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Effectiveness and cost-effectiveness of a guided internet- and mobile-based depression intervention for in individuals with chronic back pain: protocol of a multi-centre randomised controlled trial

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Abstract

Introduction: Depression often co-occurs with chronic back pain (CBP). Internet- and mobile-based interventions (IMIs) might be a promising approach for effectively treating depression in this patient group. In the present study, we will evaluate the effectiveness and cost-effectiveness of a guided depression IMI for individuals with CBP (eSano BackCare-D) integrated into orthopaedic health care.

Methods and analysis: In this multicentre randomised controlled trial (RCT) of parallel design, the groups eSano BackCare-D vs. treatment as usual will be compared. 210 participants with CBP and diagnosed depression will be recruited subsequent to orthopedic rehabilitation care. Assessments will be conducted prior to randomisation and 9 weeks (posttreatment) and 6 months after randomisation. The primary outcome is depression severity (HAM-D-17). Secondary outcomes are depression remission and response, health related quality of life, pain intensity, pain related disability, self-efficacy and work capacity. Demographic and medical variables as well as internet affinity, intervention adherence, intervention satisfaction and negative effects will also be assessed. Data will be analysed on an intention-to-treat basis and an additional per-protocol analysis. Moreover, a cost-effectiveness and cost-utility analysis will be conducted from a societal perspective after 6 months.

Discussion

The innovative approach of using an IMI to treat depression in people with CBP will substantially increase the likelihood of psychological interventions being accessible in routine health care.

Ethics and dissemination: All procedures are approved by the ethics committee of the Albert- Ludwigs-University of Freiburg and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung). The results will be published in peer-reviewed journals and presented on international conferences.

Registration details: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): (DRKS00009272).

Keywords: Guided self-help; Internet-based; Chronic back pain; Depression; after care; Randomised controlled trial, effectiveness, cost-effectiveness

Strengths and limitations of this study

- First trial examining the effectiveness of a depression IMI for individuals with CBP and comorbid depression.
- First trial examining the cost-effectiveness of a depression IMI for individuals with CBP and comorbid depression.
- IMI will be implemented as integrated part of the routine orthopaedic health care, thus overcoming the participant selection bias due to self-referral as one of the core limitation of most prior IMI trials.
- The IMI will take place after routine orthopaedic health care, examining the possibility to improve patients´ medical sector transitions by means of an e-mental-health offer.
- Use of standardised interviews for the diagnosis and use of clinical rating scales for the assessment of the severity level of depression (SKID and HAMD/QIDS).

Introduction

The two widespread conditions chronic back pain (CBP) and depression belong to the top ten causes of years lived with disability (YLDs) worldwide [1]. The global one-month adult prevalence for low back pain is estimated to be 23.2% and a substantial increase during the next decades can be expected [2]. Depression has been shown to be the leading cause of burden of diseases in middle- to high-income countries with a lifetime prevalence of about 14.6% [3]. A strong association between depression and CBP has been frequently reported with prevalence rates for depression ranging from 21% to 50% in back pain and chronic low back pain individuals [4]. Several systematic reviews highlight a significant prognostic association between comorbid depression and increased morbidity of different somatic conditions and health care costs as well as diminished quality of life [5–7]. Moreover, depression is one of the core predictors of persistent pain symptoms, increased pain-related disability, and poor treatment outcomes in pain patients [4, 8, 9].

There is strong evidence for the efficacy of psychological interventions for chronic pain [10] and especially for chronic low back pain [11] with regard to pain intensity or disability/interference. To the best of our knowledge however, there is no study that has examined the effects of psychological depression interventions for individuals with CBP and depression [12]. In order to improve health care for CBP individuals, internet- and mobile-based interventions (IMIs) are considered to be a promising approach [13, 14]. Among numerous meta-analyses highlighting the efficacy of IMIs with regard to the reduction of depressive symptoms [15–18], one meta-analysis quantified the superiority of online depression interventions

over waiting-list and treatment as usual (TAU) with standardised mean differences of d=-.68 (CI: -.85;-.52; n=8) and d=-.39 (CI:-.66;-.12; n=8) [15], albeit effect moderating factors of IMIs remain unclear [19]. As most trials used highly selective recruitment strategies, the evidence for the effectiveness of IMIs for depression (i.e., performance of an intervention when implemented within typical clinical practice, investigated by means of pragmatic trials) is far less conclusive [20] and many health systems have not included IMIs as an integrated treatment component. As an implemented part of a comprehensive care system, IMIs could reduce the deficiencies of most current health care systems in coordinating transitions of care, such as the transition from the inpatient to outpatient setting, where recommendations are regularly lost in transition [21–23].

The present WARD-BP study (**w**eb-based **a**ftercare depression intervention following **r**ehabilitation for individuals with **d**epression and chronic **b**ack **p**ain) aims to investigate the effectiveness and cost-effectiveness of the depression IMI "eSano BackCare-D" in a study population of CBP with a diagnosed depression in the aftermath of orthopaedic rehabilitation care. The primary research question is:

1) Is eSano BackCare-D effective in reducing depression in individuals with CBP and diagnosed depression compared to treatment as usual (TAU)?

Secondary research questions are:

2) Is eSano BackCare-D effective with regard to depression remission and response, health related quality of life, pain intensity, pain related disability, self-efficacy and work capacity in individuals with CBP and diagnosed depression compared to TAU?

