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Internet-based cognitive-behavioural writing therapy for reducing post-traumatic stress after severe sepsis in patients and their spouses (REPAIR): results of a randomised-controlled trial

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ABSTRACT

Objectives To investigate the efficacy, safety and applicability of internet-based, therapist-led partner-assisted cognitive-behavioural writing therapy (iCBT) for post-traumatic stress disorder (PTSD) symptoms after intensive care for sepsis in patients and their spouses compared with a waitlist (WL) control group.

Design Randomised-controlled, parallel group, open-label, superiority trial with concealed allocation.

Setting Internet-based intervention in Germany; location-independent via web-portal.

Participants Patients after intensive care for sepsis and their spouses of whom at least one had a presumptive PTSD diagnosis (PTSD-Checklist (PCL-5)≥33). Initially planned sample size: 98 dyads.

Interventions ICBT group: 10 writing assignments over a 5-week period; WL control group: 5-week waiting period.

Primary and secondary outcome measures Primary outcome: pre–post change in PTSD symptom severity (PCL-5). Secondary outcomes: remission of PTSD, depression, anxiety and somatisation, relationship satisfaction, health-related quality of life, premature termination of treatment. Outcomes measures were applied pre and post treatment and at 3, 6 and 12 months follow-up.

Results Twenty-five dyads representing 34 participants with a presumptive PTSD diagnosis were randomised and analysed (ITT principle). There was no evidence for a difference in PCL-5 pre–post change for iCBT compared with WL (mean difference −0.96, 95% CI (−5.88 to 3.97), p=0.703). No adverse events were reported. Participants confirmed the applicability of iCBT.

Conclusions ICBT was applied to reduce PTSD symptoms after intensive care for sepsis, for the first time addressing both patients and their spouses. It was applicable and safe in the given population. There was no evidence for the efficacy of iCBT on PTSD symptom severity. Due to the small sample size our findings remain preliminary but can guide further research, which is needed to determine if modified approaches to post-intensive care PTSD may be more effective.

Trial registration number DRKS00010676.

Strengths and limitations of this study

- ► This is the first study examining an intervention to reduce post-traumatic stress disorder after intensive care for both patients and their spouses.
- ► The internet-based intervention is tailored to the specific needs of postintensive care unit patients.
- ► A randomised controlled trial adhering to good clinical practice was conducted.
- ► Small sample size due to of challenging recruitment resulted in low statistical power.

INTRODUCTION

Experience of intensive care could affect mental health of both patients and their partners. About every fifth patient and an equal proportion of spouses develop a post-traumatic stress disorder (PTSD) as a long-term consequence of treatment in the intensive care unit (ICU).[1–4] Thus, PTSD has been considered as part of the postintensive care syndrome in ICU survivors (PICS) and their relatives (PICS-family).[5] Research on post-ICU consequences revealed that mental health of patients and their spouses following ICU experiences are interrelated and that couples seem to react as a dyadic system to a life-threatening situation.[6–9] In the context of dyadic coping research, it has been suggested to use the term 'we-disease' to describe that both, the patient and his/her partner, face the illness 'as a shared 'we-event' and a 'we-experience' rather than an individual problem of one partner requiring support from the other' (p. 595).[10] The concept of 'we-disease' also implies that the treatment of mental distress associated with the illness should always include both partners as they both suffer but also have resources and can jointly contribute to the coping

process.[6 10] Therefore, a partner-assisted intervention appears to be reasonable for treating PTSD symptoms after ICU experiences.

In the past few years, various intervention approaches have been developed to address PTSD in patients or family members that might be classified as interventions during ICU care to prevent PTSD or as interventions to treat PTSD in the long run. Preventive PTSD interventions usually consider a broad target group of ICU patients or family members at risk for post-ICU PTSD.[11–16] Contrasting, interventions addressing post-ICU PTSD are usually provided several months after ICU discharge and so far, these were designed as multitarget approaches focusing primarily on, for example, the improvement of quality of life[17] or reducing anxiety and depression.[18] In those previous intervention trials, PTSD symptom severity was considered as secondary outcome only and post-ICU patients were included irrespective of their mental health status. Based on this evidence and the research gaps revealed, it has been suggested for future trials to specifically address individuals who are at high risk for psychological distress after ICU discharge[18] and to develop targeted interventions that involve partners in the treatment, both as resource for the patient and as clients themselves.[19]

For the treatment of PTSD, clinical guidelines in general strongly recommend trauma-focused psychotherapy with cognitive-behavioural components of exposure and/or cognitive restructuring.[20 21] In the last decades, several treatment manuals of trauma-focused psychotherapy delivered via the internet have been developed, for example, internet-based cognitive-behavioural writing therapy (iCBT). The iCBT 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.[22 23] ICBT was demonstrably applicable in various patient populations such as rape victims, veterans and patients with chronic somatic diseases.[24–26] Meta-analytical evidence has proven the efficacy of iCBT across these patient populations to be moderate to large (effect sizes 0.60–0.83) in PTSD symptom reduction compared with waitlist (WL) control.[24 25] Moreover, the safety of iCBT has been confirmed in numerous trials although the evidence base on negative effects is sparser than on positive.[27 28] The particular potentials of iCBT lie in providing easy access for mobility-impaired patients or patients with speech and hearing difficulties,[29] ensuring low-threshold due to visual anonymity and enabling a treatment that is independent in space and time.[26 30] These advantages render iCBT particularly suitable for patients after critical illness. Therefore, as part of research within the Center for Sepsis Control and Care (CSCC), we designed a therapist-guided partner-assisted iCBT for reducing post-traumatic stress after intensive care for sepsis in patients and their spouses. We specifically focused on sepsis because it represents a major cause of morbidity in ICU[31 32] and is known as a global burden.[33]

The primary objective of the randomised-controlled REPAIR (Reducing post-traumatic stress after severe sepsis in patients and their spouses) trial was to investigate the efficacy, safety and applicability of this newly developed iCBT compared with a WL control group. Second, considering the interrelation of mental health between patients and partners, the study aimed at examining dyadic concordance in treatment effects, that is, indirect effects of the treatment in the respective spouse of the treated participant.

MATERIALS AND METHODS

Patient and public involvement

Representatives of the self-help organisation German Sepsis Aid were asked to comment on the concept of the study and the perceived acceptability of the proposed intervention resulting in positive feedback. A representative couple participated in a preceding pilot study to check the comprehensibility of the instructions, the functionality of the treatment platform and assessment routines.[34]

Participants

Inclusion and exclusion criteria for study participation were determined a priori recruitment. We included dyads (each member ≥18 years) comprising a former patient, who was treated for sepsis on an ICU for more than 5 days and discharged from ICU more than 1 month ago, and his/her spouse (married or cohabited). Eligibility decisions were based on empirical findings proving ICU length of stay and sepsis significant risk factors for post-ICU PTSD symptoms in patients[35 36] and time since ICU discharge as predictor of PTSD symptoms in relatives.[8] A patient-spouse dyad was included if at least one of them presented a presumptive PTSD diagnosis (PTSD checklist for DSM-5 (PCL-5) ≥33)[37] with regard to the life-threating event. Reasons for exclusion on dyad-level were not having a spouse as well as acute psychosis, suicidal ideation, use of neuroleptics, not being fluent in German or ongoing psychotherapeutic treatment elsewhere of at least one dyad member.

Broad measures were taken for recruitment purposes including press releases, articles in the member journal of the German Sepsis Aid and a German health magazine. Besides, we sent study leaflets and further information to all weaning centres in Germany, early rehabilitation clinics, patient self-help groups, patient organisations and informational websites for transplanted patients in Germany, Austria and Switzerland. We established a study website and a Facebook account with study information. Furthermore, we cooperated with current and finished projects and collaborators inside and outside JUH to identify and contact former patients treated on the ICU.

Participants were screened for eligibility in a telephone interview by using the PCL-5 and completed the Life Event

Checklist for DSM-5 to ensure, that PTSD symptoms are due to the critical illness and ICU experiences.[38] Written informed consent was obtained by the patients and their spouses. In a second telephone contact, patients and their spouses with presumptive PTSD diagnosis according to PCL-5 completed the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[39] and the Structured Clinical Interview for DSM-IV[40] conducted by a trained clinical psychologist (RG). Furthermore, participants were asked to provide medical data (eg, length of intensive care, length of mechanical ventilation (if applicable) and time since ICU discharge).

Intervention

Participants allocated to the treatment condition participated in an iCBT targeted to the traumatic ICU situation. They completed two 50 min internet-based writing assignments per week over a 5-week period (ten essays in total). The number of sessions is based on findings that interventions with fewer than 10 sessions had only a moderate effect.[24] The duration of the sessions is based on the duration in face-to-face sessions. The treatment consisted of three modules: (1) resource-oriented biographical reconstruction of the participants' life (three essays), (2) in sensu trauma exposure sessions (ie, detailed description of the traumatic situation with all sensations; four essays) and (3) cognitive reconstruction (to form a new perspective on the traumatic event and to regain a sense of control; three essays). Originally, the intervention was derived from 'Interapy'[41] and was later adapted for specific target populations, such as refugees or military personnel. In REPAIR, it was tailored to traumatic ICU experiences and extended to a dyadic perspective. The intervention combines effective face-to-face treatment techniques of CBT (exposure, cognitive reconstruction) and biographical reconstruction taken from the Narrative Exposure Therapy.[42] The efficacy of this intervention has already been proven effective in reducing PTSD symptoms for various populations.[24]

After completion of each assignment, the therapist provided individual feedback and further writing instructions to the participant within one workday. Integrated in the third module, the treated participant received a supportive letter from his/her respective partner. Here, the respective partner should announce acknowledgement for the participant as well as his/her strengths and the shared future. This dyadic treatment component, that is, the interaction between the partners, was added as a new element based on discussions with experts in face-to-face couple interventions.

Participants without clinically relevant PTSD symptoms (PCL-5 <33) only completed the assessments and received psychoeducational information about mental health problems after traumatic events. Participants allocated to the WL control group also received iCBT after 5 weeks of waiting (duration of treatment), but without a supportive letter from their spouses. For details, see study protocol (online supplemental material 1).

Outcomes

Primary outcome was change in PTSD symptom severity score from baseline to the end of treatment/waiting time (about 5 weeks after randomisation) measured via the German version of PCL-5[37 43] covering the four DSM-5 symptom clusters. A cut-off of 33 was used for a presumptive PTSD diagnosis.[44] A change of 10 points or more is regarded as clinically relevant.[37]

Secondary efficacy outcomes were (A) symptoms of psychological distress, (B) relationship satisfaction, (C) health-related quality of life and (D) remission at the end of treatment/waiting time. Safety endpoints were (1) the number of suicide alerts (ie, alert which was automatically activated by specific response pattern indicating suicide ideation during assessment), (2) the number of participants with a clinically relevant PCL-5 deterioration and (3) the percentage of participants leaving the study early (during treatment phase) due to any reason. An additional secondary endpoint was dyadic concordance in treatment effects (in terms of PCL-5). Psychological distress was measured using the German version of the Brief Symptom Inventory-18 including subscales of anxiety, depression and somatisation (BSI-18).[45 46] Relationship satisfaction was assessed with the German version of the Relationship Assessment Scale (RAS).[47 48] The German version of the health questionnaire of the EuroQol-5 Dimension-5-Level group (EQ-5D-5L)[49 50] was used to measure health-related quality of life on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Remission was only considered for participants diagnosed with PTSD before treatment/waiting period via CAPS-5.[39] For those, remission was defined as being free of PTSD diagnosis after the intervention/waiting period. PTSD was diagnosed by a trained clinical psychologist (RG) as described above (for details, (online supplemental material 2). Outcomes were also measured at 3, 6 and 12 months post-treatment.[29]

Sample size

The sample size calculation was based on Student's t-test for a parametric two-group comparison, even though more complex models that address the clustering would be used for the confirmatory analysis. In accordance with a recent meta-analysis,[24] we considered effect sizes quantified by Cohen's d of 0.95 as realistic. To detect differences between the treatment groups at a two-sided significance level of 0.05 with a comparison-wise power of 0.9, a sample size of 2×34, that is, 68 patient-spouse dyads, is required for the intention-to-treat (ITT) analysis. Assuming a dropout rate of 30%, the total sample size would be 98 dyads. A higher power was chosen to address the fact that a more complex statistical analysis approach would be used.

Randomisation

Dyads of a post-ICU patient and his/her spouse were randomly assigned to either iCBT or to a WL control group (allocation ratio 1:1) with the dyad being the unit

of randomisation. Concealed allocation was performed centrally using computer-generated random numbers provided by an independent person at the Centre for Clinical Trials of the JUH and stratified by the occurrence of PTSD symptoms within the dyad of the post-ICU patient and the spouse (stratum 1: both post-ICU patient and spouse with PTSD, stratum 2: post-ICU patient with PTSD and spouse without PTSD, stratum 3: post-ICU patient without PTSD and spouse with PTSD).

Blinding

Due to the nature of the study design and intervention, blinding of therapists and participants was not possible[29] (online supplemental material 1). The clinical psychologist who conducted the CAPS-5 clinical interview was also not blinded.

Statistical methods

We relied on two populations. The dyad population included randomised participants irrespective of their presumptive PTSD diagnosis. The PTSD population only comprised participants with a presumptive PTSD diagnosis. Primary and secondary efficacy/safety outcomes were analysed in the PTSD population, while dyadic concordance is was assessed in the dyad population.

The handling of missing data was predefined in the study protocol and/or the statistical analysis plan. Based on the expected high internal consistency of the scores, we substituted missing items with the mean of the provided items of the respective participant if 10% or fewer items were missing. We applied the ITT and the per-protocol (PP) principle to both populations. In case of the PP principle, we included randomised participants (with a presumptive PTSD diagnosis) who provided pretreatment(t0) and post-treatment/waiting (t1) information. In case of the ITT principle, we considered all randomised participants (with a presumptive PTSD diagnosis). Missing score values were replaced, stratified by intervention group and type of treatment (defined according to the stratum for the randomisation), according to best-case/worst-case substitution. We denoted this data set as 'primary analysis set'. As additional sensitivity analysis that was not prespecified in the study protocol, we used multiple imputation by chained equations (MICE) using fully conditional specification[51] (for details, online supplemental material 2).

