be implemented in studies of psychotherapy.

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List of abbreviations

ACDT: Activating Cognitive Depression Therapy; ACT: Acceptance and Commitment Therapy; ADP-IV: Assessment of DSM-IV Personality Disorders; AE: adverse event; AMG: Germans medicines Law; ANOVA: analysis of variance; BADS: Behavioural Activation for Depression Scale; CBASP: Cognitive Behavioural Analysis System of Psychotherapy; CPP: Completers per protocol; DSM: Diagnostic and Statistical Manual of Mental Disorders ; GCP: Good Clinical Practice; GSES: General Self-efficacy Scale; HDT: Hypnotherapeutic Depression Therapy; HGSHS: Harvard Harvard Group Scale of Hypnotic Susceptibility; HT: Hypnotherapy ; IPT: Interpersonal Psychotherapy; ITT: Intention to treat; CBT: Cognitive behavioural therapy; LIFE: Longitudinal Interval Follow-up Evaluation for DSM-IV; MADRS: Montgomery–Åsberg Depression Rating Scale; MBCT: Mindfulness-based Cognitive Therapy; MDD: Major Depressive Disorder; MEG: Milton Erickson Gesellschaft; MMST: Mini-Mental State Test; PHQ-9: Patient Health Questionnaire; QIDS: Quick Inventory of Depressive Symptoms; RSQ: Response Styles Questionnaire; SAE: severe adverse event; SCID: Structured Clinical Interview for DSM-IV; WAI: Working Alliance Inventory; WHO: World Health Organisation; WHODAS: WHO Disability Assessment Schedule; WHOQOL: WHO Quality of Life; ZKS: Centre for Clinical Trials.

Author's contributions

AB wrote the first version of this study protocol when submitted to the Milton Erickson Gesellschaft (MEG). CS was involved in the grant application. CM was involved with the statistical analysis section of the study protocol. KF finalised the study protocol for submission to the ethics committee and was involved in the selection of the assessments used for the secondary aims of the study. All authors have read and approved the final manuscript.

Funding

This study is funded by the Milton Erickson Gesellschaft (MEG), Waisenhausstraße 55, 80637 Munich, Germany. The funding body was not involved in the design of the study and will not be involved in the data collection, analysis, or interpretation of the data. We acknowledge support from Deutsche Forschungsgemeinschaft and Open Access Publishing Fund of University of Tuebingen.

Competing interests

Not applicable.

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Table 1

Assessments

Variables	t1: Baseline assessment	Treatment period (24 weeks)	t2: end of treatment 6 months	Follow-up t3 (12 months)	Follow-up t4 (18 months)
Clinician-administered assessments					
SCID-I	X	-	-	-	-
SCID-II	X	-	-	-	-
MADRS	X	-	X	X	X
QIDS	X	-	X	X	X
LIFE	-	-	X	X	X
Self-report measures					
Sociodemographic data	X	-	-	-	-
ADP-IV	X	-	-	-	-
PHQ-9	X	X weekly	X	X	X
WHOQOL-BREF	X	-	X	-	-
WHODAS	X	-	X	-	-
RSQ	X	-	X	-	-
BADS	X	-	X	-	-
GSES	X	-	X	-	-
Expectations regarding treatment/ contentment with treatment	X	-	X	-	-
HGSHS	X	-	X	-	-
WAI-P	-	X*	-	-	-
WAI-T	-	X*	-	-	-

Documentation during treatment					
Documentation concerning techniques applied by therapists	-	weekly	-	-	-

SCID = Structured Clinical Interview for DSM-IV; MADRS = Montgomery Asperg Depression Scale; QIDS = Quick Inventory of Depressive Symptomatology; LIFE = Longitudinal Interval Follow-Up Evaluation; ADP-IV = Assessment of DSM-IV Personality Disorders Questionnaire; PHQ-9 = Patient Health Questionnaire; WHOQOL-BREF = World Health Organization Quality of Life Instruments-BREF; WHODAS = World Health Organization Disability Assessment Schedule; RSQ = Response Styles Questionnaire; BADS = Behavioural Activation for Depression Scale; GSES = General Self-efficacy Scale; HGSHS = Harvard Group Scale of Hypnotic Susceptibility; WAI-P = Working Alliance Inventory – patient perspective; WAI-T = Working Alliance Inventory – therapist perspective.

