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Internet-based cognitive-behavioural writing therapy for reducing posttraumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): Study protocol for a randomised-controlled trial

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ABSTRACT

Introduction: As a consequence of intensive care for sepsis, considerable proportions of patients but also of their spouses develop a posttraumatic stress disorder (PTSD). However, only a very small number receive psychotherapeutic treatment. Internet-based cognitive-behavioural writing therapy (IB-CBWT) has proven to be an effective treatment option for PTSD. It seems to fit the specific needs of this cohort and to overcome treatment barriers. Aim of the REPAIR trial is to examine the efficacy, safety, and applicability of IB-CBWT for PTSD in patients and their spouses after intensive care for sepsis.

Methods and analysis: Participants will be assigned randomly either to a treatment or a wait-list (WL) control group. The treatment group receives IB-CBWT for PTSD with actively involving the partners of the participants. IB-CBWT will be guided by a therapist and comprises two written assignments per week over a 5-week period. After completing the assignments, the participants obtain individual response from the therapist. Participants of the WL control group will receive treatment after a waiting period of 5 weeks. The primary outcome is PTSD symptom severity in self-rated PTSD Checklist for DSM-5 at the end of treatment and waiting time, respectively. Secondary outcomes are remission of PTSD, depression, anxiety, and somatization measured by the Brief Symptom Inventory-18, marital satisfaction measured by the Relationship Assessment Scale, health-related quality of life measured by the EQ-5D-5L, and the feasibility of IB-CBWT for that cohort (i.e. dropout rate). Statistical analysis will be performed according to the intent-to-treat principle.

Ethics and dissemination: The study is conducted according to the principles of Good Clinical Practice and has been approved by the ethics committee of the Friedrich-Schiller University Jena, Germany. Results will be disseminated at scientific conferences, published in peer-reviewed journals, and provided to consumers of health care.

Trial registration: German Clinical Trials Register (DRKS); no. DRKS00010676.

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Strengths and limitations of this study

- This randomised-controlled trial will provide new evidence concerning the treatment of PTSD in patients after intensive care for sepsis and their spouses.
- For the first time also the spouses of patients with PTSD will be involved in their partners' internet-based cognitive-behavioural writing therapy.
- Intervention effects will be compared against a wait-list control group.
- It is not possible to ensure a complete blinding of patients and therapists.

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INTRODUCTION

Psychopathological reactions, i.e. acute stress disorder (ASD; ICD-10 F43.0) and posttraumatic stress disorder (PTSD; F43.1), are common consequences of life-threatening events such as sepsis and negatively affect patients' long-term functioning and quality of life.[1-3] Critical illness can also be a traumatic and stressful experience for family members as a result of uncertainty and the fear of the patient's physical disability or death. DSM-5[4] explicitly defined the diagnostic criteria of a traumatic event as an exposure to actual death or serious injury experienced by witness in person or which has occurred to a close family member. Family members, particularly spouses, who care for the critically ill patient during the time of intensive care, are therefore a vulnerable cohort.[5-7] In a recent study, up to 69% of the patients, who had survived a sepsis, and 62% of the spouses of sepsis patients suffered from clinically relevant PTSD symptoms.[8] It has been further shown that both physical and mental health of patients and their spouses are interrelated. More specifically, results of a dyadic analysis indicated that the mental quality of life of a person (patient or spouse) is negatively impacted by posttraumatic stress symptoms of the respective partner. Furthermore, it has been shown that PTSD symptoms of the patient who survived a sepsis are a significant predictor of PTSD symptoms of the respective spouse.[9] Based on these results, it has been concluded that couples react as a dyadic system with interdependent emotional responses to critical illness. Thus, the inclusion of spouses in the treatment of mental long-term consequences of critical illness appears to be inevitable.[8] However, patients suffering from PTSD after critical illness are often untreated or undertreated hereof. Accordingly, Mehlhorn *et al*[10] suggest in their review of interventions for the postintensive care syndrome, that "postintensive care patients may benefit from interventions like trauma-focused cognitive-behavioural therapy […] but often they do not have access to those interventions." (p. 1268).

With regard to the treatment of PTSD, several evidence-based interventions exist. There is striking evidence for the efficacy of trauma-focused cognitive-behavioural therapy (TFCBT)

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with large effect sizes (standardized mean difference SMD = 1.62; 95% confidence interval (CI) [1.21; 2.03] in a meta-analysis of 28 studies) compared against wait-list (WL) control.[11] Nevertheless, only a minority of individuals suffering from PTSD seeks psychological treatment due to different barriers (e.g. fear of stigmatization, embarrassment, lack of availability of specialised therapists). In recent years, internet-based interventions based on CBT techniques have overcome these face-to-face treatment barriers by treating mobility-impaired patients, being independent in space and time as well as easily accessible and due to visual anonymity being low-threshold.[12-14] The internet-based approach is usually based on a manualised, therapist-assisted treatment which is operationalised via written assignments. In general, treatment as well as the diagnostic screenings (before and after the treatment) are conducted without any face-to-face contact in a secure web portal.[12 15 16] Meta-analytic evidence has proven the efficacy of internet-based cognitive-behavioural writing therapy (IB-CBWT) to be large (Hedges´ g = 0.95; 95% CI [0.46; 1.43]; 8 studies) in PTSD symptom reduction compared to WL control.[14]

Up to now, IB-CBWT has not been considered as a treatment approach for PTSD after critical illness and intensive care. Moreover, therapeutic approaches for PTSD that include spouses in addition to the patients are very scarce.

Objectives

Primary aims of the REPAIR trial are to investigate the efficacy, safety, and applicability of IB-CBWT for posttraumatic stress in patients after intensive care for sepsis and their spouses compared to a WL control group and to assess maintenance of possible treatment gains at 3, 6, and 12 months post-treatment. Second, the study aims at examining dyadic concordance in treatment effects, i.e. indirect effects of the treatment in the respective spouse of the participant of the treatment. Third, the influence of dyadic coping on the treatment effects will be explored.

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METHODS AND ANALYSIS

Study design and setting

REPAIR is a randomised-controlled, parallel group, superiority trial. The current study will be conducted at the Jena University Hospital with recruiting participants from German speaking countries (e.g., Germany, Austria, and Switzerland). Participants will be contacted via telephone for initial screening and via internet for delivering the treatment and conducting all assessments.

Eligibility criteria

We will include adult (18+ years) patients after intensive care (>5 days) for sepsis[17] and their spouses (married or unmarried) who are fluent in written German. A patient-spouse dyad will be included if at least one of them (patient or spouse or both) scores above the PCL-5 cut-off (score $\geq$ 33)[18] for a presumptive PTSD diagnosis. PTSD should be based on a trauma, which is associated with the stay in the intensive care unit (ICU). Patients will be excluded, if they do not have a spouse. According to the German clinical guideline on the treatment of PTSD[19] acute psychosis and suicidal intentions will be criteria for exclusion. Furthermore, the use of neuroleptics, or an ongoing psychotherapeutic treatment elsewhere will be reasons for exclusion.