Participant characteristics (dyad population) and outcomes (PTSD population) were summarised as absolute and relative frequencies for nominal variables or as medians together with the first and third quartile (Q1, Q3) for ordinal/continuous variables. Rough group comparisons were done by Fisher's exact test or Mann-Whitney-U test. For the primary outcome PCL-5 change, we applied generalised estimating equation (GEE) modelling (independent variables: baseline PCL-5 value, treatment condition; cluster: dyad) in the primary analysis set. We performed several sensitivity analyses (ITT principle with MICE, PP principle, extension of the above defined GEE model by inclusion of further possible confounders as independent variables). For the secondary efficacy outcomes, we adapted the GEE modelling accordingly. For primary and secondary efficacy outcomes, model coefficients (adjusted mean differences or OR) with 95% CIs and p values are presented. In addition, we provide the corresponding between-group effect sizes (standardised mean differences, derived from the main analyses with GEE modelling, Cohen's *d*). For illustration, we also provide between-group effect sizes and within-group effect sizes in iCBT and WL control group for pre–post change, both as standardised mean differences (Cohen's d) based on unadjusted means applying the PP principle. For the safety outcomes, we provide absolute and relative frequencies based on the PP principle. Dyadic concordance in treatment effects (in terms of PCL-5) was assessed with Spearman correlation (together with the corresponding 95% CIs) independently from the treatment condition between post-ICU patients and his/her spouse in the dyad population according to both ITT and PP principle. We applied a two-sided significance level of 0.05 to the primary confirmatory analysis and did not correct for multiple testing otherwise as the other analyses were considered exploratory. We used R (V.3.6.0) for statistical analyses (for details, see online supplemental material 2).

RESULTS

Participants

Between February 2017 and January 2019, we received 57 enquiries from either a post-ICU patient or his/her spouse. After screening for eligibility 25 dyads were randomised, 12 to iCBT and 13 to WL (figure 1). Median age of the study participants was 55 years (Q1–Q3, 47–62).

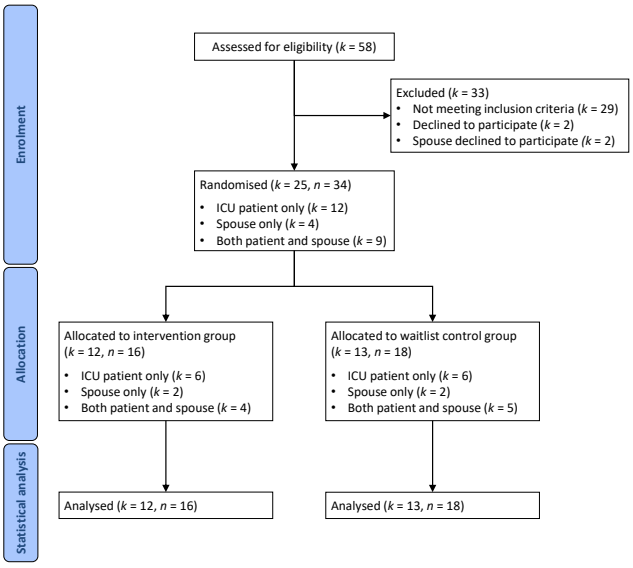

Figure 1 Flow diagram. The number of dyads (k) and the number of participants with PTSD symptoms (n) are provided. Reasons for exclusions are given. ICU, intensive care unit; PTSD, post-traumatic stress disorder.

Table 1 Characteristics of participants—overall as well as stratified by treatment group

Characteristic	Overall (N=50, k=25)	Treatment group: iCBT (N=24, k=12)	Treatment group: WL control (N=26, k=13)	P value
Male sex; n (%)	26 (52.0)	12 (50.0)	14 (53.8)	1.000
Age, in years; median (Q1, Q3)	55 (47, 62)	56 (52, 64)	54 (46, 59)	0.101
Among post-ICU patients‡				
Time since ICU treatment, in years; median (Q1, Q3)	1.8 (1.1, 3.7)	1.9 (1.2, 4.6)	1.6 (1.0, 2.0)	0.231
Duration of ICU treatment, in days; median (Q1, Q3)	21 (13, 40)	28 (12, 42)	21 (13, 28)	0.662
Mechanical ventilation				1.000
Yes; n (%)	18 (72.0)	9 (75.0)	9 (69.2)	
No; n (%)	5 (20.0)	2 (16.7)	3 (23.1)	
Not specified; n (%)	2 (8.0)	1 (8.3)	1 (7.7)	
Duration of mechanical ventilation among ventilated patients, in days; median (Q1, Q3)§	24 (16, 28)	28 (28, 35)	18 (8, 23)	0.048
College or university degree; n (%)	17 (34.0)	7 (29.2)	10 (38.5)	0.559
Pre-existing mental disorder (prior to sepsis); n (%)	16 (32.0)	9 (37.5)	7 (26.9)	0.547
Treatment of pre-existing mental disorder				
Prior to sepsis; n (%)	15 (30.0)	8 (33.3)	7 (26.9)	0.760
Post sepsis; n (%)	6 (12.0)	4 (16.7)	2 (7.7)	0.409
Presumptive PTSD diagnosis				
Post-ICU patient only; n (%)†	12 (48.0)	6 (50.0)	6 (46.2)	1.000
Spouse only; n (%)‡	4 (16.0)	2 (16.7)	2 (15.4)	1.000
Both dyad members; n (%)*	9 (36.0)	4 (33.3)	5 (38.5)	1.000
Relationship				
Duration, in years; median (Q1, Q3)*	22.2 (16.2, 32.9)	24.5 (19.1, 34.6)	21.8 (12.5, 29.4)	0.414
Marital status: married; n (%)*	21 (84.0)	10 (83.3)	11 (84.6)	1.000

The numbers are based on the dyad population. Overall, there are 25 dyads —12 dyads in the iCBT group and 13 dyads in the WL control group. Note that each dyad comprises one post-ICU patient and one spouse. The overall number of dyads (k) and the overall number of individuals (N) are provided. Characteristics are summarised as median with first and third quartile (Q1, Q3) or as absolute (n) and relative frequency (%). P values are derived from Mann-Whitney U test and Fisher's exact test, respectively, while excluding patients with missing (including non-specified) information on the respective characteristic.
*Refers to dyad.
†Refers to former ICU patient.
‡Refers to partner.
§Missing for nine patients (iCBT group: six, WL control group: three).
iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; WL, waitlist.

Thirty-four participants had a presumable PTSD diagnosis (9 dyads with affected post-ICU patient and spouse, 12 with post-ICU patient only, 4 with spouse only). Of those, 25 were initially diagnosed with PTSD in the clinical interview (iCBT: 14; WL: 11). Further characteristics of the participants are shown in table 1 (for stratification by post-ICU patient/spouse, online supplemental Table S1; for descriptive summary of the outcomes, online supplemental Table S2 and S3). Of note, one participant dropped-out directly after randomisation. For details on missing data and its impact/handling, we refer to online supplemental material 2.

Primary outcome

Individual, time-dependent PCL-5 curves are shown in figure 2. In the primary analysis set, we did not observe evidence for differences between groups in the primary outcome. The adjusted mean difference in PCL-5 score change was −0.96 (95% CI −5.88 to 3.97; p=0.703; table 2) when comparing iCBT to WL. Sensitivity analyses also showed no evidence for differences in PCL-5 change between the iCBT and the WL control group (ITT with MICE: 4.01; 95% CI −1.89 to 9.91; p=0.181; PP: 2.40; 95% CI −2.29 to 7.08; p=0.316; table 2). The corresponding between-group effect sizes varied between −0.14 (95% CI −0.81 to 0.54) and 0.48 (95% CI −0.21 to 1.16) (online supplemental table S9). The extended multivariable models revealed similar results (with a treatment group association in the multivariable models III with the PP and the ITT principle with MICE; online supplemental table S4).

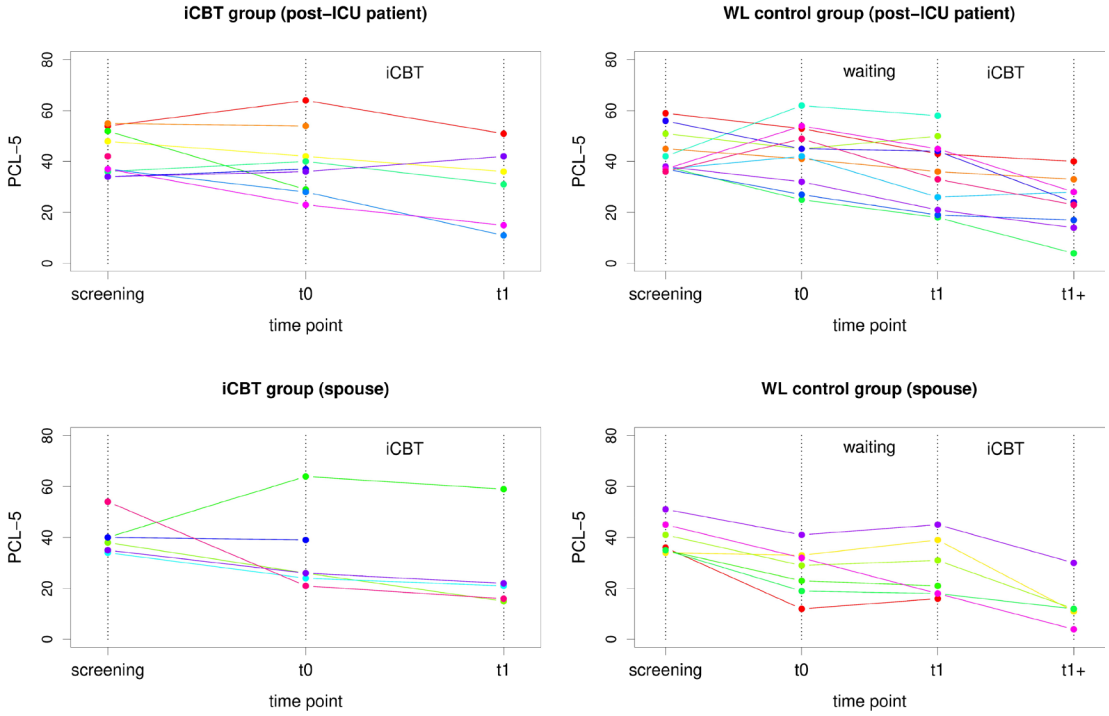

Figure 2 Observed PTSD symptoms (PCL-5 total score) in participants at trial assessments. Scores are stratified by post-ICU patient and his/her spouse as well as by treatment group (iCBT/WL control group). Pertreatment condition, dyad membership is colour-coded. Higher PCL-5 scores indicate more severe symptoms. Note that one participant (former ICU patient in iCBT group) dropped out directly after randomisation. Values are provided for several time points (including approximately time specifications): screening (t0—4 weeks); t0, start of intervention (iCBT group)/waiting (WL control group); t1 (t0 +5 weeks), end of intervention (iCBT group)/waiting (WL control group). In the WL control group, the end of intervention is at t1+ (t1 +5 weeks). iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; WL, waitlist.

Within-group effect sizes for pre–post changes in PCL-5 were similarly small in both groups (online supplemental table S10). Likewise, the proportion of participants with clinically relevant improvement in PCL-5 (ie, at least 10 points) was nearly identical in iCBT and WL control group (27.3% vs 27.8%) (online supplemental table S11).

Secondary efficacy outcomes

In the primary analysis set, we found that iCBT led to a larger RAS change than waiting (1.11; 95% CI 0.64 to 1.57; p<0.001; online supplemental table S5), with effects in favour of waiting. The corresponding between-group effect sizes for RAS change was large with −1.67 (95% CI −2.45 to −0.89); online supplemental table S9). This observation was consistent across all sensitivity analyses (online supplemental table S5). For all other secondary efficacy outcomes, we did not observe evidence for an association between score changes and iCBT in the primary analysis set (online supplemental table S6-S8) with corresponding effect sizes of 0.04 (95% CI −0.64 to 0.71) for BSI-18 and 0.25 (95% CI −0.42 to 0.93) for EQ-5D-5L (online supplemental table S9). Among patients with initial PTSD diagnosis (according to CAPS-5), remission rates were 64% after iCBT and 27% after waiting. Of note, 95% CIs for the iCBT effect for remission are wide in both ITT and, particularly, in the PP analyses; a smaller number of participants was considered in theses analyses as only participants with a presumptive PTSD diagnosis at baseline were included (online supplemental table S6).

Safety and applicability

Overall, there were five suicide alerts. All of them were clarified in immediate therapeutic contacts by telephone (see ref. [29] for a description of safety management). Three were false alarms, two were caused by reasons not related to the study and the suicidal ideations subsided quickly. During iCBT/waiting, there were no clinically relevant deteriorations in regard of the PCL-5 score. Seven participants prematurely terminated in the iCBT group and two during waiting time, respectively. All drop-outs appeared for reasons other than study or treatment participation, for example, physical deterioration, change in life circumstances (for further details on the safety endpoints, online supplemental table S10 and S11). In-depth interviews with participants after the treatment confirmed the applicability of the intervention. It was positively highlighted that iCBT met the specific needs of the patients and the spouses. In terms of feasibility, no major technical problems emerged and the internet literacy of the participants was sufficient to complete the treatment.

Dyadic concordance in treatment effects

No evidence for a correlation between the PCL-5 changes of post-ICU patients and those of his/her spouse could

Table 2 Results for PCL-5 (PTSD checklist for DSM-5) change from multivariable generalised estimating equation modelling

Variable	Mean difference (95% CI)	P value
ITT (best-case/worst-case)		
iCBT (ref.: no)	−0.96 (−5.88 to 3.97)	0.703
Baseline value (t0)	0.09 (−0.05 to 0.23)	0.225
ITT (MICE)		
iCBT(ref.: no)	4.01 (−1.89 to 9.91)	0.181
Baseline value (t0)	0.16 (−0.02 to 0.33)	0.078
PP		
iCBT(ref.: no)	2.40 (−2.29 to 7.08)	0.316
Baseline value (t0)	0.10 (−0.03 to 0.23)	0.123

Model coefficients (mean difference) together with 95% CIs and p values are provided. Positive values indicate effects in favour of iCBT. Results from both ITT approaches (best-case/worst-case as main analysis, MICE as sensitivity analysis) and the PP analysis (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were five participants in the iCBT group and none in the waitlist control group with missing information (missing PCL-5 change: 5, missing baseline value: 1; Supplemental Digital Content 1, online supplemental figures A3, A4).
iCBT, internet-based cognitive-behavioural writing therapy; ITT, intention-to-treat; MICE, multiple imputation by chained equations; PP, per-protocol; PTSD, post-traumatic stress disorder.

be observed—neither in case of only one dyad member nor in case both dyad members had a presumptive PTSD diagnosis (online supplemental table S12).