* only applied in session .6

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Table 2

Registration details (according to WHO Data Set)

1	**Primary Registry and Trial Identifying Number:** Trial Registration Number: NCT02375308 (clinicaltrials.gov)
2	**Date of Registration in Primary Registry:** February 24, 2015
3	**Secondary Identifying Numbers:** not applicable
4	**Source of Monetary or Material support:** Milton Erickson Gesellschaft (MEG), Waisenhausstraße 55, 80637 Munich, Germany
5	**Primary Sponsor:** Professor Anil Batra; Department of Psychiatry and Psychotherapy, University Hospital of Tuebingen, Calwer Str. 14, D-72076 Tuebingen, Germany; anil.batra@med.uni-tuebingen.de
6	**Secondary Sponsor(s):** not applicable
7	**Contact for Public Queries:** see 5.
8	**Contact for Scientific Queries:** see 5.
9	**Public Title:** Psychotherapy for depression (WIKI-D)
10	**Scientific Title:** Efficacy of hypnotherapy compared to cognitive behavioural therapy for mild to moderate depression – study protocol of a randomiszed controlled rater-blind trial (WIKI-D)
11	**Countries of Recruitment:** Germany
12	**Health Condition(s) or Problem(s) Studied:** Mild to moderate Major Depressive Episode
13	**Intervention(s):** 1) ACDT (Cognitive behavioural therapy - Activating Cognitive Depression Therapy) 2) HDT (Hypnotherapeutic Depression Therapy)
14	**Key Inclusion and Exclusion Criteria:** Inclusion criteria:

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	• Mild to moderate depressive disorder according to DSM-5 • 18 – 70 years of age Exclusion criteria: • Lifetime diagnosis of a bipolar disorder or psychotic disorder • Diagnosis of chronic MDD (duration >/= 2 years) or severe Major Depressive Episode (MDE) • Other severe mental disorders to be treated
15	**Study Type:** Randomised controlled rater-blind trial
16	**Date of First Enrollment:** April 15, 2015
17	**Target Sample Size:** *N* = 160
18	**Recruitment Status:** still recruiting
19	**Primary Outcome(s):** Depressive symptoms assessed via the Montgomery–Åsberg Depression Rating Scale (MADRS) between baseline and the end of treatment
20	**Key Secondary Outcomes:** Reponse rate, rate of remission, predictors for response (sociodemographic and disorder-related variables)

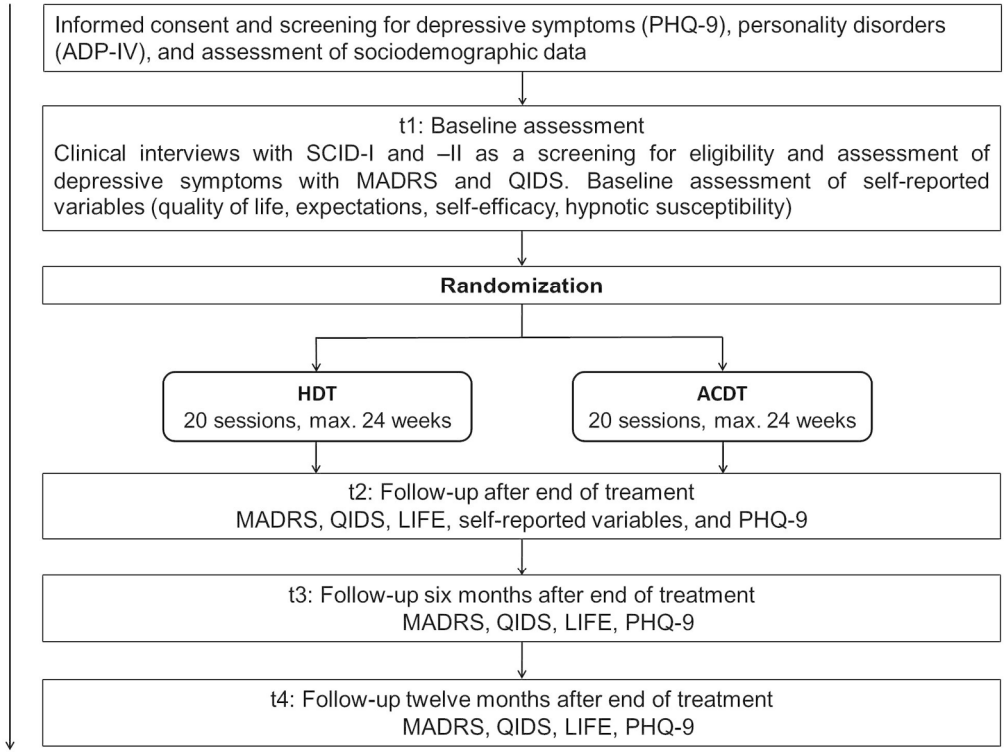

Figure 1.
Study flow chart.

163x123mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	32-33
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 24
	5b	Name and contact information for the trial sponsor	24
	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	24
	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)	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	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	6
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
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	12-13
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)	29-31

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	9-10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13
	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	14

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	____18, 19____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____15-17____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____17___
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____15-16____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____18_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____18 _____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____18_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____18_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____19_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
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	2, 20
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	19
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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