Procedures

Recruitment

First, all persons, i.e., patients or spouses, who had requested free of charge advice from the German Sepsis Aid's National Helpline (http://www.sepsis-hilfe.org), will be contacted and informed about the study. Second, patients of the Mid-German Sepsis Cohort (MSC; trial registration: German Clinical Trials Register, no. DRKS00010050) who are positively screened for PTSD at one of the MSC study assessments will be informed about the study. Third, participants will be recruited via advertisements in health journals and distribution of information brochures in hospitals and rehabilitation centres. In a first telephone contact,

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participants will be screened for eligibility by using the Life Event Checklist for DSM-5 (LEC 5)[20] and the PTSD checklist for DSM-5 (PCL-5)[18]. Written informed consent will be obtained by the patients and their spouses (see Figure 1). In a second telephone contact, patients and their spouses will complete the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[21] and the Structured Clinical Interview for DSM-IV (SCID-I)[22] conducted by a trained psychologist. Medical data will be assessed (e.g., length of intensive care and (if) length of mechanical ventilation, time since ICU discharge).

Randomisation

All eligible patient-spouse dyads consenting to participation will be randomly assigned to either IB-CBWT or to a WL control group (allocation ratio 1:1) with the patient-spouse dyad being the unit of randomisation. Randomisation will be conducted using a central internet-based registration system provided by the Center for Clinical Studies of the Jena University Hospital. This system automatically randomises patients and generates a message noting the assigned treatment. The underlying randomisation list will be developed by an independent biometrician using a computer-based algorithm. Allocation will be concealed and stratified by the occurrence of PTSD symptoms within the dyads of sepsis patient and the spouse: strata 1 - both, sepsis patient and spouse with PTSD; strata 2 - sepsis patient with PTSD/spouse without, and strata 3 - spouse with PTSD/sepsis patient without.

Baseline assessment (t0)

Before the start of the treatment participants, i.e. patients and their spouses, will be asked to complete the following questionnaires: PTSD checklist for DSM-5 (PCL-5)[18], Brief Symptom Inventory (BSI)[23], Resilience Scale (RS13)[24], Proaactive Coping Inventory (PCI)[25], Multidimensional Fatigue Inventory (MFI)[26], EQ-5D-5L health questionnaire[27], Index for Measuring Limitations of Social Participation (IMET)[28], Dyadic Coping Inventory (DCI)[29], and Relationship Assessment Scale (RAS)[30]. Additionally, Posttraumatic Cognitions Inventory (PTCI)[31] will be assessed only in participants PCL $\geq$ 33 points (Table 1).

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Intervention phase

Internet-based writing therapy

Patients and/or spouses being diagnosed with PTSD, who are allocated to the treatment condition, will participate in an IB-CBWT. They will be asked to complete two 50-minute writing assignments per week over a five-week period (10 essays in total). The therapy consists of three treatment modules (Table 2): 1) resource-oriented biographical reconstruction (three essays), 2) in sensu trauma exposure sessions (four essays), and 3) cognitive reconstruction (three essays).

Integrated in the third module, the respective partner of the treated participant diagnosed with PTSD receives instructions to write a supportive letter to him/her. Here, the respective partner should announce acknowledgement for the participant as well as his/her strengths and the shared future. Partners without clinically relevant PTSD symptoms will also receive access to an individual web portal where they complete the assessments and write the supportive letter. They further receive psychoeducational information about mental health problems after traumatic events (i.e. explanation of PTSD symptoms and treatment options).

At the beginning of each writing module, participants propose individual timetables as to when they plan to write. After completion of each assignment, therapists provide individual feedback and further writing instructions within one workday. Important aspects of this feedback are acknowledgement of the participant's courage to disclose and describe their traumatic experiences, reinforcement of the participant's work on the essays, positive feedback and motivation, and frequent summaries and encouragement of participants to voice their questions and doubts. Study participants will complete writing assignments through a secure web portal, ensuring that all correspondence is confidential and encrypted. Communication between participants and their therapist will occur asynchronously.

Every participant (patient and spouse) will receive access to a private, secure user account within the web portal. During treatment, all communication will be conducted within this

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account. Additionally, the therapist accounts are located in the web portal being secure and only accessible for the therapists. A database located at the server of the Jena University Hospital is connected with the web-portal, saving data using anonymous codes meeting the highest security standards.

Therapists

Therapists will be licensed clinical psychologists with previous experience in IB-CBWT. They will receive specialised training in the administration of the treatment and will be supervised continuously throughout the trial. Participants will be consecutively assigned to the therapists. When both, patient and spouse, have clinically relevant PTSD symptoms, they will have different therapists.

Measurement during the course of treatment

During treatment, i.e. after modules 3, 7, and 10, the Multiperspective Assessment of General Change Mechanisms in Psychotherapy (SEWIP),[32] measuring resource activation, problem actuation, mastery, clarification of meaning, emotional bond, and agreement on collaboration, will be applied to participants of the IB-CBWT group. Additionally, PCL-5, BSI, and RAS will be administered during therapy (after modules 3 and 7).

Measurement at the end of treatment/waiting (t1)

At the end of treatment or waiting time, respectively, the following measures will be applied to the participants: PCL-5, BSI, RS13, PCI, MFI, EQ-5D-5L, IMET, DCI, and RAS. Again, PTCI will be assessed only in participants PCL $\geq$ 33 points (Table 1). Additionally, participants will be interviewed by using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).

Wait-list control group

Treatment effects will be compared against a WL control group to allow for the provision of care (if delayed) to all trial participants. After 5 weeks of waiting (duration of treatment), participants allocated to the WL control group will receive IB-CBWT. During and after this

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delayed application of IB-CBWT, the same measures as in the treatment condition will be assessed. However, these participants will not receive a supportive letter from their spouses. This will allow for evaluating the effect ascribed to the supportive letter.

Follow-up phase

Participants will be followed up 3, 6, and 12 months, respectively. Outcome measures will be assessed again (Table 1).

Discontinuation

If a participant meets any of the following criteria, the study intervention will be discontinued: withdrawal of consent to receive the study intervention, emergence of an adverse event (suicidal intentions, severe symptom increase), or start of a psychotherapy elsewhere. The participant will be invited to continue completing the planned assessments. If participants withdraw consent to study participation, they will not be contacted for assessments in the future. Participants have the right to initiate deletion of their study data. If a participant does not make use of this right, all data will be included in the analyses.

Outcome measures

Primary outcome

Primary outcome is the change in PTSD symptom severity score from baseline to 5 weeks after randomisation (t1; at the end of treatment/waiting time) measured via the PTSD Checklist (PCL-5) covering the four DSM-5 clusters.[18]

Secondary outcomes

Secondary outcomes will be remission at t1 and the percentage of participants leaving the study early (during treatment phase) due to any reason (until t1). Furthermore, anxiety, depression, and somatization (Brief Symptom Inventory-18[23]), marital satisfaction (Relationship Assessment Scale[30]), and health-related quality of life (EQ-5D-5L[27]) all measured as summary scores at t1 and at follow-up (t2-t4: 3, 6, and 12 months). Additionally,

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we will assess dyadic coping with stress in the patient-spouse dyads using the Dyadic Coping Inventory[29] at baseline (t0), at the end of treatment/waiting time (t1), and at follow-up (t2-t4).

Sample size estimation

The sample size calculation is based on the parametric evaluation of a two group comparison using Students' t-test, though a more complex statistical model will be used as primary test. To detect large effect sizes as revealed by a meta-analysis,[14] i.e. effects of Cohen's d = 0.95, while requiring $\alpha = 0.05$ (two-sided) while aiming at a comparison-wise power of $1 - \beta = 0.9$ (a higher power was chosen to address the problem that a more complex statistical analysis will be used), a sample size of $n = 2 \times 34 = 68$ patient-spouse dyads is necessary for the intent-to-treat (ITT) analysis. Dropout rates in IB-CBWT are encouragingly low; in a previous study with older adults (65+, comparable in age to the population of the proposed study), 89% of the participants completed every step of treatment.[15] However, additional dropouts in a sample of sepsis patients may be due to medical reasons, i.e. health impairment or sudden death. Thus, we decided to increase the power by assuming a dropout rate of 30%, so that altogether 98 dyads have to be randomised to either IB-CBWT or WL control group. Exploring the potential impact of dropouts (i.e. missingness not completely at random) on the results will be especially addressed in sensitivity analyses that will be outlined in the statistical analysis plan (SAP).