DISCUSSION

Strengths and limitations

Aim of this randomised controlled trial was to test the efficacy, safety and applicability of an iCBT for reducing PTSD symptoms in patients and their spouses. We included 25 dyads resulting in 34 treated participants. To our knowledge, this is the first study that evaluated an intervention involving both patients and spouses using a partner-assisted approach with the goal of reducing PTSD symptoms after intensive care. As a novelty, we implemented writing a supportive letter to the respective spouse as a dyadic treatment component in the iCBT.[29]

As already highlighted,[18] it is important to address individuals who are at high risk for psychological distress following critical illness and to develop interventions that should be targeted to defined subpopulations of survivors. Therefore, we sought only patients and/or spouses with clinically relevant PTSD symptoms and offered them a treatment tailored to their specific needs and their experiences during the critical illness. In addition to a self-report measure of PTSD symptom severity, we applied a clinical interview for formally diagnosing PTSD, which has been recommended as ideal but is a rare exception in clinical studies.[1]

There are, however, several important limitations that may have affected the results. First, we did not achieve the planned sample size. Despite tremendous efforts and a significant extension of the recruitment period, we experienced serious problems in recruiting participants. We can only speculate about the reasons. Although clinical research has proven the efficacy, applicability and safety of iCBT, also in the treatment of PTSD, internet-delivered psychotherapy is not yet part of routine care in the German healthcare system. So far, psychotherapy has been carried out predominantly via face to face. There might have been concerns and caveats about the practicability of the iCBT intervention[28] and the (primarily) elderly patients might be less open for such 'new' approaches. This may indicate that the newly developed treatment approach is not very desirable, at least in some age groups, and other treatment formats have to be developed and tested. Furthermore, there are no specialised post-ICU rehabilitation and outpatient ICU follow-up clinics in Germany, making it difficult to 'find' and contact patients after hospital discharge. The small sample size has resulted in a lack of statistical power. Hence, our results should be regarded as preliminary and further trials are needed to prove the efficacy of iCBT in the context of post-ICU PTSD.

Another problem emerged from missing data due to premature termination. To follow the ITT principle, we imputed missing data based on the best-case/worst-case substitution as the most rigorous method (as specified in the study protocol; online supplemental material 1). We further included sensitivity analyses applying multiple imputation and relying on the PP principle. Note that there are differences in the assumptions of these approaches reflecting common challenges in dealing with missing data. Hence, our conclusions remain fraught with uncertainty.

A further limitation concerns the selection of outcome measures. We mainly used outcome measures that depict clinically relevant symptomatology. This is not consistent with the fact that we also address spouses who do not have clinically relevant PTSD symptoms and are mentally healthy and support their partner in doing iCBT. Future studies examining dyadic interventions should also use more measures pertaining to partner well-being. Although the Impact of Event Scale-revised is recommended as core outcome measure of PTSD in post-ICU outpatient care,[52 53] we applied the PCL-5 for the assessment of PTSD symptom severity, because it is a widely used self-report questionnaire with good diagnostic accuracy, which reflects the most recent diagnostic PTSD criteria of DSM-5.[43]

With respect to the study design, it is important to consider that neither participants nor therapists were blinded. Finally, it has to be noted, that information about medical data was derived via self-report of the participants. It has to be questioned if all critical illness survivors and/or spouses were able to remember, for example,

the length or critical illness and mechanical ventilation, as well as time since ICU discharge. Therefore, it would be more reliable to use medical records for assessing this information.

Generalisability

External validity of our results is limited because we only included sepsis patients and their spouses from Germany. Since sepsis is highly frequent in ICU,[31 32] our findings might apply to a large proportion of ICU patients. Participating patients were treated in ICU about 3 weeks and most of them were mechanically ventilated. In comparison to ICU patients, both with and without sepsis,[32] we included a severely critically ill patient population. Median time after ICU discharge was 1.8 years, which is a quite long time. However, it is known that PTSD, if untreated or undertreated, might become chronic[54] and that PTSD symptoms might persist even for years after ICU discharge.[6 55] Although the iCBT manual was developed in German language, the treatment might be easily transferable in other languages, for example, English, enabling future studies with higher recruitment potential.

Interpretation

With regard to our primary outcome, we could not observe evidence that iCBT led to a larger reduction of PTSD symptom severity than waiting. This was not expected, as meta-analyses showed evidence for the efficacy of iCBT on reducing PTSD symptoms.[24 25] In particular, trauma-focused iCBT, as used in this study, was shown to produce greater effects than non-trauma-focused iCBT.[25] However, effects of the included trials were heterogeneous underpinning the need to identify patient as well as intervention characteristics which influence treatment outcome.

With regard to secondary outcomes, the comparison of remission rates in both groups (iCBT: 64%; waiting: 27%) may suggest that remission may nevertheless be an indicator of the treatment's potential effectiveness in this population. Contrary to our hypotheses, we found a relatively larger decrease of relationship satisfaction in the iCBT compared with the WL control group. There is evidence, although limited, that trauma-focused therapy is associated with higher levels of stress and is seen as demanding in terms of effort and time,[56 57] and individual stress is known to have a negative impact on relationship satisfaction.[58 59] It would be important to examine if the decrease in relationship satisfaction is a short-term "side" effect or persists over a longer time.

There was no evidence for dyadic concordance in any of the treatment effects. Beyond efficacy, participating in iCBT was safe, as no adverse events such as suicidality or clinically relevant PTSD symptom deterioration occurred that were therapy-related. Although seven participants prematurely terminated in the iCBT group, all dropouts appeared for reasons other than study or treatment participation. Compared with other iCBT studies, the dropout rate in our study (20.6%) is in the lower range, however, it should be noted that dropout rates are very heterogeneous across studies (9%–63%).[60]

Furthermore, participants confirmed the applicability of iCBT and the feasibility of the implementation and managed to reach the goals of each individual session. However, we did not formally evaluate their feedback or conducted a content analysis of their writing assignments. Based on our results, iCBT can be regarded as an applicable intervention in the particular population of post-ICU patients and their spouses.

The treatment of PTSD after traumatic ICU experiences has been subject of several randomised studies, tailored either as interventions during ICU care to prevent PTSD or as interventions to treat PTSD in the long run. Preventive interventions delivered early in ICU to reduce later PTSD symptoms of patients did not prove efficacious,[11 12 15 16] while the effectiveness of preventive approaches targeting partners' PTSD varies.[13 14] There are only few randomised controlled trials on the efficacy of treatments for reducing PTSD after ICU discharge. A nurse-led post-ICU recovery programme consisting of three consultations (one face to face, two via telephone) in the course of ten months after ICU discharge was not superior to standard care.[17] While previous treatments for post-ICU PTSD have focused exclusively on either the patient or the partner at an individual level,[11–17] dyadic approaches have received little consideration in the development of new interventions. An RCT including ICU survivors and their family members tested a telephone-based and web-based coping skills training intervention delivered by clinical psychologists against an education programme[18] with no effect on PTSD symptom reduction. In both trials,[17 18] post-ICU patients were included irrespective of their mental health status, and PTSD symptom severity was considered as secondary outcome only.

The need for ICU follow-up care to diagnose and treat PICS impairments after hospital discharge is apparent. Post-ICU patients show an increased utilisation of outpatient specialist services, including psychiatric services, higher medication intake and impaired quality of life.[61] Specialised post-ICU outpatient clinics could provide the necessary services specific to ICU survivors' healthcare needs,[5] but are however not yet established nationwide in Germany. Internet-based treatment approaches like iCBT in the follow-up of ICU patients can be particularly helpful for physically impaired patients or patients living a considerable distance from the hospital or specialised outpatient care, regardless of whether they are cared for in an ICU follow-up clinic or not.

Generally, it seems to be a difficult challenge to address the problem of post-ICU PTSD. It remains largely unknown when interventions to reduce PTSD symptoms should be initiated. The range of time after discharge from ICU in our sample was 3 –60 months. However, due to the small sample size in our study, we could not examine differences in iCBT efficacy based on the time since ICU discharge.

It seems that while some participants benefit from iCBT, others do not. In this regard, iCBT may be more appropriate as an initial intervention in a stepped pathway of care when additional treatment will be provided if the patient fails to benefit sufficiently from iCBT.[25] Moreover, predictors of treatment success should be further examined to better tailor the intervention to the participants.

CONCLUSIONS

We could not prove the efficacy of iCBT in contrast to waiting in patients and spouses after intensive care treated sepsis with a presumptive PTSD diagnosis, although such differences were observed in some sensitivity analyses. We demonstrated that iCBT is safe and applicable for both post-ICU patients and their spouses. While some participants benefited from iCBT, others did not. Hence, predictors of treatment success should be further examined. The largest limitation of the REPAIR trial was the small sample size. Therefore, our results remain preliminary. Future research could benefit by considering our findings and experiences in the planning of further tailored randomised-controlled trials. We suggest researchers informing patients early about PICS, treatment needs and trial participation, that is, before hospital discharge. Successful future studies might be designed as multicentre trials with broad support from scientific organisations and clinical institutions, for example, rehabilitation clinics or weaning centres. Promising scientific issues for future studies could be the provision of iCBT as part of a blended treatment (combining treatment modules delivered via internet and telephone or face-to-face contact) or as initial intervention in a stepped pathway of care.

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Contributors JR and CK conceived the study. CK, MB and HN developed the iCBT treatment manual. AS a priori conducted the power analysis and defined the statistical methods. MK was in charge of the statistical analysis and interpretation of the data. RG recruited patients, collected the data for the study and conducted all clinical interviews. MB and HN carried out the treatment of the participants. JR, MK and RG drafted the paper. All authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Data availability statement Technical appendix, statistical code and datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Open Access Protocol

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Internet-based cognitive–behavioural writing therapy for reducing post-traumatic 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 post-traumatic 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 Diagnostic and Statistical Manual Fifth Edition 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 (ie, 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 healthcare.

Strengths and limitations of this study

- This randomised-controlled trial will provide new evidence concerning the treatment of post-traumatic stress disorder (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.

Trial registration number: Pre-results, DRKS00010676.

INTRODUCTION

Psychopathological reactions, that is, acute stress disorder (International Classification of Diseases 10th Revision: F43.0) and post-traumatic 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. Diagnostic and Statistical Manual Fifth Edition (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 post-traumatic 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 with large effect sizes (standardised mean difference=1.62; 95% CI (1.21 to 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 (eg, 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 to 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 post-traumatic 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, that is, 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.

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 (eg, Germany, Austria and Switzerland) at least 1 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 ≥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, that is, 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 2 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 the MSC study assessments will be informed about the study. The MSC aims at following-up about 1000 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 (eg, length of intensive care and (if) length of mechanical ventilation, time since ICU discharge).

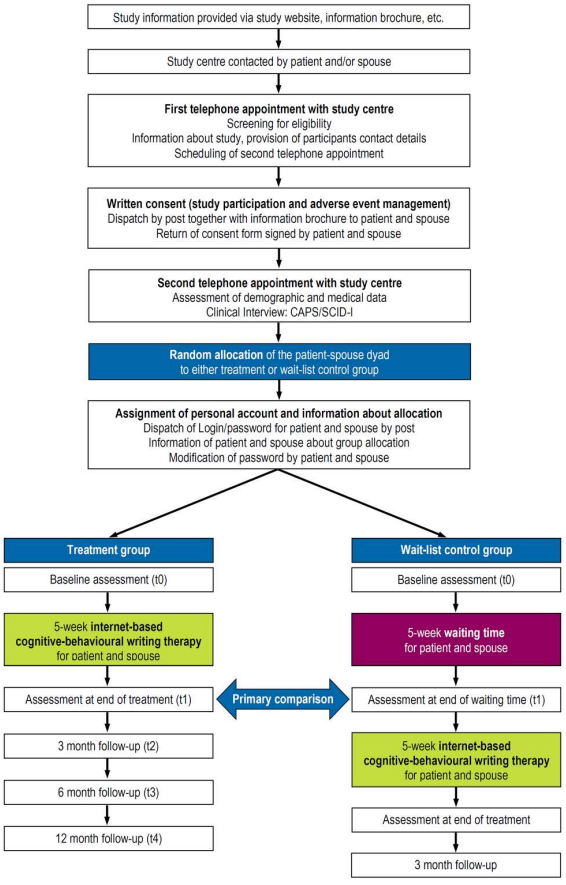

Figure 1 Study flow chart. CAPS/SCID-I, Clinician-Administered PTSD Scale for DSM-5/Structured Clinical Interview for DSM-IV DSM, Diagnostic and Statistical Manual; PTSD, post-traumatic stress disorder.

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)

Before the start of the treatment participants, that is, 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] Proactive 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 min writing assignments per week over a 5-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 (ie, explanation of PTSD symptoms and treatment options).

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			

*SEWIP is only applied to patients with PCL scores ≥33.
BSI, Brief Symptom Inventory; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; DCI, Dyadic Coping Inventory; EQ-5D-5L, health questionnaire of the EuroQol group; IB-CBWT, Internet-based cognitive–behavioural writing therapy; ILQ, Internet Literacy Questionnaire; IMET, Index for Measuring Limitations of Social Participation; LEC-5, Life Event Checklist for DSM-5; MFI, Multidimensional Fatigue Inventory; PCI, Proactive Coping Inventory; PCL-5, Post-traumatic stress disorder checklist; PTCI, Post-traumatic Cognitions Inventory; RAS, Relationship Assessment Scale; RS13, Resilience Scale; S3, after treatment session 3; S7, after treatment session 7; SCID-I, Structured Clinical Interview for DSM-IV; SEWIP, Multiperspective Assessment of General Change Mechanisms in Psychotherapy; 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); tx, time of enrolment.

At the beginning of each writing assignment, 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 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, that is, after assignments 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

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 solve 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. eg, "Has something positive resulted from the events?"

IB-CBWT, Internet-based cognitive–behavioural writing therapy.

collaboration, will be applied to participants of the IB-CBWT group. Additionally, PCL-5, BSI and RAS will be administered during therapy (after assignments 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 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.

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 post-traumatic 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 (S3, S7) and at the end of treatment (t1), we will assess common therapeutic factors in patients with PCL scores ≥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] that is, effects of Cohen's d=0.95, while requiring α=0.05 (two-sided) while aiming at a comparison-wise power of 1—β=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=2×34=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, that is, 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.

Statistical analyses

The primary end point of the efficacy assessment (PCL-5 change score at the end of the treatment, t1, ie, ~6 weeks after randomisation; relative to the randomisation t0) will be compared between both groups (ie, 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 component to address the possible intradyad 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 α=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 (ie, 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, for example, in the per-protocol (PP) population or stratified by patient and spouse. All additional analyses and the analyses of secondary end points will be carried out exploratively, that is, 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

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.

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 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 (number 4777-04/16, 11 May 2016). The trial is registered in the German Clinical Trials Register (DRKS); number 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 data set. 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 healthcare. 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.