Methods against bias

Selection bias will be minimized by random and concealed central allocation of the patient-spouse dyads to treatment and control group using a centralized randomisation by the Center for Clinical Studies of the Jena University Hospital. However, performance bias might not be ruled out because blinding of patients/spouses could not be realised due to intervention characteristics. Similarly, therapists cannot be fully blinded to group assignment since participants receiving treatment the first weeks of recruitment must have been automatically allocated to the treatment group. Treatments will be carefully manualised and predefined in

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terms of the content and number of sessions. To assure treatment fidelity, verbatim scripts of the correspondence between patients and therapist will be reviewed. Treatment fidelity checks will be performed based on a random selection of 30% of treatment sessions. Data will be analysed using an ITT approach. To ensure data quality, diagnoses will be made on the basis of a validated clinical interview conducted by a clinically experienced and trained psychologist. Questionnaires that will be used in the proposed study have been proven to be psychometrically sound instruments.

Statistical analyses

The primary endpoint of the efficacy assessment (PCL-5 change score at the end of the treatment, t1, i.e. ~6 weeks after randomisation; relative to the randomisation t0) will be compared between both groups (i.e. experimental group and WL control group). The null hypothesis $\mu_{EXP} = \mu_{WL}$, which implies that the PCL-5 change scores are identical in expectation, will be tested against the (two-sided) alternative hypothesis that there will be a difference between the groups ($\mu_{EXP} \neq \mu_{WL}$). The confirmatory analysis will be performed in the ITT population. These hypotheses will be tested using a general linear model for the primary outcome and the group factor adjusted for PCL-5 at baseline (t0) with Generalized Estimating Equations (GEE) component to address the possible intra-dyad clustering. The null hypothesis will be rejected when the two-sided p-value for the group variable is equal to or less than the two-sided significance level $\alpha = 0.05$. The average mean difference in the PCL-5 change scores at t1 is assumed to be clinically relevant when the mean PCL-5 score is more than 10 points lower for the experimental group than for the WL control group.[18]

Additionally, there will be sensitivity analyses, e.g., in the per-protocol (PP) population or stratified by patient and spouse. All additional analyses and the analyses of secondary endpoints will be done exploratively, i.e., without adjustment for multiplicity. We will use adequate standard descriptive and inferential statistical techniques that are described in detail in the SAP. For the third explorative objective – dyadic interference in mental health – we

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will use a longitudinal Actor-Partner-Interdependence Model. To examine the impact of dyadic coping on treatment effects, we will extend the previously applied regression models.

Data collection and management

Data collection

Relevant data will be collected via telephone and using questionnaires delivered via the web-portal. Telephonically assessed data will be documented in writing and transferred to the study management software "OpenClinica®". Data assessed by using standardised questionnaires within the web-portal, will be collected via a secure network (HTTPS) using input forms in the web browser. Data will be saved by using anonymised codes on a server of the Jena University Hospital ensuring highest safety standards.

Data management

Data management will be conducted by using the study management software "OpenClinica®" meeting common regulatory requirements (GCP, 21CFRPart11). To ensure a pseudonymised data analysis, every participant will receive a distinct ID. Data will be checked regularly for accuracy, implausible or missing data will be enquired in the study centre.

Study monitoring

The current study will be monitored by an independent data manager of the Centre for Clinical Studies of the Jena University Hospital including periodic inspections of the completeness and correctness of study documents and study data.

Premature termination of the study

Reasons for a premature termination of the study will be unjustifiable risks of continuation, new scientific findings during study duration, or inadequate recruiting rate. Decision about discontinuation will be taken jointly by the principal investigators, the study biometrician, and the Data Safety and Monitoring Board (DSMB).

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Reporting of adverse events

Assessment of safety will include recording any adverse effects during the treatment period by asking participants for experienced adverse events at the end of the treatment. In addition, during treatment participants are provided a telephone contact for emergency cases. In such a case, adverse events will be documented by the study team.

Ethical considerations and dissemination

Informed consent

All eligible participants will be informed orally and by an information brochure about aims, content, procedure, and length of the study, and about any potential risks and advantages in a true manner. After providing the opportunity to ask questions, written consent will be obtained. Participation is voluntary at any time. Participants will be informed about the voluntariness of study participation and the opportunity to interrupt or prematurely terminate study participation without giving reasons.

Ethics review

The study has been approved by the ethics committee of the Friedrich-Schiller University Jena, Germany (no. 4777-04/16, 11 May 2016). The trial is registered in the German Clinical Trials Register (DRKS); no. DRKS00010676.

Dissemination

Results of this study will be presented at scientific conferences and published in peer-reviewed journals. Furthermore, we will disseminate results and conclusions to consumers of health care. The study will be implemented and reported in line with the CONSORT statement. Authorship is granted to authors who make important contributions to the creation of the final publication.

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DISCUSSION

This study aims to provide new evidence of treatment approaches particularly designed for patients after critical illness such as sepsis. The current study also involves the spouse of the affected patient since critical illness has consequences not only for the patient itself, but also for his/her spouse who shares concerns, sorrows, and problems.

The limitation of this study is that the intervention effects will be compared against a WL control group which might overestimate the efficacy of the treatment to a certain degree.[33] This will be taken into account in the interpretation of the results. Moreover, evidence-based treatment approaches of in post-ICU patients are rare.[10] This argues against an active control condition. Alternatively, psychological treatment placebo faces the problem that the development of such a control condition in PTSD trials "is very difficult, if not impossible".[11] Moreover, performance bias will possibly influence the effects since participants cannot be blinded because they are aware of their group allocation. Additionally, therapist will not be blinded to group assignment. However, manualisation of the treatment and treatment fidelity checks will counter the risk of bias.

Despite these limitations, this is the first randomised controlled trial to assess the efficacy, safety, and applicability of an IB-CBWT in patients after sepsis and their spouses. Given the sparse number of existing treatment approaches for this group of patients IB-CBWT might be a valuable addition in the treatment of PTSD after sepsis. The results of this study will hopefully improve health care for patients after sepsis and their spouses. Given the efficacy, safety, and applicability of this approach, the treatment could be easily transferred to other languages and thereby disseminated internationally.

Current trial status

The REPAIR trial will begin recruiting participants in October 2016. Data collection will be completed in November 2018.

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Contributors

JR and CK conceived and designed the study, and drafted the grant proposal. RG and JR drafted the protocol of the study, and organised and supervised study implementation. HN, MB, AS, and CK refined the study protocol and study implementation. HN, MB, and CK developed the treatment manual. AS provided methodological and statistical expertise. CK supervised the therapists. All authors critically reviewed and approved the final version of the manuscript.

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Competing interests

None declared.

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Table 1. Schedule of the assessments

	STUDY PERIOD							
	Enrolment	Allocation	Intervention			Follow-up		
TIMEPOINT	tx	t0	S3	S7	t1	t2	t3	t4
ENROLMENT:								
Informed consent	x							
Eligibility screen	x							
Allocation		x						
INTERVENTIONS:								
IB-CBWT			←	—	→			
Wait-list control group			←	···	→			
ASSESSMENTS:								
Demographic and medical information		x						
CAPS-5		x			x			
SCID-I		x						
PCL-5	x	x	x	x	x	x	x	x
LEC-5		x						
BSI		x	x	x	x	x	x	x
RAS		x	x	x	x	x	x	x
IMET		x			x	x	x	x
RS-13		x			x	x	x	x
EQ-5D-5L		x			x	x	x	x
MFI		x			x	x	x	x
DCI		x			x	x	x	x
PTCI		x			x	x	x	x
PCI		x			x	x	x	x
SEWIP#			x	x	x			
Adverse events			x	x	x			

tx = time of enrolment, t0 = Baseline, before start of treatment/waiting, t1 = after end of treatment/ waiting, t2 = 3 months after end of treatment, t3 = 6 months after end of treatment, t4 = 12 months after end of treatment, (t2-t4 only for intervention group); S3 = after treatment session 3, S7 = after treatment session 7, S10 = after treatment session 10, IB-CBWT = Internet-based cognitive-behavioural writing therapy, CAPS-5 = Clinician-Administered PTSD Scale for DSM-5, SCID-I = Structured Clinical Interview for DSM-IV, PCL-5 = Posttraumatic stress disorder checklist, LEC-5 = Life Event Checklist for DSM-5, BSI = Brief Symptom Inventory, RAS = Relationship Assessment Scale, IMET = Index for Measuring Limitations of Social Participation, RS13 = Resilience Scale, EQ-5D-5L = health questionnaire of the EuroQol group, MFI = Multidimensional Fatigue Inventory, DCI = Dyadic Coping Inventory, PTCI = Posttraumatic Cognitions Inventory, PCI = Proactive Coping Inventory, SEWIP = Multiperspective Assessment of General Change Mechanisms in Psychotherapy. #SEWIP is only applied to patients with PCL ≥ 33.

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Table 2. Framework of the 10 writing assignments delivered during IB-CBWT for patients after sepsis and their spouses

Session number	Session goals	Suggested Structure	Suggested tools
1-3	Resource-oriented biographical reconstruction.	Explaining the reason of the reconstruction. Provide a list of life-events. Provide a summary and give individual feedback.	Provide list of possible important personal life events „What problems did you have and how do you solved it?“
4-7	In sensu exposure. Detailed description of the trauma with all sensations.	Explain the need of exposure. Explain how to describe the trauma in a written way. Provide a summary and give individual feedback.	Provide a list of questions due to the traumatic event and the sensations.
Text of partner (between 7 and 8)	Supportive letter: Acknowledgment of traumatic event. Strength of partner. Joint future.	Explaining reason of participation. Explain the session goals.	Provide a list of questions due to the goals of the letter.
8-10	Cognitive reconstruction: Writing a letter to an imaginary friend. Writing a letter to oneself.	Explaining reason of reconstruction. Explain session goals. Provide a summary and give individual feedback.	Provide a list of questions due to the goals of the letter. e.g. “Has something positive resulted from the events?”

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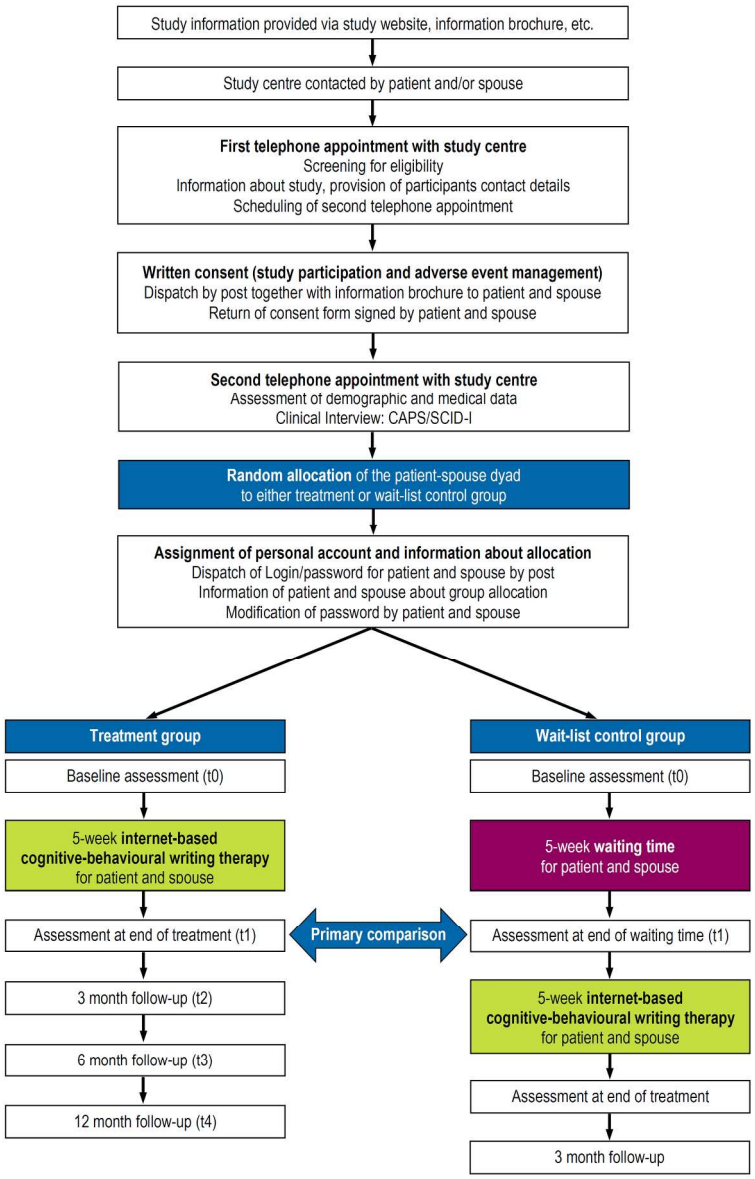

Figure 1. Study flow chart

81x127mm (600 x 600 DPI)

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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	3, 15
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	18
	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	18
	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)	

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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	5 f.
	6b	Explanation for choice of comparators	6, 16
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)	7 f.
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	7
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9 f.
	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)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1, Figure 1

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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	12
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	8
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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12 f.
	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	14, Table 1
	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	11

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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	14
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	13 f.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13 f.
	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)	13 f.
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	14
	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	
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	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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)	

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	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	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	
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	
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	15 f.
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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.

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Internet-based cognitive-behavioural writing therapy for reducing posttraumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): Study protocol for a randomised-controlled trial

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Intensive care
Keywords:	Posttraumatic stress disorder, Sepsis, Internet, Cognitive behavior therapy, Randomized controlled trial

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Internet-based cognitive-behavioural writing therapy for reducing posttraumatic stress after intensive care for sepsis in patients and their spouses (REPAIR): Study protocol for a randomised-controlled trial

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ABSTRACT

Introduction: As a consequence of sepsis and intensive care, considerable proportions of patients but also of their spouses develop a posttraumatic stress disorder (PTSD). However, only a very small number receive psychotherapeutic treatment. Internet-based cognitive-behavioural writing therapy (IB-CBWT) has proven to be an effective treatment option for PTSD. It seems to fit the specific needs of this cohort and to overcome treatment barriers. Aim of the REPAIR trial is to examine the efficacy, safety, and applicability of IB-CBWT for PTSD in patients and their spouses after intensive care for sepsis.