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 healthcare 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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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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Supplemental material 2 to

Internet-based cognitive-behavioural writing therapy for reducing posttraumatic stress after severe sepsis in patients and their spouses (REPAIR): results of a randomised-controlled trial

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Detailed description of methods

Gawlytta R, *et al. BMJ Open* 2022; 12:e050305. doi: 10.1136/bmjopen-2021-050305

Outcomes measures

Primary efficacy outcome measure

PCL-5:

- 20-item self-report measure
- total symptom severity score: sum of all items (range: 0-80)
- higher scores indicating more severe symptoms

Secondary efficacy outcome measures

BSI-18:

- 3 subscales (anxiety, depression, and somatisation) with 6 items each
- Global Severity Index (GSI): sum of all subscales (range: 0-72)
- higher scores indicating more severe symptoms

RAS:

- 7 items
- total score: mean across all items (range: 1-7)
- higher scores indicating higher satisfaction

EQ-5D-5L:

- 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 levels (range: no problems to extreme problems)
- utility values:
    - derived according to Ludwig et al. (1)
    - range: -0.661 to 1
    - lower values indicating worse quality of life

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Statistical methods

Definition of analysis populations

The dyad population includes randomised participants irrespective of their presumptive PTSD diagnosis. The PTSD population only comprises participants with a presumptive PTSD diagnosis. We apply the intention-to-treat (ITT) and the per-protocol (PP) principle to both populations. In case of the ITT principle, we consider all randomised participants (with a presumptive PTSD diagnosis). In case of the PP principle, we consider randomised participants (with a presumptive PTSD diagnosis) who provided pre- (t0) and post-treatment/waiting (t1) information. For further details on the populations, we refer to the section "Missing data".

Statistical analysis

Participant characteristics (dyad population) are summarised as absolute and relative frequencies or as medians together with the first and third quartile (Q1, Q3). Furthermore, each outcome (PTSD population) was summarised as median together with Q1 and Q3. Additionally, we provide p-values from Fisher's exact test and Mann-Whitney-U test, respectively.

For the primary outcome PCL-5 change (analysed in the PTSD population), we applied multivariable generalised estimating equation (GEE) modelling with the identity as link function, with the sandwich estimator and with an assumed unstructured correlation structure. We included the treatment group (iCBT or WL control group; binary) as well as the baseline PCL-5 value (t0) as independent variables and the dyad membership as cluster. The primary analysis was performed according to the ITT principle with best-case/worst-case substitution (see section "Missing data" for definition). We performed several sensitivity analyses. First, we extended the aforementioned sparse multivariable model by (i) a binary variable related to the occurrence of PTSD symptoms within the dyads (both dyad members suffering from PTSD) and (ii) additionally by age (numeric), post-ICU patient (binary) and pre-existing mental disorder (binary). Secondly, we repeated the modelling according to the ITT principle gained by multiple imputation by chained equations (MICE; see section "Missing data" for definition) and according to the PP principle. In case of MICE, data was pooled according to Rubin (2). We provide regression coefficients with 95% confidence intervals (CIs) and p-values.

For the secondary efficacy outcomes (analysed in the PTSD population), we adapted the GEE modelling for the primary outcome with respect to the included dependent and independent variables. Of note, remission of PTSD was analysed in the population of participants with a PTSD diagnosis (according to CAPS-5) before the treatment/waiting period and with the logit-

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link in the respective GEEs. For remission, we could not include the variable "baseline value (t0)" in the extended multivariable models, because all included participants showed PTSD symptoms at baseline. Furthermore, we did not apply the extended multivariable model (ii) for remission due to sample size issues.

For primary and secondary outcomes, we calculated within-group and between-group effect sizes (standardized mean difference, Cohen´s d) with 95% CIs.

For the safety outcomes (analysed in the PTSD population), we provided absolute and relative frequencies according to the PP principle. Dyadic concordance in treatment effects (in terms of PCL-5; analysed in the dyad population) was assessed with Spearman correlation (together with the corresponding 95% CIs) independently from the treatment condition between post-ICU patients and his/her spouse according to both ITT (both approaches) and PP principle.

We applied a two-sided significance level of 0.05 and did not correct for multiple testing. We used R (version 3.6.0) for statistical analyses and, in particular, the R packages gee (version 4.13-20; 3), mice (version 3.8.0; 4), norm (version 1.0-9.5; 5), psych (version 1.9.12; 6) and effsize (version 0.8.1).

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Missing data

Overview

Overall, the number of missing data increases with proceeding time since study initiation (Supplemental Digital Content 2, Supplemental Table S2). One participant (iCBT group, post-ICU patient) dropped-out directly after randomisation. For this participant, baseline data was collected but there is no data related to the intervention/waiting time. Missing information on score changes is mainly driven by missing data at t1. The missing data pattern in the iCBT and the WL control group are provided for the dyad population in Additional Figures A1 and A2 as well as for the PTSD population in Additional Figures A3 and A4 (at the end of this document), respectively.

Based on the expected adequate/high consistency of the scores, we substituted missing items with the mean of the provided items of the respective participant if 10% or fewer items were missing. Due to the small sample size, we decided to replace the remaining missing score values when following the ITT principle. The remaining missing values were then replaced, stratified by intervention group and type of treatment (defined according to the strata for the randomisation), (i) according to best-case/worst-case substitution and (ii) with multiple imputation by chained equations (MICE). We decided to use MICE as sensitivity analysis for the best-case/worst-case substitution, because the latter is the most rigorous method for handling missing data.

Best-case/worst-case substitution

For missing information on the change score from t0 to t1, missing values were substituted with the worst observed change for participants in the iCBT group and with the best observed change for participants in the WL control group.

Missing values at the pre-treatment time point (t0) were replaced in a three-step approach (under consideration of the defined respective score range). (i) If the post-treatment value was available, the pre-treatment value was calculated relying on the already substituted change. (ii) In case of the PCL-5 score, the value was substituted by the screening value (approximately four weeks earlier than t0) if the pre-treatment value was still missing. (iii) Otherwise, the pre-treatment missing value was replaced by relying on the worst observed (iCBT group) and best observed (WL control group) post-treatment value (t1), respectively, and the already replaced change score.

Multiple imputation

For missing information in the data, we applied multiple imputation by chained equations (MICE) using fully conditional specification (4). We imputed 20 data sets, used 20 iterations and applied predictive mean matching (4,7). Score values imputed with predictive mean matching are restricted to observed score values (4,8). For imputation, we relied on baseline characteristics that we expected to be relevant for the score values and its change. To impute post-treatment values, we additionally used the respective pre-treatment values. The considered baseline characteristics comprised patient status (post-ICU patient or spouse), sex, age (in years), time since ICU discharge (in years), duration of intensive care treatment (in days), need of mechanical ventilation, highest educational qualification, duration of relationship (between post-ICU patient and spouse; in years), marital status, internet literacy, pre-existing mental illness (prior to sepsis), treated mental illness both before and after sepsis as well as treatment group (iCBT or WL control group) and type of treatment (related to occurrence of PTSD symptoms within the dyads). Characteristics of the imputed data (dyad population) are provided in Additional Figures A5-A9 (at the end of this document).

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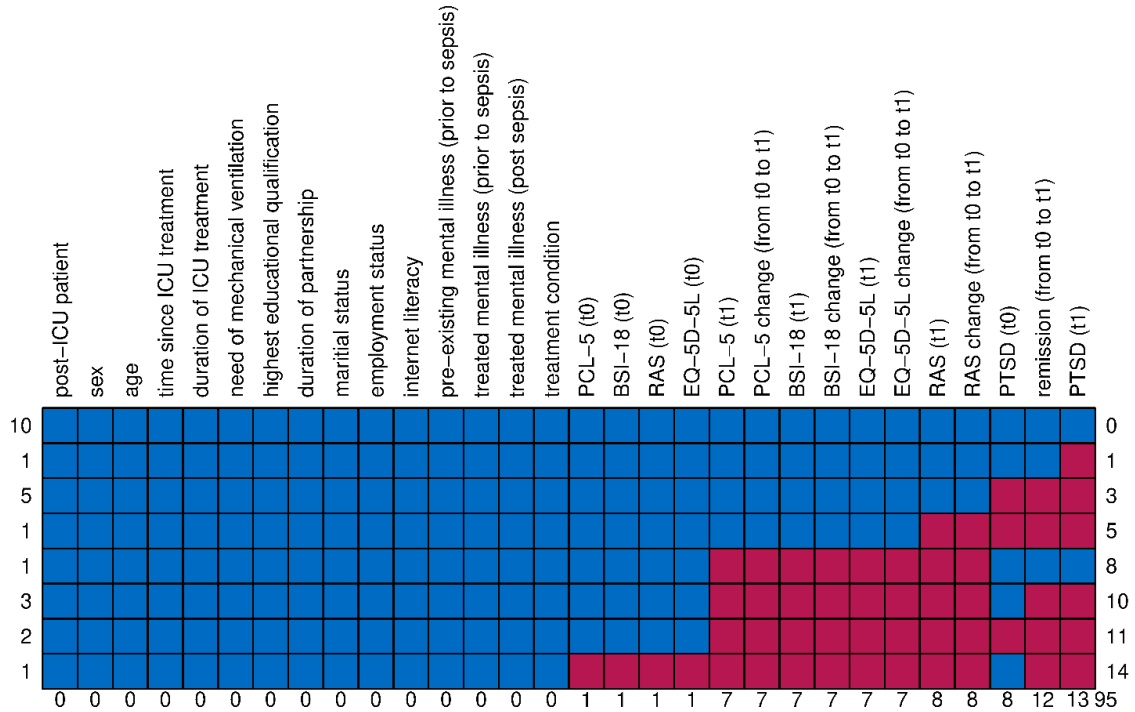
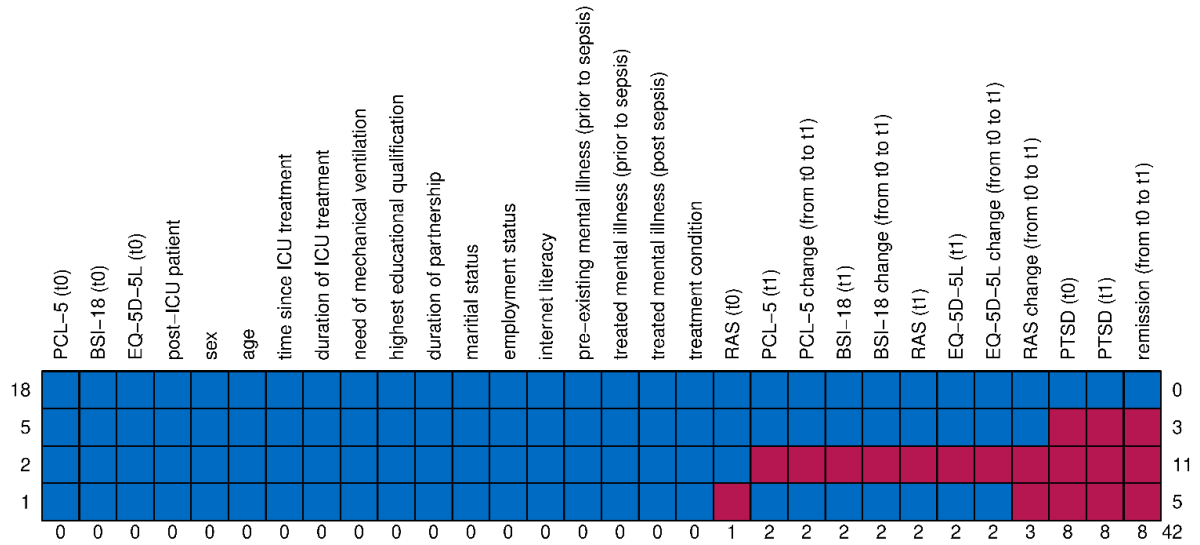
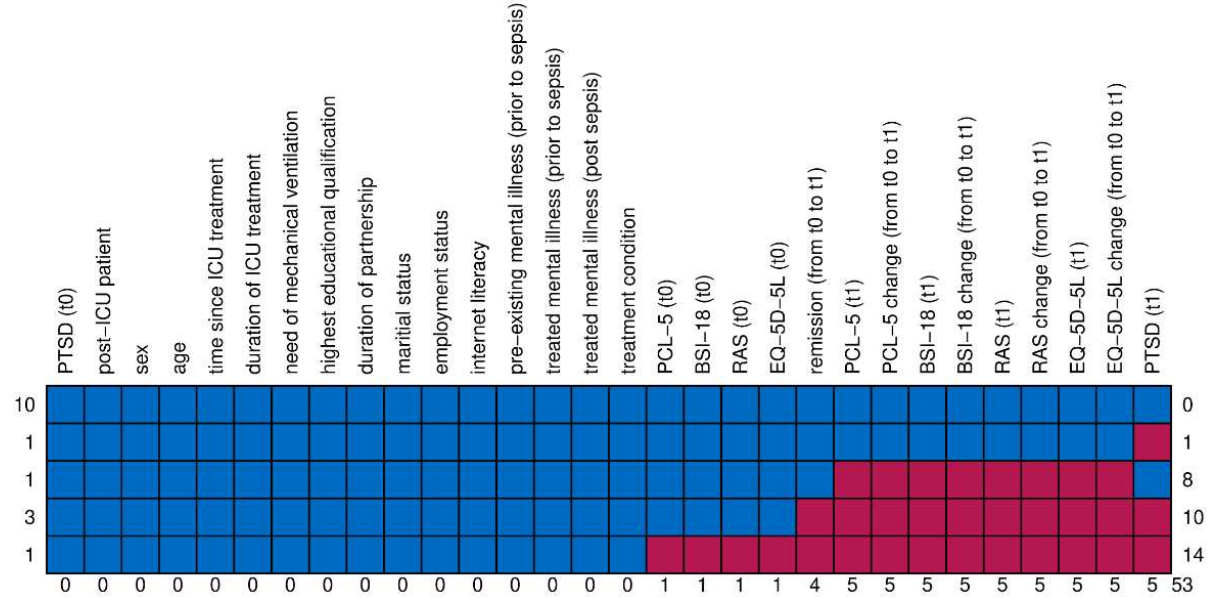
Additional figures



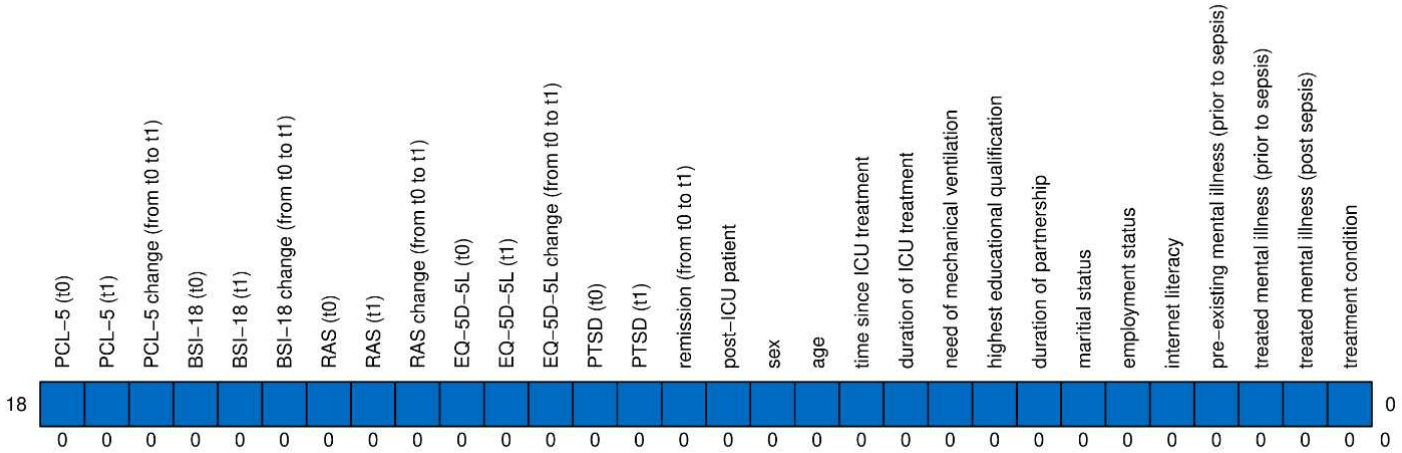
Additional Figure A1. Missing data pattern in the iCBT group of the dyad population. Baseline variables used for imputation and imputed variables are provided. t0 denotes the time point at which the intervention (iCBT group) / waiting (WL control group) begins and t1 the time point where the intervention (iCBT group) / waiting (WL control group) ends. Numbers on the left side indicates the frequency with which this missing data pattern occurs. Numbers in the bottom indicates the number of missing data of the respective variable. Numbers on the right side indicates the number of missing variables in the respective missing data pattern. Color coding: blue, not missing; red, missing. Abbreviations: BSI, Brief Symptom Inventory; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Satisfaction Scale; WL, waitlist.



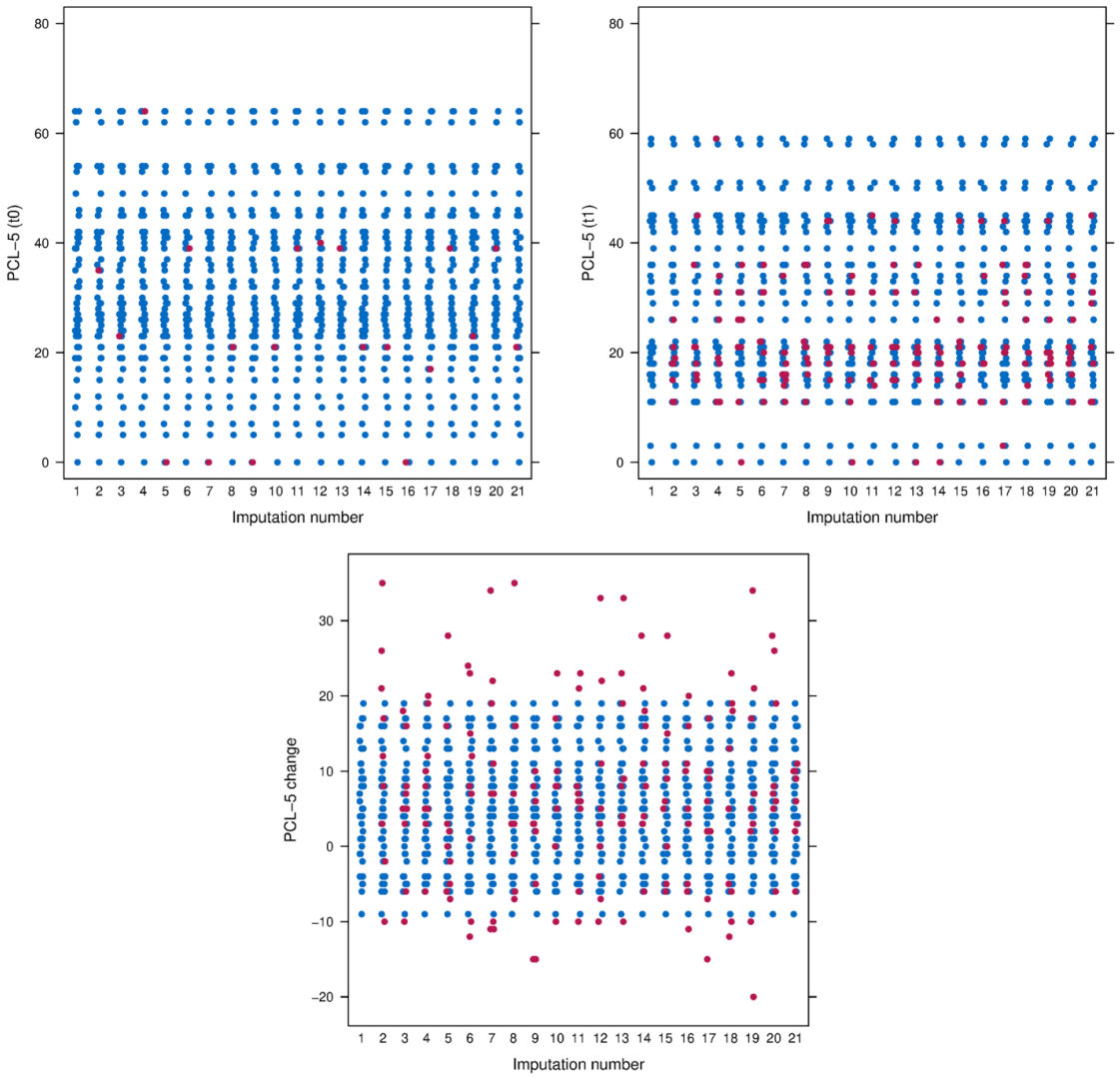
Additional Figure A2. Missing data pattern in the WL control group of the dyad population. Baseline variables used for imputation and imputed variables are provided. t0 denotes the time point at which the intervention (iCBT group) / waiting (WL control group) begins and t1 the time point where the intervention (iCBT group) / waiting (WL control group) ends. Numbers on the left side indicates the frequency with which this missing data pattern occurs. Numbers in the bottom indicates the number of missing data of the respective variable. Numbers on the right side indicates the number of missing variables in the respective missing data pattern. Color coding: blue, not missing; red, missing. Abbreviations: BSI, Brief Symptom Inventory; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Satisfaction Scale; WL, waitlist.



Additional Figure A3. Missing data pattern in the iCBT group of the PTSD population. Baseline variables used for imputation and imputed variables are provided. t0 denotes the time point at which the intervention (iCBT group) / waiting (WL control group) begins and t1 the time point where the intervention (iCBT group) / waiting (WL control group) ends. Numbers on the left side indicates the frequency with which this missing data pattern occurs. Numbers in the bottom indicates the number of missing data of the respective variable. Numbers on the right side indicates the number of missing variables in the respective missing data pattern. Color coding: blue, not missing; red, missing. Abbreviations: BSI, Brief Symptom Inventory; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Satisfaction Scale; WL, waitlist.



Additional Figure A4. Missing data pattern in the WL control group of the PTSD population. Baseline variables used for imputation and imputed variables are provided. t0 denotes the time point at which the intervention (iCBT group) / waiting (WL control group) begins and t1 the time point where the intervention (iCBT group) / waiting (WL control group) ends. Numbers on the left side indicates the frequency with which this missing data pattern occurs. Numbers in the bottom indicates the number of missing data of the respective variable. Numbers on the right side indicates the number of missing variables in the respective missing data pattern. Color coding: blue, not missing; red, missing. Abbreviations: BSI, Brief Symptom Inventory; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Satisfaction Scale; WL, waitlist.



Additional Figure A5. Original (imputation number 1) and the imputed data sets (dyad population) for PCL-5 (imputation numbers 2 to 21). PCL-5 denotes the PTSD Checklist for DSM-5. Imputed values (red) and original values (blue) are provided for the pre- (t0) and post-treatment (t1) value as well as the change from t0 to t1.

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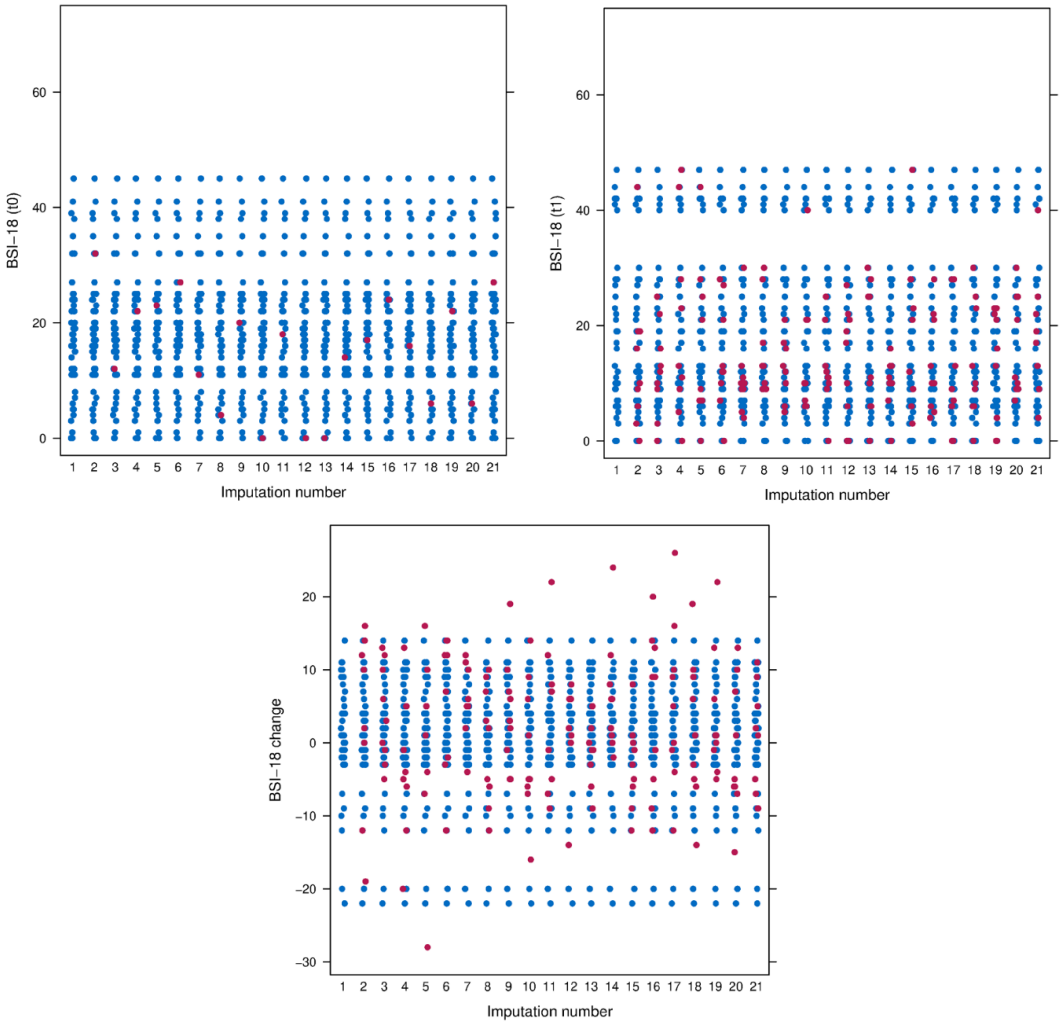

Additional Figure A6. Original (imputation number 1) and the imputed data sets (dyad population) for BSI-18 (imputation numbers 2 to 21). BSI-18 denotes the Brief Symptom Inventory-18. Imputed values (red) and original values (blue) are provided for the pre- (t0) and post-treatment (t1) value as well as the change from t0 to t1.