Methods and analysis: Participants will be assigned randomly either to a treatment or a wait-list (WL) control group. The treatment group receives IB-CBWT for PTSD, actively involving the partners of the participants. IB-CBWT will be guided by a therapist and comprises two written assignments per week over a 5-week period. After completing the assignments, the participants obtain individual responses from the therapist. Participants of the WL control group will receive treatment after a waiting period of 5 weeks. The primary outcome is PTSD symptom severity in self-rated PTSD Checklist for DSM-5 at the end of treatment and waiting time, respectively. Secondary outcomes are remission of PTSD, depression, anxiety, and somatisation measured by the Brief Symptom Inventory-18, marital satisfaction measured by the Relationship Assessment Scale, health-related quality of life measured by the EQ-5D-5L, and the feasibility of IB-CBWT for this cohort (i.e. dropout rate). Statistical analysis will be performed according to the intent-to-treat principle.

Ethics and dissemination: The study is conducted according to the principles of Good Clinical Practice and has been approved by the ethics committee of the Friedrich-Schiller University Jena, Germany. Results will be disseminated at scientific conferences, published in peer-reviewed journals, and provided to consumers of health care.

Trial registration: German Clinical Trials Register (DRKS); no. DRKS00010676.

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Strengths and limitations of this study

- This randomised-controlled trial will provide new evidence concerning the treatment of PTSD after intensive care for sepsis in patients and their spouses.
- For the first time also the spouses of patients with PTSD will be involved in their partners' internet-based cognitive-behavioural writing therapy.
- Intervention effects will be compared against a wait-list control group.
- It is not possible to ensure a complete blinding of patients and therapists.

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INTRODUCTION

Psychopathological reactions, i.e. acute stress disorder (ASD; ICD-10 F43.0) and posttraumatic stress disorder (PTSD; F43.1), are common consequences of life-threatening events such as sepsis and negatively affect patients' long-term functioning and quality of life.[1-4] Critical illness can also be a traumatic and stressful experience for family members as a result of uncertainty and the fear of the patient's physical disability or death. DSM-5[5] explicitly defined the diagnostic criteria of a traumatic event as an exposure to actual death or serious injury experienced in person or which has occurred to a close family member. Family members, particularly spouses, who care for the critically ill patient during the time of intensive care, are therefore a vulnerable cohort.[6-8] In a recent study, up to 69% of the patients, who had survived sepsis, and 62% of the spouses of sepsis survivors suffered from clinically relevant PTSD symptoms.[9] It has been further shown that both physical and mental health of patients and their spouses are interrelated. More specifically, results of a dyadic analysis indicated that the mental quality of life of a person (patient or spouse) is negatively impacted by posttraumatic stress symptoms of the respective partner. Furthermore, it has been shown that PTSD symptoms of the patient who survived sepsis are a significant predictor of PTSD symptoms of the respective spouse.[10] Based on these results, it has been concluded that couples react as a dyadic system with interdependent emotional responses to critical illness. Thus, the inclusion of spouses in the treatment of mental long-term consequences of critical illness appears to be inevitable.[9] However, patients suffering from PTSD after critical illness are often untreated or undertreated hereof. Accordingly, Mehlhorn *et al.*[11] suggest in their review of interventions for the postintensive care syndrome, that "postintensive care patients may benefit from interventions like trauma-focused cognitive-behavioural therapy […] but often they do not have access to those interventions." (p. 1268).

With regard to the treatment of PTSD, several evidence-based interventions exist. There is striking evidence for the efficacy of trauma-focused cognitive-behavioural therapy (TFCBT)

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with large effect sizes (standardised mean difference SMD = 1.62; 95% confidence interval (CI) [1.21; 2.03] in a meta-analysis of 28 studies) compared against wait-list (WL) control.[12] Nevertheless, only a minority of individuals suffering from PTSD seeks psychological treatment due to different barriers (e.g. fear of stigmatisation, embarrassment, lack of availability of specialised therapists). In recent years, internet-based interventions based on CBT techniques have overcome these face-to-face treatment barriers by treating mobility-impaired patients, being independent in space and time as well as easily accessible and due to visual anonymity being low-threshold.[13-15] The internet-based approach is usually based on a manualised, therapist-assisted treatment which is operationalised via written assignments. In general, treatment as well as the diagnostic screenings (before and after the treatment) are conducted without any face-to-face contact in a secure web portal.[13 16 17] Meta-analytic evidence has proven the efficacy of internet-based cognitive-behavioural writing therapy (IB-CBWT) to be large (Hedges´ g = 0.95; 95% CI [0.46; 1.43]; 8 studies) in PTSD symptom reduction compared to WL control.[15]

Up to now, IB-CBWT has not been considered as a treatment approach for PTSD after critical illness and intensive care. Moreover, therapeutic approaches for PTSD that include spouses in addition to the patients are very scarce.

Objectives

Primary aims of the REPAIR trial are to investigate the efficacy, safety, and applicability of IB-CBWT for posttraumatic stress after intensive care for sepsis in patients and their spouses compared to a WL control group and to assess maintenance of possible treatment gains at 3, 6, and 12 months post-treatment. Second, the study aims at examining dyadic concordance in treatment effects, i.e. indirect effects of the treatment in the respective spouse of the participant of the treatment. Third, the influence of dyadic coping on the treatment effects will be explored.

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METHODS AND ANALYSIS

Study design and setting

REPAIR is a randomised-controlled, parallel group, superiority trial. The current study will be conducted at the Jena University Hospital, recruiting participants from German speaking countries (e.g., Germany, Austria, and Switzerland) at least one month after discharge from the intensive care unit (ICU). Participants will be contacted via telephone for initial screening and via internet for delivering the treatment and conducting assessments.

Eligibility criteria

We will include adult (18+ years) patients after intensive care (>5 days) for sepsis[18] and their spouses (married or cohabited) who are fluent in written German. A patient-spouse dyad will be included if at least one of them (patient or spouse or both) scores above the PCL-5 cut-off (score $\geq$ 33)[19] for a presumptive PTSD diagnosis. PTSD should be based on a trauma, which is associated with the critical illness and/or ICU stay. Patients will be excluded, if they do not have a spouse. According to the German clinical guideline on the treatment of PTSD[20] acute psychosis and suicidal ideation will be criteria for exclusion. Furthermore, the use of neuroleptics, or an ongoing psychotherapeutic treatment elsewhere will be reasons for exclusion.

Procedures

Recruitment

Since the treatment is delivered internet-based, German speaking patients/spouses could participate from all over the world. For recruitment, we follow a multipartite strategy. First, all persons, i.e., patients or spouses, who request free of charge advice from the German Sepsis Aid's National Helpline (http://www.sepsis-hilfe.org) or had requested advice in the past two years (altogether about 600 requests), will be contacted and informed about the study. Second, patients of the Mid-German Sepsis Cohort (MSC; trial registration: German Clinical Trials Register, no. DRKS00010050) who are positively screened for PTSD at one of

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the MSC study assessments will be informed about the study. The MSC aims at following-up about 1.000 patients after sepsis per year, of whom we expect about 20% to have PCL scores ≥ 33 points at least at one follow-up assessment. Third, participants will be recruited via advertisements in health journals and distribution of information brochures in hospitals and rehabilitation centres. In a first telephone contact, participants will be screened for eligibility by using the Life Event Checklist for DSM-5 (LEC 5)[21] and the PTSD checklist for DSM-5 (PCL-5)[19]. Written informed consent will be obtained by the patients and their spouses (see Figure 1). One signed version of the informed consent will be sent back to the study centre. After that, an appointment for a second telephone interview will be terminated. In this second telephone contact, patients and their spouses will complete the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[22] and the Structured Clinical Interview for DSM-IV (SCID-I)[23] conducted by a trained psychologist. Medical data will be assessed (e.g., length of intensive care and (if) length of mechanical ventilation, time since ICU discharge).