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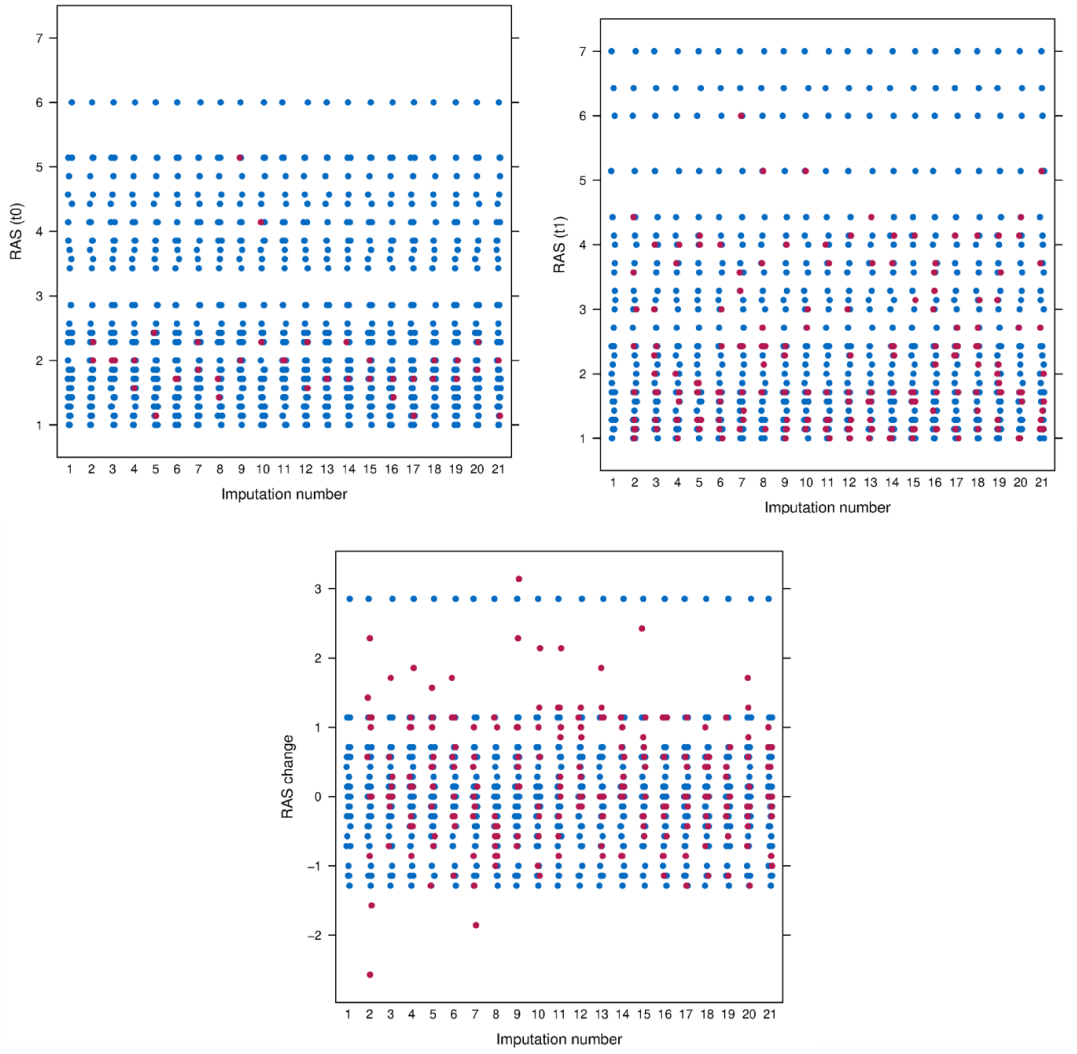
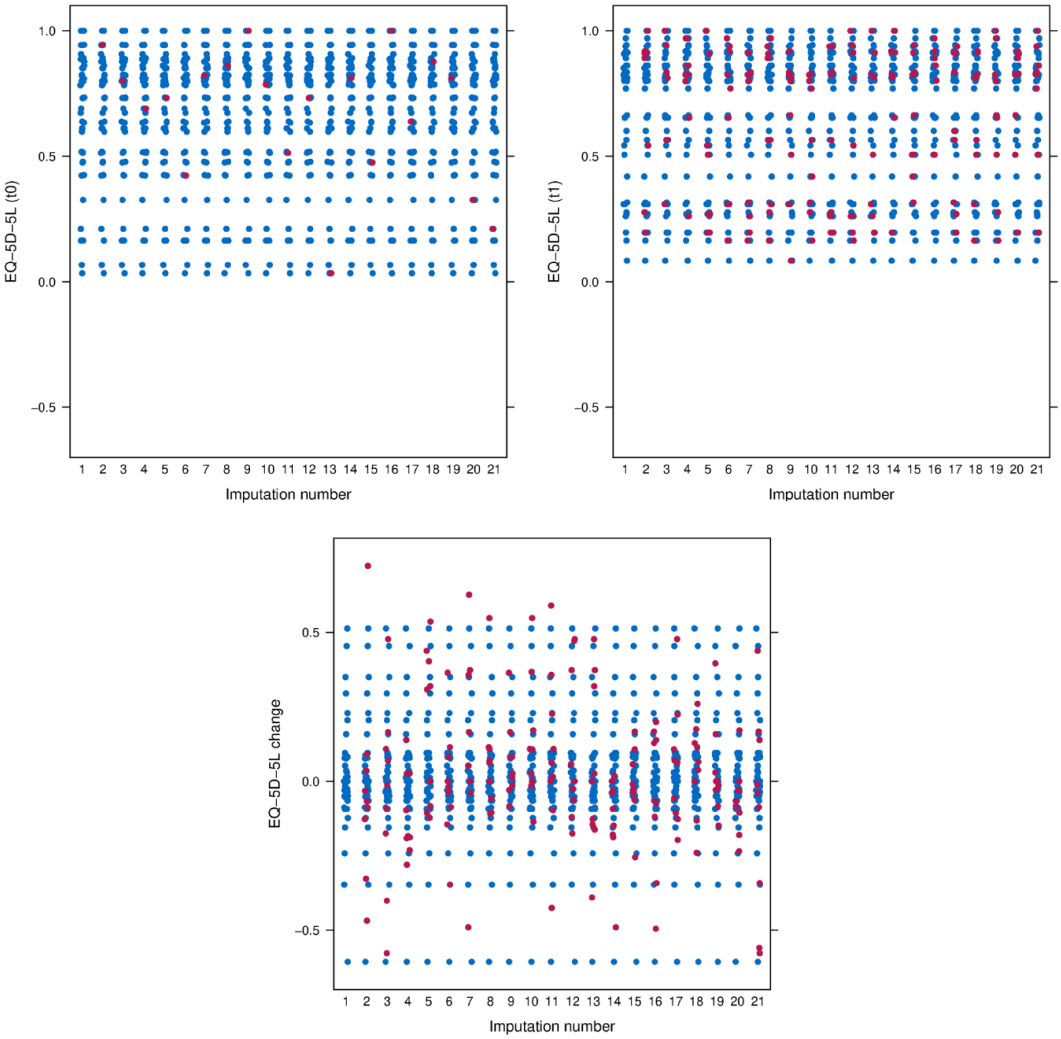


Additional Figure A7. Original (imputation number 1) and the imputed data sets (dyad population) for RAS (imputation numbers 2 to 21). RAS denotes the Relationship Satisfaction Scale. Imputed values (red) and original values (blue) are provided for the pre- (t0) and post-treatment (t1) value as well as the change from t0 to t1.



Additional Figure A8. Original (imputation number 1) and the imputed data sets (dyad population) for EQ-5D-5L (imputation numbers 2 to 21). EQ-5D-5L denotes the Health questionnaire of the EuroQol group in five dimensions with five levels. Imputed values (red) and original values (blue) are provided for the pre- (t0) and post-treatment (t1) value as well as the change from t0 to t1.

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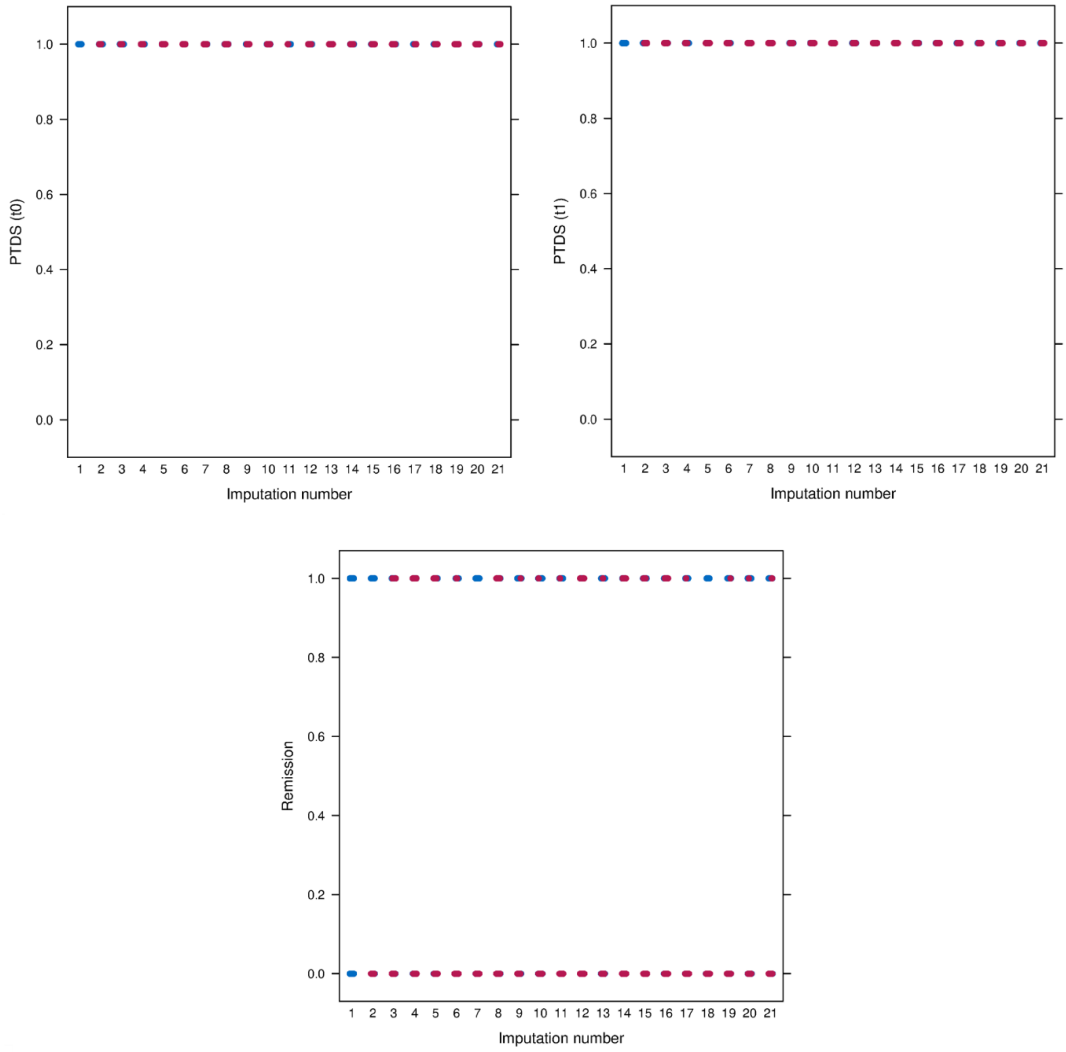

Additional Figure A9. Original (imputation number 1) and the imputed data sets (dyad population) for post-traumatic stress disorder (PTSD) and remission (imputation numbers 2 to 21). Note that results are based on those dyad members exhibiting PTSD symptoms at t0. Imputed values (red) and original values (blue) are provided for the pre- (t0) and post-treatment (t1) value as well as the change from t0 to t1.

Supplemental material 3 to

Internet-based cognitive-behavioural writing therapy for reducing posttraumatic stress after severe sepsis in patients and their spouses (REPAIR): results of a randomised-controlled trial

Romina Gawlytta; Miriam Kesselmeier; André Scherag; Helen Niemeyer; Maria Boettche; Christine Knaevelsrud, Jenny Rosendahl

Supplemental tables

List of tables

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Table S1. Characteristics of participants - stratified by post-ICU patient/spouse status and by treatment group.

Characteristic	Post-ICU patient			Spouse		
	Overall (*N* = 25)	Treatment group		Overall (*N* = 25)	Treatment group	
		iCBT (*N* = 12)	WL control (*N* = 13)		iCBT (*N* = 12)	WL control (*N* = 13)
Male sex; *n* (%)	17 (68.0)	7 (58.3)	10 (76.9)	9 (36.0)	5 (41.7)	4 (30.8)
Age, in years; median (Q1, Q3)	56 (48, 65)	57 (54, 67)	55 (46, 59)	54 (47, 61)	55 (51, 63)	53 (46, 58)
Among post-ICU patients						
Time since ICU treatment, in years; median (Q1, Q3)	1.8 (1.1, 3.7)	1.9 (1.2, 4.6)	1.6 (1.0, 2.0)	-	-	-
Duration of ICU treatment, in days; median (Q1, Q3)	21 (13, 40)	28 (12, 42)	21 (13, 28)	-	-	-
Mechanical ventilation						
Yes; *n* (%)	18 (72.0)	9 (75.0)	9 (69.2)	-	-	-
No; *n* (%)	5 (20.0)	2 (16.7)	3 (23.1)	-	-	-
Not specified; *n* (%)	2 (8.0)	1 (8.3)	1 (7.7)	-	-	-
Duration of mechanical ventilation among ventilated patients, in days; median (Q1, Q3)**	24 (16, 28)	28 (28, 35)	18 (8, 23)	-	-	-
College or university degree; *n* (%)	7 (28.0)	2 (16.7)	5 (38.5)	10 (40.0)	5 (41.7)	5 (38.5)
Pre-existing mental disorder (prior to sepsis); *n* (%)	9 (36.0)	5 (41.7)	4 (30.8)	7 (28.0)	4 (33.3)	3 (23.1)
Treatment of pre-existing mental disorder						
Prior to sepsis; *n* (%)	8 (32.0)	4 (33.3)	4 (30.8)	7 (28.0)	4 (33.3)	3 (23.1)
Post sepsis; *n* (%)	4 (16.0)	3 (25.0)	1 (7.7)	2 (8.0)	1 (8.3)	1 (7.7)
Presumptive PTSD diagnosis						

Only one member of the dyad; *n* (%)	12 (48.0)	6 (50.0)	6 (46.2)	4 (16.0)	2 (16.7)	2 (15.4)
Both dyad members; *n* (%)*	9 (36.0)	4 (33.3)	5 (38.5)	9 (36.0)	4 (33.3)	5 (38.5)
Relationship						
Duration, in years; median (Q1, Q3)*	22.2 (16.2, 32.9)	24.5 (19.1, 34.6)	21.8 (12.5, 29.4)	22.2 (16.2, 32.9)	24.5 (19.1, 34.6)	21.8 (12.5, 29.4)
Marital status: married; *n* (%)*	21 (84.0)	10 (83.3)	11 (84.6)	21 (84.0)	10 (83.3)	11 (84.6)

The numbers are based on the dyad population. Overall, there are 25 dyads - 12 dyads in the iCBT group and 13 dyads in the WL control group. Note that each dyad comprises one post-ICU patient and one spouse. The overall number of randomised individuals (*N*) are provided. Characteristics are summarised as median with first and third quartile (Q1, Q3) or as absolute (*n*) and relative frequency (%). Abbreviations: -, not applicable; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; WL, waitlist.
* refers to dyad; ** missing for 9 patients (iCBT group: 6, WL control group: 3)

Table S2. Outcomes of participants with presumptive PTSD diagnosis - overall as well as stratified by treatment group.

Outcome	# participants with missing values	Overall (n = 34)	Treatment group	
			iCBT (n = 16)	WL control (n = 8)
PCL-5[a]; median (Q1, Q3)				
Change from t0 to t1	5	5 (1, 10)	6 (4, 10)	4 (-1, 10)
Screening	0	38 (36, 47)	39 (36, 49)	38 (36, 45)
t0	1	36 (26, 45)	36 (26, 41)	37 (28, 45)
t1	5	31 (18, 43)	22 (16, 39)	32 (20, 44)
t1+	4	-	-	20 (12, 28)
BSI-18[b]; median (Q1, Q3)				
Change from t0 to t1	5	1 (-3, 4)	3 (-1, 5)	-1 (-3, 4)
t0	1	19 (12, 25)	19 (14, 24)	20 (11, 25)
t1	5	17 (9, 28)	13 (9, 21)	20 (10, 28)
t1+	4	-	-	12 (7, 18)
RAS[c]; median (Q1, Q3)				
Change from t0 to t1	5	0 (0, 0)	0 (0, 1)	0 (-1, 0)
t0	1	2 (2, 4)	2 (2, 4)	2 (2, 2)
t1	5	2 (1, 3)	1 (1, 4)	2 (2, 3)
t1+	4	-	-	2 (1, 3)
EQ-5D-5L[d]; median (Q1, Q3)				
Change from t0 to t1	5	0.01 (-0.05, 0.09)	0.01 (-0.05, 0.06)	0.01 (-0.05, 0.14)

t0	1	0.69 (0.48, 0.82)	0.73 (0.49, 0.84)	0.66 (0.49, 0.82)
t1	5	0.66 (0.32, 0.83)	0.80 (0.55, 0.85)	0.66 (0.31, 0.82)
t1+	4	-	-	0.79 (0.68, 0.90)
PTSD; *n* (%)				
t0	0	25 (73.5%)	14 (87.5%)	11 (61.1%)
t1	5	13 (44.8%)	1 (9.1%)	12 (66.7%)
Remission from t0 to t1[*]	4	12 (57.1%)	9 (90.0%)	3 (27.3%)

The overall number of treated individuals (*n*) are provided. Outcomes are summarised as median with first and third quartile (Q1, Q3) or as absolute (*n*) and relative frequency (%). Percentages refer to number of participants with information for the respective value; number of participants with missing values are provided. Values are provided for several time points: t0, start of intervention (iCBT group) / waiting (WL control group); t1, end of intervention (iCBT group) / waiting (WL control group); t1+, end of intervention in WL control group. Abbreviations: -, not applicable; #, number of; BSI-18, Brief Symptom Inventory-18; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Satisfaction Scale; WL, waitlist.