Randomisation

All eligible patient-spouse dyads consenting to participation will be randomly assigned to either IB-CBWT or to a WL control group (allocation ratio 1:1) with the patient-spouse dyad being the unit of randomisation. Randomisation will be conducted using a central internet-based registration system provided by the Center for Clinical Studies of the Jena University Hospital. This system automatically randomises patients and generates a message noting the assigned treatment. The underlying randomisation list will be developed by an independent biometrician using a computer-based algorithm. Allocation will be concealed and stratified by the occurrence of PTSD symptoms within the dyads of sepsis survivor and the spouse: strata 1 - both, sepsis survivor and spouse with PTSD; strata 2 - sepsis survivor with PTSD/spouse without, and strata 3 - spouse with PTSD/sepsis survivor without.

Baseline assessment (t0)

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Before the start of the treatment participants, i.e. patients and their spouses, will be asked to complete the following questionnaires: PTSD checklist for DSM-5 (PCL-5)[19], Brief Symptom Inventory (BSI)[24], Resilience Scale (RS13)[25], Proaactive Coping Inventory (PCI)[26], Multidimensional Fatigue Inventory (MFI)[27], EQ-5D-5L health questionnaire[28], Index for Measuring Limitations of Social Participation (IMET)[29], Dyadic Coping Inventory (DCI)[30], Relationship Assessment Scale (RAS)[31], and Internet Literacy Questionnaire (ILQ; subscale technical expertise)[32]. Additionally, Posttraumatic Cognitions Inventory (PTCI)[33] will be assessed only in participants with PCL scores ≥ 33 points (Table 1).

Intervention phase

Internet-based writing therapy

Patients and/or spouses with PCL scores ≥ 33 points, who are allocated to the treatment condition, will participate in an IB-CBWT. They will be asked to complete two 50-minute writing assignments per week over a five-week period (10 essays in total). The therapy consists of three treatment modules (Table 2): 1) resource-oriented biographical reconstruction (three essays), 2) in sensu trauma exposure sessions (four essays), and 3) cognitive reconstruction (three essays).

Integrated in the third module, the respective partner of the treated participant diagnosed with PTSD receives instructions to write a supportive letter to him/her. Here, the respective partner should announce acknowledgement for the participant as well as his/her strengths and the shared future. Partners without clinically relevant PTSD symptoms will also receive access to an individual web portal where they complete the assessments and write the supportive letter. They further receive psychoeducational information about mental health problems after traumatic events (i.e. explanation of PTSD symptoms and treatment options).

At the beginning of each writing module, participants propose individual timetables as to when they plan to write. After completion of each assignment, therapists provide individual feedback and further writing instructions within one workday. Important aspects of this

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feedback are acknowledgement of the participant's courage to disclose and describe their traumatic experiences, reinforcement of the participant's work on the essays, positive feedback and motivation, and frequent summaries and encouragement of participants to voice their questions and doubts. Study participants will complete writing assignments through a secure web portal, ensuring that all correspondence is confidential and encrypted. Communication between participants and their therapist will occur asynchronously.

Every participant (patient and spouse) will receive access to a private, secure user account within the web portal. During treatment, all communication will be conducted within this account. Additionally, the therapist accounts are located in the web portal being secure and only accessible for the therapists. A database located at the server of the Jena University Hospital is connected with the web-portal, saving data using anonymous codes meeting the highest security standards.

Therapists

Therapists will be licensed clinical psychologists with previous experience in IB-CBWT. They will receive specialised training in the administration of the treatment and will be supervised continuously throughout the trial. Participants will be consecutively assigned to the therapists. When both, patient and spouse, have clinically relevant PTSD symptoms, they will have different therapists.

Measurement during the course of treatment

During treatment, i.e. after modules 3, 7, and 10, the Multiperspective Assessment of General Change Mechanisms in Psychotherapy (SEWIP),[34] measuring resource activation, problem actuation, mastery, clarification of meaning, emotional bond, and agreement on collaboration, will be applied to participants of the IB-CBWT group. Additionally, PCL-5, BSI, and RAS will be administered during therapy (after modules 3 and 7).

Measurement at the end of treatment/waiting (t1)

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At the end of treatment or waiting time, respectively, the following measures will be applied to the participants: PCL-5, BSI, RS13, PCI, MFI, EQ-5D-5L, IMET, DCI, and RAS. Again, PTCI will be assessed only in participants with PCL scores ≥ 33 points (Table 1). Additionally, participants will be interviewed by using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).

Wait-list control group

Treatment effects will be compared against a WL control group to allow for the provision of care (if delayed) to all trial participants. After 5 weeks of waiting (duration of treatment), participants allocated to the WL control group will receive IB-CBWT. During and after this delayed application of IB-CBWT, the same measures as in the treatment condition will be assessed. However, these participants will not receive a supportive letter from their spouses. This will allow for evaluating the effect ascribed to the supportive letter.

Follow-up phase

Participants assigned to the treatment group will be followed up 3, 6, and 12 months after treatment, respectively. Participants assigned to the WL control group will be followed up 3 months after treatment. Outcome measures will be assessed again (Table 1).

Discontinuation

If a participant meets any of the following criteria, the study intervention will be discontinued: withdrawal of consent to receive the study intervention, emergence of an adverse event (suicidal ideation, severe symptom increase), or start of psychotherapy elsewhere. The participant will be invited to continue completing the planned assessments. If participants withdraw consent to study participation, they will not be contacted for assessments in the future. Participants have the right to initiate deletion of their study data. If a participant does not make use of this right, all data will be included in the analyses.

If either the spouse or patient drops out of the study for any reason, the other participant will be allowed to continue with the intervention and study participation.

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Outcome measures

Primary outcome

Primary outcome is the change in PTSD symptom severity score from baseline to 5 weeks after randomisation (t1; at the end of treatment/waiting time) measured via the PTSD Checklist (PCL-5) covering the four DSM-5 clusters.[19]

Secondary outcomes

Secondary outcomes will be remission at t1 and the percentage of participants leaving the study early (during treatment phase) due to any reason (until t1). Furthermore, anxiety, depression, and somatisation (Brief Symptom Inventory-18[24]), marital satisfaction (Relationship Assessment Scale[31]), and health-related quality of life (EQ-5D-5L[28]) all measured as summary scores at t1 and at follow-up (t2-t4: 3, 6, and 12 months).

Other measures

Additionally, we will assess dyadic coping with stress in the patient-spouse dyads using the Dyadic Coping Inventory[30], coping with stress on an individual level using the Proaactive Coping Inventory[26], social participation using the Index for Measuring Limitations of Social Participation[29], resilience (defined as the capacity to withstand life stressors, and to thrive and make meaning from challenges[35]) using the Resilience Scale-13[25], fatigue using the Multidimensional Fatigue Inventory[27], and posttraumatic cognitions using the Posttraumatic Cognitions Inventory[33]. All of these measures will be applied at baseline (t0), at the end of treatment/waiting time (t1), and at follow-up (t2-t4). During (S1, S2) and at the end of treatment (t1), we will assess common therapeutic factors in patients with PCL scores $\geq$ 33 using the Multiperspective Assessment of General Change Mechanisms in Psychotherapy[34].