[*] Both percentage and number of missing values refer to number of participants with PTSD at t0.

[a] Total scores of the PCL-5 range from 0 to 80 (higher scores indicate greater severity of PTSD symptoms). PCL-5 was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

[b] Total scores of BSI-18 range from 0 to 72 (higher scores indicate greater severity of symptoms). BSI-18 was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

[c] RAS mean scores range from 1 to 7 (higher scores represent higher relationship satisfaction). RAS was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

[d] Total scores of EQ-5D-5L range from -0,661 to 1 (lower scores indicating worse quality of life), anchored at 0 (death) and 1 (perfect health). EQ-5D-5L was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

Table S3. Outcomes of participants with presumptive PTSD diagnosis - overall as well as stratified by post-ICU patient/spouse status and by treatment group.

Outcome	# participants with missing values	Post-ICU patient			Spouse		
		Overall (n = 21)	Treatment group		Overall (n = 13)	Treatment group	
			iCBT (n = 10)	WL control (n = 11)		iCBT (n = 6)	WL control (n = 7)
PCL-5[a]; median (Q1, Q3)							
Change from t0 to t1	5	8 (5, 11)	8 (6, 12)	8 (4, 10)	2 (-2, 5)	5 (4, 5)	-2 (-4, 2)
Screening	0	38 (37, 51)	40 (36, 51)	38 (37, 48)	38 (35, 41)	39 (36, 40)	36 (35, 43)
t0	1	42 (31, 50)	37 (29, 42)	45 (36, 51)	26 (23, 33)	26 (24, 36)	29 (21, 32)
t1	5	36 (21, 44)	34 (19, 40)	36 (24, 44)	21 (18, 33)	21 (16, 22)	21 (18, 35)
t1+	4	-	-	24 (17, 28)	-	-	12 (11, 12)
BSI-18[b]; median (Q1, Q3)							
Change from t0 to t1	5	3 (-2, 5)	4 (3, 8)	0 (-2, 4)	-1 (-3, 2)	1 (-3, 2)	-1 (-8, 2)
t0	1	22 (16, 28)	22 (16, 24)	23 (14, 30)	15 (11, 22)	14 (12, 18)	18 (8, 22)
t1	5	19 (10, 27)	14 (10, 23)	21 (14, 28)	12 (8, 28)	9 (9, 17)	13 (9, 29)
t1+	4	-	-	16 (10, 20)	-	-	7 (4, 7)
RAS[c]; median (Q1, Q3)							
Change from t0 to t1	5	0 (0, 1)	1 (1, 1)	0 (-1, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
t0	1	2 (2, 3)	2 (2, 4)	2 (2, 2)	2 (2, 4)	3 (2, 4)	2 (2, 2)
t1	5	2 (1, 3)	1 (1, 2)	2 (1, 3)	2 (2, 4)	4 (1, 4)	2 (2, 3)

t1+	4	-	-	2 (2, 2)	-	-	2 (1, 3)
EQ-5D-5L[d]; median (Q1, Q3)							
Change from t0 to t1	5	0.00 (-0.07, 0.09)	-0.01 (-0.06, 0.07)	0.00 (-0.09, 0.13)	0.02 (-0.04, 0.09)	0.01 (-0.04, 0.03)	0.09 (-0.02, 0.16)
t0	1	0.56 (0.37, 0.73)	0.51 (0.42, 0.73)	0.61 (0.34, 0.74)	0.82 (0.73, 0.89)	0.84 (0.81, 0.87)	0.82 (0.66, 0.95)
t1	5	0.60 (0.31, 0.80)	0.63 (0.35, 0.76)	0.56 (0.31, 0.79)	0.82 (0.62, 0.87)	0.84 (0.80, 0.86)	0.81 (0.47, 0.89)
t1+	4	-	-	0.77 (0.66, 0.79)	-	-	0.91 (0.86, 0.91)
PTSD; *n* (%)							
t0	0	15 (71.4%)	9 (90.0%)	6 (54.5%)	10 (76.9%)	5 (83.3%)	5 (71.4%)
t1	5	10 (55.6%)	1 (14.3%)	9 (81.8%)	3 (27.3%)	0 (0.0%)	3 (42.9%)
Remission from t0 to t1*	4	5 (41.7%)	5 (83.3%)	0 (0.0%)	7 (77.8%)	4 (100.0%)	3 (60.0%)

The overall number of treated individuals (*n*) are provided. Outcomes are summarised as median with first and third quartile (Q1, Q3) or as absolute (*n*) and relative frequency (%). Percentages refer to number of participants with information for the respective value; number of participants with missing values are provided. Values are provided for several time points: t0, start of intervention (iCBT group) / waiting (WL control group); t1, end of intervention (iCBT group) / waiting (WL control group); t1+, end of intervention in WL control group. Abbreviations: -, not applicable; #, number of; ; BSI-18, Brief Symptom Inventory-18; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Satisfaction Scale; WL, waitlist.

[*] Both percentage and number of missing values refer to number of participants with PTSD at t0.

[a] Total scores of the PCL-5 range from 0 to 80 (higher scores indicate greater severity of PTSD symptoms). PCL-5 was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

[b] Total scores of BSI-18 range from 0 to 72 (higher scores indicate greater severity of symptoms). BSI-18 was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

[c] RAS mean scores range from 1 to 7 (higher scores represent higher relationship satisfaction). RAS was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

[d] Total scores of EQ-5D-5L range from -0,661 to 1 (lower scores indicating worse quality of life), anchored at 0 (death) and 1 (perfect health). EQ-5D-5L was self-reported by participants at first login to the REPAIR web portal before starting treatment / waiting period.

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Table S4. Results for PCL-5 (PTSD Checklist for DSM-5) change from generalised estimating equation (GEE) modelling.

Variable	ITT (best-case/worst-case)		ITT (MICE)		PP	
	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Multivariable models I						
iCBT [ref.: no]	-0.96 (-5.88, 3.97)	0.703	4.01 (-1.89, 9.91)	0.181	2.40 (-2.29, 7.08)	0.316
Baseline value (t0)	0.09 (-0.05, 0.23)	0.225	0.16 (-0.02, 0.33)	0.078	0.10 (-0.03, 0.23)	0.123
Multivariable models II						
iCBT [ref.: no]	-1.80 (-5.90, 2.30)	0.390	3.74 (-2.15, 9.64)	0.212	1.53 (-2.79, 5.84)	0.488
Both suffering from PTSD [ref.: no]	0.06 (-0.09, 0.20)	0.445	0.14 (-0.03, 0.30)	0.098	0.09 (-0.03, 0.21)	0.154
Baseline value (t0)	-1.80 (-5.90, 2.30)	0.390	3.74 (-2.15, 9.64)	0.212	1.53 (-2.79, 5.84)	0.488
Multivariable models III						
iCBT [ref.: no]	-0.21 (-3.99, 3.57)	0.913	5.90 (0.05, 11.75)	0.048	4.11 (0.66, 7.55)	0.019
Both suffering from PTSD [ref.: no]	0.04 (-0.15, 0.22)	0.700	0.06 (-0.15, 0.26)	0.579	0.04 (-0.09, 0.17)	0.555
Baseline value (t0)	-0.21 (-0.48, 0.06)	0.134	-0.36 (-0.71, -0.02)	0.04	-0.31 (-0.60, -0.02)	0.034
Age, in years	0.80 (-4.84, 6.45)	0.780	3.03 (-2.67, 8.72)	0.297	2.34 (-3.15, 7.82)	0.404
Post-ICU patient [ref.: no]	-3.94 (-7.75, -0.13)	0.043	-1.32 (-6.44, 3.79)	0.611	-3.37 (-7.29, 0.55)	0.092
Pre-existing mental disorder [ref.: no]	-0.21 (-3.99, 3.57)	0.913	5.90 (0.05, 11.75)	0.048	4.11 (0.66, 7.55)	0.019

Model coefficients (mean difference) together with 95% confidence intervals (CIs) and *p*-values are provided. Positive values indicate effects in favour of iCBT. Results from both intention-to-treat (ITT) approaches (best-case/worst-case as main analysis, multiple imputation by chained equations (MICE) as sensitivity analysis) and the per-protocol (PP) analyses (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were five participants in the iCBT group and none in the waitlist control group with missing information (missing PCL-5 change: 5, missing baseline value: 1; Supplemental Digital Content 1, Additional Figures A3 and A4). Abbreviations: iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; t0, time point at beginning of intervention/waiting.

Table S5. Results for RAS (Relationship Satisfaction Scale) change from generalised estimating equation (GEE) modelling.

Variable	ITT (best-case/worst-case)		ITT (MICE)		PP	
	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Multivariable models I						
iCBT [ref.: no]	1.11 (0.64, 1.57)	<0.001	0.72 (0.19, 1.26)	0.008	0.80 (0.23, 1.37)	0.006
Baseline value (t0)	0.12 (-0.07, 0.32)	0.214	-0.01 (-0.27, 0.25)	0.933	0.07 (-0.20, 0.34)	0.604
Multivariable models II						
iCBT [ref.: no]	1.43 (0.76, 2.10)	<0.001	0.72 (0.19, 1.25)	0.008	0.91 (0.45, 1.38)	<0.001
Both suffering from PTSD [ref.: no]	0.03 (-0.19, 0.25)	0.774	0.00 (-0.25, 0.26)	0.991	0.15 (-0.05, 0.36)	0.142
Baseline value (t0)	1.43 (0.76, 2.10)	<0.001	0.72 (0.19, 1.25)	0.008	0.91 (0.45, 1.38)	<0.001
Multivariable models III						
iCBT [ref.: no]	1.23 (0.92, 1.53)	<0.001	0.87 (0.36, 1.39)	0.001	1.05 (0.66, 1.44)	<0.001
Both suffering from PTSD [ref.: no]	0.11 (-0.01, 0.24)	0.079	0.05 (-0.16, 0.26)	0.643	0.10 (-0.07, 0.28)	0.255
Baseline value (t0)	-0.01 (-0.03, 0.01)	0.332	-0.01 (-0.04, 0.02)	0.494	-0.01 (-0.03, 0.02)	0.619
Age, in years	0.67 (0.14, 1.20)	0.013	0.49 (-0.04, 1.02)	0.069	0.68 (0.12, 1.24)	0.018
Post-ICU patient [ref.: no]	-0.07 (-0.30, 0.15)	0.528	-0.22 (-0.69, 0.26)	0.369	-0.15 (-0.48, 0.17)	0.353
Pre-existing mental disorder [ref.: no]	1.23 (0.92, 1.53)	<0.001	0.87 (0.36, 1.39)	0.001	1.05 (0.66, 1.44)	<0.001

Model coefficients (mean difference) together with 95% confidence intervals (CIs) and *p*-values are provided. Negative values indicate effects in favour of iCBT. Results from both intention-to-treat (ITT) approaches (best-case/worst-case as main analysis, multiple imputation by chained equations (MICE) as sensitivity analysis) and the per-protocol (PP) analyses (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were five participants in the iCBT group and none in the waitlist control group with missing information (missing RAS change: 5, missing baseline value: 1; Supplemental Digital Content 1, Additional Figures A3 and A4). Abbreviations: iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; t0, time point at beginning of intervention/waiting.

Table S6. Results for remission from generalised estimating equation (GEE) modelling.

Variable	ITT (best-case/worst-case)		ITT (MICE)		PP	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Multivariable models I						
iCBT [ref.: no]	4.28 (0.89, 20.65)	0.070	4.28 (0.89, 20.65)	0.070	21.97 (2.22, 217.80)	0.008
Multivariable models II						
iCBT [ref.: no]	4.05 (0.80, 20.45)	0.090	4.05 (0.80, 20.45)	0.090	35.33 (3.40, 367.00)	0.003
Both suffering from PTSD [ref.: no]	0.74 (0.14, 3.98)	0.728	0.74 (0.14, 3.98)	0.728	3.37 (0.32, 35.68)	0.314

Note that results are based on those dyad members with PTSD diagnosis according to CAPS-5 at t0 (iCBT: 14 participants, WL: 11 participants; Supplemental Digital Content 2, Supplemental Table S2). Furthermore, all former ICU patients with remission were treated and in each dyad comprising a spouse without remission was a former ICU patient with PTSD. Odds ratios (OR) together with 95% confidence intervals (CIs) and *p*-values are provided. Results from both intention-to-treat (ITT) approaches (best-case/worst-case as main analysis, multiple imputation by chained equations (MICE) as sensitivity analysis) and the per-protocol (PP) analyses (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were four participants in the iCBT group and none in the waitlist control group with missing information on remission (Supplemental Digital Content 2, Supplemental Table A3 and A4). Furthermore, the multivariable models III were not applied – due to the small sample size. Abbreviations: iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; t0, time point at beginning of intervention/waiting.

Table S7. Results for BSI-18 (Brief Symptom Inventory-18) change from generalised estimating equation (GEE) modelling.