Sample size estimation

The sample size calculation is based on the parametric evaluation of a two-group comparison using Students' t-test, though a more complex statistical model will be used as the primary test. To detect large effect sizes as revealed by a meta-analysis,[15] i.e. effects of Cohen's d =

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0.95, while requiring $\alpha = 0.05$ (two-sided) while aiming at a comparison-wise power of $1 - \beta = 0.9$ (a higher power was chosen to address the problem that a more complex statistical analysis will be used), a sample size of $n = 2 \times 34 = 68$ patient-spouse dyads is necessary for the intent-to-treat (ITT) analysis. Dropout rates in IB-CBWT are encouragingly low; in a previous study with older adults (65+ years, comparable in age to the population of the proposed study), 89% of the participants completed every step of treatment.[16] However, additional dropouts in a sample of sepsis survivors may be due to medical reasons, i.e. health impairment or sudden death. Thus, we decided to increase the power by assuming a dropout rate of 30%, so that altogether 98 dyads have to be randomised to either IB-CBWT or WL control group.

Methods against bias

Selection bias will be minimised by random and concealed central allocation of the patient-spouse dyads to treatment and control group using a centralised randomisation by the Center for Clinical Studies of the Jena University Hospital. However, performance bias might not be ruled out because blinding of patients/spouses could not be realised due to intervention characteristics. Similarly, therapists cannot be fully blinded to group assignment since participants receiving treatment the first weeks of recruitment must have been automatically allocated to the treatment group. Treatments will be carefully manualised and predefined in terms of the content and number of sessions. To assure treatment fidelity, verbatim scripts of the correspondence between participants and therapists will be reviewed. Treatment fidelity checks will be performed based on a random selection of 30% of treatment sessions. Data will be analysed using an ITT approach. To ensure data quality, diagnoses will be made on the basis of a validated clinical interview conducted by a clinically experienced and trained psychologist. Questionnaires that will be used in the proposed study have been proven to be psychometrically sound instruments. To reduce the risk of sampling bias and to assure external validity, we will use a multipartite recruitment strategy and apply less restrictive eligibility criteria.

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Statistical analyses

The primary endpoint of the efficacy assessment (PCL-5 change score at the end of the treatment, t1, i.e. ~6 weeks after randomisation; relative to the randomisation t0) will be compared between both groups (i.e. experimental group and WL control group). The null hypothesis $\mu_{EXP} = \mu_{WL}$, which implies that the PCL-5 change scores are identical in expectation, will be tested against the (two-sided) alternative hypothesis that there will be a difference between the groups ($\mu_{EXP} \neq \mu_{WL}$). The confirmatory analysis will be performed in the ITT population. These hypotheses will be tested using a general linear model for the primary outcome and the group factor adjusted for PCL-5 at baseline (t0) with Generalised Estimating Equations (GEE) component to address the possible intra-dyad clustering. The null hypothesis will be rejected when the two-sided p-value for the group variable is equal to or less than the two-sided significance level $\alpha = 0.05$. The average mean difference in the PCL-5 change scores at t1 is assumed to be clinically relevant when the mean PCL-5 score is more than 10 points lower for the experimental group than for the WL control group.[19]

We will address missing values by replacing all missing change scores with the worst change observed. Furthermore, we will explore the potential impact of dropouts (i.e. missingness not completely at random) on the results in sensitivity analyses that will be outlined in the statistical analysis plan (SAP).

Additionally, there will be sensitivity analyses, e.g., in the per-protocol (PP) population or stratified by patient and spouse. All additional analyses and the analyses of secondary endpoints will be done exploratively, i.e., without adjustment for multiplicity. We will use adequate standard descriptive and inferential statistical techniques that are described in detail in the SAP. For the third explorative objective – dyadic interference in mental health – we will use a longitudinal Actor-Partner-Interdependence Model. To examine the impact of dyadic coping on treatment effects, we will extend the previously applied regression models.

Data collection and management

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Data collection

Relevant data will be collected via telephone and using questionnaires delivered via the web-portal. Telephonically assessed data will be documented in writing and transferred to the study management software "OpenClinica®". Data assessed by using standardised questionnaires within the web-portal, will be collected via a secure network (HTTPS) using input forms in the web browser. Data will be saved by using anonymised codes on a server of the Jena University Hospital ensuring highest safety standards.

Data management

Data management will be conducted by using the study management software "OpenClinica®" meeting common regulatory requirements (GCP, 21CFRPart11). To ensure a pseudonymised data analysis, every participant will receive a distinct ID. Data will be checked regularly for accuracy, implausible or missing data will be enquired in the study centre.

Study monitoring

The current study will be monitored by an independent data manager of the Centre for Clinical Studies of the Jena University Hospital including periodic inspections of the completeness and correctness of study documents and study data.

Premature termination of the study

Reasons for a premature termination of the study will be unjustifiable risks of continuation, new scientific findings during study duration, or inadequate recruiting rate. Decision about discontinuation will be taken jointly by the principal investigators, the study biometrician, and the Data Safety and Monitoring Board (DSMB).

Reporting of adverse events

Assessment of safety will include recording any adverse effects during the treatment period by asking participants for experienced adverse events at the end of the treatment. In addition,

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during treatment participants are provided a telephone contact for emergency cases. In such a case, adverse events will be documented by the study team.

Ethical considerations and dissemination

Informed consent

All eligible participants will be informed orally by a trained clinical psychologist about aims, content, procedure, and length of the study; and about any potential risks and advantages in a true manner. After providing the opportunity to ask questions, written consent will be obtained by sending the informed consent document back to the study centre. Participants further receive a brochure with detailed information about the study. Participation is voluntary at any time. Participants will be informed about the voluntariness of study participation and the opportunity to interrupt or prematurely terminate study participation without giving reasons.

Ethics review

The study has been approved by the ethics committee of the Friedrich-Schiller University Jena, Germany (no. 4777-04/16, 11 May 2016). The trial is registered in the German Clinical Trials Register (DRKS); no. DRKS00010676. Modifications in the study protocol will be communicated to the ethics committee as well as the DRKS.

Access to data

Principal investigators and the study statistician will have access to the final dataset. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Dissemination

Results of this study will be presented at scientific conferences and published in peer-reviewed journals. Furthermore, we will disseminate results and conclusions to consumers of health care. The study will be implemented and reported in line with the CONSORT

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statement. Authorship is granted to authors who make important contributions to the creation of the final publication.

DISCUSSION

This study aims to provide new evidence of treatment approaches particularly designed for patients after critical illness such as sepsis. The current study also involves the spouse of the affected patient since critical illness has consequences not only for the patient itself, but also for his/her spouse who shares concerns, sorrows, and problems.

The limitation of this study is that the intervention effects will be compared against a WL control group which might overestimate the efficacy of the treatment to a certain degree.[36] This will be taken into account in the interpretation of the results. Moreover, evidence-based treatment approaches of in post-ICU patients are rare.[11] This argues against an active control condition. Alternatively, psychological treatment placebo faces the problem that the development of such a control condition in PTSD trials "is very difficult, if not impossible".[12] Moreover, performance bias will possibly influence the effects since participants cannot be blinded because they are aware of their group allocation. Additionally, therapists will not be blinded to group assignment. However, manualisation of the treatment and treatment fidelity checks will counter the risk of bias.

Despite these limitations, this is the first randomised controlled trial to assess the efficacy, safety, and applicability of an IB-CBWT after sepsis in patients and their spouses. Given the sparse number of existing treatment approaches for this group of patients IB-CBWT might be a valuable addition in the treatment of PTSD after sepsis. The results of this study will hopefully improve health care after sepsis for patients and their spouses. Given the efficacy, safety, and applicability of this approach, the treatment could be easily transferred to other languages and thereby disseminated internationally.

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Current trial status

The REPAIR trial will begin recruiting participants in January 2017. Data collection will be completed in February 2019.

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Contributors

JR and CK conceived and designed the study, and drafted the grant proposal. RG and JR drafted the protocol of the study, and organise and supervise study implementation. HN, MB, AS, and CK refined the study protocol and study implementation. HN, MB, and CK developed the treatment manual. AS provides methodological and statistical expertise. CK supervises the therapists. All authors critically reviewed and approved the final version of the manuscript.

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Competing interests

None declared.

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Table 1. Schedule of the assessments

	STUDY PERIOD							
	Enrolment	Allocation	Intervention			Follow-up		
TIMEPOINT	tx	t0	S3	S7	t1	t2	t3	t4
ENROLMENT:								
Informed consent	x							
Eligibility screen	x							
Allocation		x						
INTERVENTIONS:								
IB-CBWT			←	—	→			
Wait-list control group			←	···	→			
ASSESSMENTS:								
Demographic and medical information		x						
ILQ		x						
CAPS-5		x			x			
SCID-I		x						
PCL-5	x	x	x	x	x	x	x	x
LEC-5		x						
BSI		x	x	x	x	x	x	x
RAS		x	x	x	x	x	x	x
IMET		x			x	x	x	x
RS-13		x			x	x	x	x
EQ-5D-5L		x			x	x	x	x
MFI		x			x	x	x	x
DCI		x			x	x	x	x
PTCI		x			x	x	x	x
PCI		x			x	x	x	x
SEWIP#			x	x	x			
Adverse events			x	x	x			

tx = time of enrolment, t0 = Baseline, before start of treatment/waiting, t1 = after end of treatment/ waiting, t2 = 3 months after end of treatment, t3 = 6 months after end of treatment, t4 = 12 months after end of treatment, (t2-t4 only for intervention group); S3 = after treatment session 3, S7 = after treatment session 7, S10 = after treatment session 10, IB-CBWT = Internet-based cognitive-behavioural writing therapy, ILQ = Internet Literacy Questionnaire, CAPS-5 = Clinician-Administered PTSD Scale for DSM-5, SCID-I = Structured Clinical Interview for DSM-IV, PCL-5 = Posttraumatic stress disorder checklist, LEC-5 = Life Event Checklist for DSM-5, BSI = Brief Symptom Inventory, RAS = Relationship Assessment Scale, IMET = Index for Measuring Limitations of Social Participation, RS13 = Resilience Scale, EQ-5D-5L = health questionnaire of the EuroQol group, MFI = Multidimensional Fatigue Inventory, DCI = Dyadic Coping Inventory, PTCI = Posttraumatic Cognitions Inventory, PCI = Proactive Coping Inventory, SEWIP = Multiperspective Assessment of General Change Mechanisms in Psychotherapy. #SEWIP is only applied to patients with PCL scores ≥ 33.

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Table 2. Framework of the 10 writing assignments delivered during IB-CBWT after sepsis for patients and their spouses

Session number	Session goals	Suggested Structure	Suggested tools
1-3	Resource-oriented biographical reconstruction.	Explaining the reason of the reconstruction. Provide a list of life-events. Provide a summary and give individual feedback.	Provide list of possible important personal life events „What problems did you have and how do you solved it?“
4-7	In sensu exposure. Detailed description of the trauma with all sensations.	Explain the need of exposure. Explain how to describe the trauma in a written way. Provide a summary and give individual feedback.	Provide a list of questions due to the traumatic event and the sensations.
Text of partner (between 7 and 8)	Supportive letter: Acknowledgment of traumatic event. Strength of partner. Joint future.	Explaining reason of participation. Explain the session goals.	Provide a list of questions due to the goals of the letter.
8-10	Cognitive reconstruction: Writing a letter to an imaginary friend. Writing a letter to oneself.	Explaining reason of reconstruction. Explain session goals. Provide a summary and give individual feedback.	Provide a list of questions due to the goals of the letter. e.g. “Has something positive resulted from the events?”

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Figure legends

Figure 1. Study flow chart

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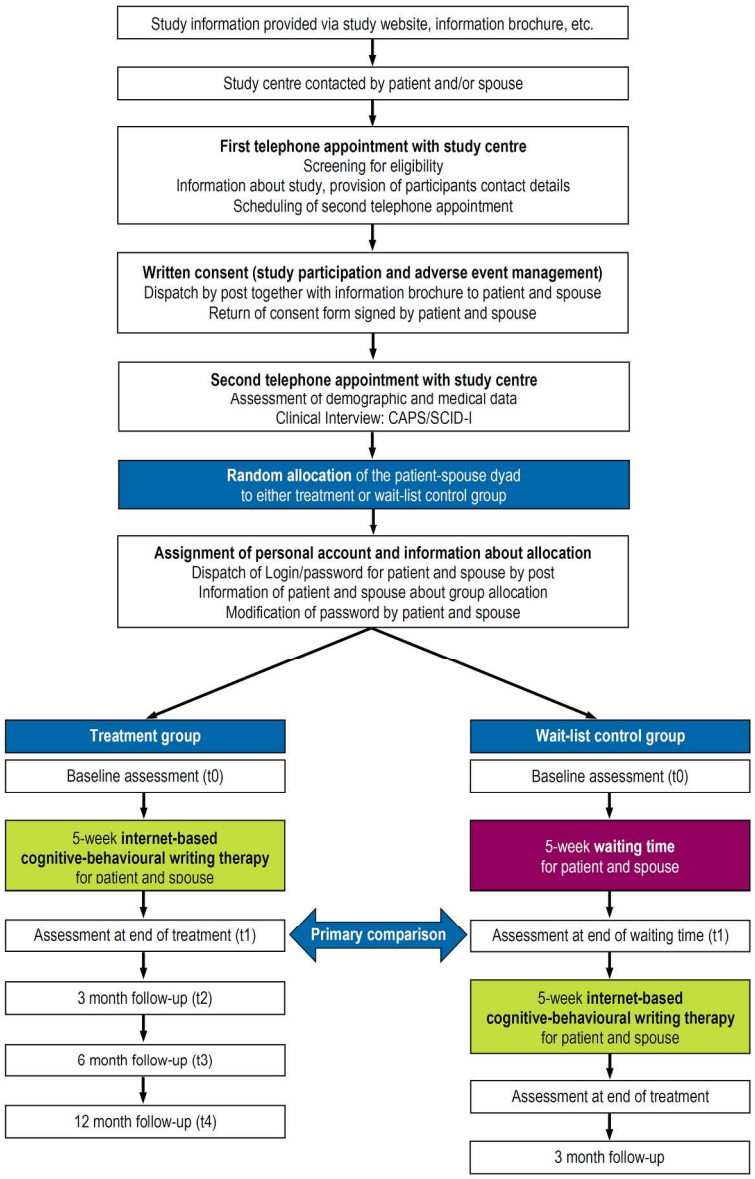

Figure 1. Study flow chart

81x127mm (600 x 600 DPI)

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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	3, 16
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	18 f.
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18 f.
	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	18 f.
	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)	n.a.

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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	5 f.
	6b	Explanation for choice of comparators	6, 16
Objectives	7	Specific objectives or hypotheses	6 f.
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 f.
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	7 f.
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9 f.
	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)	11 f.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	9-12, Table 1
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)	Table 1, Figure 1

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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	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7 f.
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	8
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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13,
	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	15, Table 1
	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	11 f.

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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 f.
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	14 f.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14 f.
	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)	14 f.
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
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	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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)	16

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17 f.
	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	n.a.
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.

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