Variable	ITT (best-case/worst-case)		ITT (MICE)		PP	
	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Multivariable models I						
iCBT [ref.: no]	0.26 (-4.70, 5.21)	0.919	4.36 (-1.58, 10.30)	0.149	3.24 (-1.49, 7.97)	0.180
Baseline value (t0)	-0.09 (-0.25, 0.07)	0.279	0.00 (-0.20, 0.20)	0.978	-0.05 (-0.19, 0.10)	0.534
Multivariable models II						
iCBT [ref.: no]	-0.29 (-4.71, 4.14)	0.899	4.21 (-1.74, 10.16)	0.164	2.59 (-1.45, 6.64)	0.209
Both suffering from PTSD [ref.: no]	-0.12 (-0.26, 0.02)	0.088	-0.02 (-0.23, 0.18)	0.823	-0.07 (-0.21, 0.07)	0.329
Baseline value (t0)	-0.29 (-4.71, 4.14)	0.899	4.21 (-1.74, 10.16)	0.164	2.59 (-1.45, 6.64)	0.209
Multivariable models III						
iCBT [ref.: no]	0.01 (-4.08, 4.10)	0.996	5.20 (-0.87, 11.27)	0.092	2.84 (-1.28, 6.96)	0.176
Both suffering from PTSD [ref.: no]	-0.10 (-0.26, 0.06)	0.234	-0.02 (-0.25, 0.21)	0.846	-0.07 (-0.23, 0.10)	0.435
Baseline value (t0)	0.05 (-0.22, 0.32)	0.738	-0.08 (-0.44, 0.29)	0.678	0.05 (-0.32, 0.41)	0.800
Age, in years	2.03 (-3.88, 7.94)	0.500	2.91 (-4.16, 9.97)	0.419	4.00 (-2.41, 10.40)	0.221
Post-ICU patient [ref.: no]	-3.94 (-8.54, 0.67)	0.094	-2.91 (-8.91, 3.10)	0.342	-3.28 (-8.77, 2.20)	0.241
Pre-existing mental disorder [ref.: no]	0.01 (-4.08, 4.10)	0.996	5.20 (-0.87, 11.27)	0.092	2.84 (-1.28, 6.96)	0.176

Model coefficients (mean difference) together with 95% confidence intervals (CIs) and *p*-values are provided. Positive values indicate effects in favour of iCBT. Results from both intention-to-treat (ITT) approaches (best-case/worst-case as main analysis, multiple imputation by chained equations (MICE) as sensitivity analysis) and the per-protocol (PP) analyses (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were five participants in the iCBT group and none in the waitlist control group with missing information (missing BSI-18 change: 5, missing baseline value: 1; Supplemental Digital Content 1, Additional Figures A3 and A4). Abbreviations: iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; t0, time point at beginning of intervention/waiting.

Table S8. Results for EQ-5D-5L (Health questionnaire of the EuroQol group in five dimensions with five levels) change in utility values from generalised estimating equation (GEE) modelling.

Variable	ITT (best-case/worst-case)		ITT (MICE)		PP	
	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Multivariable models I						
iCBT [ref.: no]	0.04 (-0.07, 0.15)	0.499	-0.02 (-0.17, 0.13)	0.805	-0.01 (-0.12, 0.09)	0.777
Baseline value (t0)	0.19 (-0.07, 0.46)	0.150	0.27 (-0.02, 0.57)	0.065	0.24 (-0.07, 0.55)	0.133
Multivariable models II						
iCBT [ref.: no]	0.04 (-0.07, 0.15)	0.494	-0.02 (-0.18, 0.14)	0.800	-0.03 (-0.14, 0.09)	0.666
Both suffering from PTSD [ref.: no]	0.01 (-0.11, 0.14)	0.844	-0.02 (-0.16, 0.12)	0.775	-0.04 (-0.18, 0.09)	0.537
Baseline value (t0)	0.19 (-0.08, 0.45)	0.168	0.28 (0.00, 0.57)	0.050	0.27 (-0.04, 0.57)	0.091
Multivariable models III						
iCBT [ref.: no]	-0.01 (-0.11, 0.09)	0.865	-0.07 (-0.23, 0.09)	0.389	-0.07 (-0.18, 0.03)	0.172
Suffering from PTSD [ref.: no]	0.01 (-0.10, 0.11)	0.925	-0.02 (-0.15, 0.11)	0.772	-0.05 (-0.16, 0.06)	0.416
Baseline value (t0)	0.30 (-0.05, 0.64)	0.089	0.36 (-0.01, 0.73)	0.058	0.33 (-0.06, 0.71)	0.095
Age, in years	0.00 (0.00, 0.01)	0.424	0.00 (0.00, 0.01)	0.318	0.00 (0.00, 0.01)	0.375
Post-ICU patient [ref.: no]	0.05 (-0.12, 0.22)	0.553	0.04 (-0.15, 0.24)	0.671	0.02 (-0.16, 0.20)	0.811
Pre-existing mental disorder [ref.: no]	0.13 (0.02, 0.24)	0.018	0.10 (-0.03, 0.23)	0.124	0.11 (-0.01, 0.22)	0.064

Model coefficients (mean difference) together with 95% confidence intervals (CIs) and *p*-values are provided. Negative values indicate effects in favour of iCBT. Results from both intention-to-treat (ITT) approaches (best-case/worst-case as main analysis, multiple imputation by chained equations (MICE) as sensitivity analysis) and the per-protocol (PP) analyses (sensitivity analysis) are provided. For binary variables, the reference category (ref.) is provided. Note that there were five participants in the iCBT group and none in the waitlist control group with missing information (missing EQ-5D-5L change: 5, missing baseline value: 1; Supplemental Digital Content 1, Additional Figures A3 and A4). Abbreviations: iCBT,

internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; PTSD, post-traumatic stress disorder; t0, time point at beginning of intervention/waiting.

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Table S9. Between-group effect sizes (Cohen´s d, standardised mean differences) for pre-post changes in primary and secondary outcomes.

Variable	ITT (best-case/worst-case)	ITT (MICE)	PP
	d (95% CI)	*d* (95% CI)	*d* (95% CI)
Primary outcome			
PCL-5	-0.14 (-0.81, 0.54)	0.48 (-0.21, 1.16)	0.40 (-0.35, 1.16)
Secondary outcomes			
RAS	-1.67 (-2.45, -0.89)	-0.94 (-1.65, -0.23)	-1.10 (-1.90, -0.30)
BSI-18	0.04 (-0.64, 0.71)	0.51 (-0.17, 1.20)	0.54 (-0.22, 1.30)
EQ-5D-5L	-0.25 (-0.93, 0.42)	0.09 (-0.58, 0.77)	0.07 (-0.68, 0.83)

Effect sizes with 95% confidence intervals (CI) were derived from the main analyses with generalised estimating equation (GEE) modelling (Multivariable models I; Table 2, Supplemental Tables S5, S7, S8 in Supplemental Digital Content 2). Positive values indicate effects in favour of iCBT. Abbreviations: BSI-18, Brief Symptom Inventory-18; d, between-group effect size Cohen´s d; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; ITT, intention-to-treat; PCL-5, PTSD Checklist for DSM-5; PP, per protocol RAS, Relationship Satisfaction Scale.

Table S10. Within-group effect sizes (Cohen´s d, standardised mean differences) in iCBT and WL control group for pre-post changes in primary and secondary outcomes – stratified by presumptive PTSD diagnosis at t0.

Treatment group	Participants with presumptive PTSD diagnosis at t0						Participants without presumptive PTSD diagnosis at t0			
	Screening > t0		t0 > t1		t1 > t1+		Screening > t0		t0 > t1	
	N	*d* (95% CI)	*N*	*d* (95% CI)	*N*	*d* (95% CI)	*N*	*d* (95% CI)	*N*	*d* (95% CI)
Primary outcome: PCL-5										
iCBT group	15	0.42 (-0.17, 0.92)	**11**	**0.43 (0.37, 1.98)**		-	8	-0.26 (-1.31, 0.27)	6	0.30 (0.16, 2.61)
WL control group	18	0.43 (-0.07, 0.92)	18	0.35 (0.13, 1.17)	**14**	**1.01 (0.60, 2.11)**	8	-0.36 (-1.08, 0.44)	6	-0.04 (-0.93, 0.82)
Secondary outcome: RAS										
iCBT group		-	**11**	**-0.42 (-1.30, 0.06)**		-		-	5	-1.07 (-2.84, -0.05)
WL control group		-	18	0.14 (-0.09, 0.89)	**14**	**-0.24 (-1.02, 0.13)**		-	5	0.17 (-0.43, 1.74)
Secondary outcome: BSI-18										
iCBT group		-	**11**	**0.17 (-0.27, 1.01)**		-		-	6	0.47 (-0.25, 1.74)
WL control group		-	18	-0.09 (-0.64, 0.32)	**14**	**0.77 (0.08, 1.29)**		-	6	0.05 (-0.81, 0.94)
Secondary outcome: EQ-5D-5L										
iCBT group		-	**11**	**-0.05 (-0.78, 0.46)**		-		-	6	0.23 (-0.13, 1.95)
WL control group		-	18	-0.14 (-0.63, 0.33)	**14**	**0.71 (0.28, 1.59)**		-	6	-0.10 (-1.06, 0.70)

Effect sizes (Cohen´s *d*) with 95% confidence intervals (CI) are based on unadjusted means of the per-protocol population. Positive values indicate improvement to the subsequent time points (e.g., pre > post). Number of participants (*N*) with data at the respective compared time points are provided. Results are stratified for participants with / without presumptive PTSD diagnosis according to PCL-5 at t0 (PCL-5 > 35). Pre-post effect sizes for iCBT treatment are marked bold. Abbreviations: -, not applicable; BSI-18, Brief Symptom Inventory-18; d, effect size Cohen's d; EQ-5D-5L, Health questionnaire of the EuroQol group in five dimensions with five levels; iCBT, internet-based cognitive-behavioural writing therapy; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RAS, Relationship Assessment Scale; WL, waitlist; t0, start of intervention (iCBT group) / waiting (WL control group); t1, end of intervention (iCBT group) / waiting and beginning of intervention (WL control group); t1+ end of delayed intervention (WL control group).

Table S11. Number of participants with clinically relevant improvement in PCL-5 (i.e., improvement of at least 10 points) - stratified by treatment group and presumptive PTSD diagnosis at t0.

	Screening > t0	t0 > t1	t1 > t1+
Participants with presumptive PTSD diagnosis at t0			
iCBT group	5 / 15 (33.3%)	**3 / 11 (27.3%)**	-
WL control group	9 / 18 (50.0%)	5 / 18 (27.8%)	**8 / 14 (57.1%)**
Participants without PTSD diagnosis at t0			
iCBT group	0 / 8 (0.0%)	2 / 6 (33.3%)	-
WL control group	0 / 8 (0.0%)	1 / 6 (16.7%)	-

Number of participants with improvement to the subsequent time point (e.g., pre > post) as well as number of participants with data at the respective compared time points are provided (n / N) – accompanied by the respective relative frequency. Results are stratified for participants with / without presumptive PTSD diagnosis according to PCL-5 at t0 (PCL-5 > 35). Improvements during iCBT are marked bold. Abbreviations: -, not applicable; iCBT, internet-based cognitive-behavioural writing therapy; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; WL, waitlist; t0, start of intervention (iCBT group) / waiting (WL control group); t1, end of intervention (iCBT group) / waiting and beginning of intervention (WL control group); t1+ end of delayed intervention.

Table S12. Overview about safety variables - overall as well as stratified by treatment group.

Variable	Overall (*n* = 34)	Treatment group	
		iCBT (*n* = 16)	WL control (*n* = 18)
Number of suicide alerts			
False alarm; n	3	3	0
Caused by reasons not related to the study; n	2	0	2
Clinical relevant PCL-5 deterioration; *n* (%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Premature termination			
Between randomisation and t0; *n* (%)	1 (2.9%)	1 (6.3%)	0 (0.0%)
Between t0 and t1; *n* (%)	8 (23.5%)	6 (37.5%)	2 (11.1%)
Between t1 and t1+; *n* (%)	-	-	10 (55.6%)

The overall number of treated individuals (*n*) are provided. A PCL-5 (PTSD Checklist for DSM-5) change of 10 or more points is regarded as clinically relevant. Outcomes are summarised as absolute (*n*) and relative frequencies (%). Percentages refer to number of participants with information for the respective value. Values are provided for several time points: t0, start of intervention (iCBT group) / waiting (WL control group); t1, end of intervention (iCBT group) / waiting (WL control group); t1+, end of intervention in WL control group. Abbreviations: -, not applicable; iCBT, internet-based cognitive-behavioural writing therapy; WL, waitlist.

* missing for 9 participants (iCBT: 7 participants (post-ICU patient: 4, spouse: 3), WL control: 2 participants (spouse: 2))

Table S13. Overview about safety variables - overall as well as stratified by post-ICU patient/spouse status and by treatment group.

Variable	Post-ICU patient			Spouse		
	Overall (n = 21)	Treatment group		Overall (n = 13)	Treatment group	
		iCBT (n = 10)	WL control (n = 11)		iCBT (n = 6)	WL control (n = 7)
Number of suicide alerts						
False alarm; n	2	2	0	1	1	0
Caused by reasons not related to the study; n	2	0	2	0	0	0
Clinical relevant PCL-5 deterioration; n (%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Premature termination						
Between randomisation and t0; n (%)	1 (4.8%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Between t0 and t1; n (%)	3 (14.3%)	3 (30.0%)	0 (0.0%)	5 (38.5%)	3 (50.0%)	2 (28.6%)
Between t1 and t1+; n (%)	-	-	4 (36.4%)	-	-	6 (85.7%)

The overall number of treated individuals (n) are provided. A PCL-5 (PTSD Checklist for DSM-5) change of 10 or more points is regarded as clinically relevant. Outcomes are summarised as absolute (n) and relative frequencies (%). Percentages refer to number of participants with information for the respective value. Values are provided for several time points: t0, start of intervention (iCBT group) / waiting (WL control group); t1, end of intervention (iCBT group) / waiting (WL control group); t1+, end of intervention in WL control group. Abbreviations: -, not applicable; iCBT, internet-based cognitive-behavioural writing therapy; ICU, intensive care unit; WL, waitlist.

* missing for 9 patients (intervention: 7 participants (former ICU patient: 4, spouse: 3), waitlist: 2 participants (spouse: 2))

Table S14. Dyadic concordance in treatment effects in terms of PCL-5 (PTSD Checklist for DSM-5) change.

Dyad member suffering from PTSD	ITT (best-case/worst-case)	ITT (MICE)	PP
Only one	0.29 (-0.24, 0.68)	0.43 (-0.06, 0.92)	0.32 (-0.31, 0.76)
Both	-0.25 (-0.79, 0.49)	-0.06 (-0.95, 0.84)	-0.58 (-0.95, 0.44)

Spearman correlation together with 95% confidence intervals are provided. Analysis was stratified by the number of dyad members suffering from post-traumatic stress disorder (PTSD). Results from both intention-to-treat (ITT) approaches (best-case/worst-case substitution as main analysis, multiple imputation by chained equations (MICE) as sensitivity analysis) and the per-protocol (PP) analyses are provided. Note that there were nine participants with missing information on PCL-5 change (Supplemental Digital Content 1, Additional Figures A1 and A2).

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