3) Is eSano BackCare-D cost-effective in individuals with CBP and diagnosed depression compared to TAU from a societal perspective?

4) Which factors moderate and mediate the effects of eSano BackCare-D?

Methods and analysis

Study design

WARD-BP is a multi-centre pragmatic randomised controlled clinical trial (RCT) of parallel design. All participants receive TAU. We conduct assessments in both groups before randomisation (T0), nine weeks (T1= post treatment in case of regular IMI use) and six months (T2) after randomisation. Trial participants receive 15€ per completed post- and follow-up telephone assessment, see figure 1 for study flow. We conduct and report the RCT in accordance with the CONSORT 2010 Statement [24], the supplement of the CONSORT statement for pragmatic effectiveness trials [24, 25] and current guidelines for executing and reporting In-

ternet intervention research [26]. All procedures are approved by the ethics committee of the Albert-Ludwigs-University of Freiburg and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung). The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): (DRKS00009272).

- Figure 1 about here –

Randomisation

Randomisation and allocation of participants to the two groups (intervention or TAU) was prepared in advance by an independent researcher (SaS) by means of a web-based program (https://www.sealedenvelope.com/) using permuted block randomisation with variable block sizes of 4,6,8 (randomly arranged), ratio of 1:1. Participants are stratified by center. Centers are all eight orthopedic clinics where recruitment is conducted personally and a ninth (meta-)clinic, which includes all participants recruited by letter (see recruitment). An independent researcher SaS is responsible for the allocation as well as the administration of the trial and participants to trial arms and is blinded to the treatment content.

Recruitment

Recruitment has started in October 2015. Using the Patient Health Questionnaire (PHQ-9; 27), we conduct two consecutive depression screenings within 2-3 weeks. In case of only one positive screening (PHQ ≥ 5), a third PHQ will be administered two months later via telephone interview. We recruit potential participants in orthopaedic rehabilitation units in Germany with two different recruitment strategies.

In the first recruitment setting (personal recruitment), patients with two positive screenings receive information on the intervention by clinic staff during their orthopedic care. Patients providing their informed consent (model consent form available on request) are contacted by the study team in order to clarify further eligibility criteria by means of an online- and telephone assessment including a telephone administered clinical interview. Recruitment efforts (i.e. selection of back pain patients, screening procedure, informed consent, documentation according to CONSORT, providing access to medical records) are completed by the clinic staff who are compensated with a case payment of 320€ per randomised participant. The second recruitment strategy (recruitment by letter) involves a letter with information flyers and

study process for back pain patients after discharge from orthopaedic rehabilitation units across Germany with a link to fill out an online PHQ-screening. Individuals screened positive, providing informed consent are contacted for the second PHQ-screening and a clinical interview via telephone equivalent to the first recruitment strategy.

Inclusion/exclusion criteria

We include patients if they fulfil the following inclusion criteria: 1) age 18 years or older, 2) CBP assessed by physician for at least six months assessed during telephone interview, 3) mild to moderate depression or dysthymia according to SCID assessment, assessed during telephone interview 4) sufficient knowledge of German language, 5) Internet and PC access. Patients are excluded in case of 6) receiving ongoing psychotherapy or beginning psychotherapy within the next three months, 7) being currently suicidal or reporting suicidal attempts in the past five years or 8) a current diagnosis of severe depression (ICD-10 F32.2/F32.3/F33.2/F33.3 diagnosis), see table 1. The exclusion of individuals with severe depression is due to ethical concerns and based on ICD-10 criteria for severe depression according to the German treatment guidelines for depression [28]. A trained psychotherapist (HB, LS, EM or SaS) contacts the participant to initiate further actions when severe depression is classified. We invite participants with a depression severity of PHQ $\geq$ 5, who do not fulfil the criteria to participate, in a parallel conducted trial for CBP and subclinical depressive symptoms: eSano BackCare-DP [29].

Procedure on suicidal ideation

Participants who are currently suffering from suicidal ideation are identified by suicide screenings within the telephone interviews (SCID, HAM-D, QIDS) and questionnaires (PHQ-9). Following a suicide protocol adapted from prior trials [30–32] we send an email with detailed information on available health services and the advice to seek professional help if participants report low suicidal ideation (HAM-D, QIDS or PHQ-9 item score = 1). In case of moderate to high suicidal ideation during the assessments or any suicidal thoughts or intentions reported to an eCoach or the study administration, a trained psychotherapist from the study team (HB, LS, EM or SaS) contacts the participant and initiate further actions, including the possibility to amend or terminate the intervention as well as unblinding respective study participants.

- Table 1 about here -

Intervention development

eSano BackCare-D is based on cognitive behaviour therapy (CBT), systematic behavioural activation [33–35] and problem solving [36]. The depression-specific components are based upon a prior IMI "GET.ON Mood Enhancer", that has been evaluated in numerous RCTs in different samples [32, 37, 38] and shown to be effective in lowering depressive symptoms in individuals with diabetes mellitus type 1 and 2 with an intention to treat (ITT) effect size of d=0.89 at two-months post treatment [37]and d=0.83 at 6 months follow up [39]. We added CBP-relevant information, videos and audio clips, based on existing literature on psychological back pain treatment [40, 41], our clinical experience, and an existing IMI for chronic pain individuals based on acceptance and commitment therapy [42]. Think-aloud interviews with five persons with CBP helped us to further improve the feasibility and acceptability. Access to the platform proceeds through a unique username password combination and is available on a 24/7 basis. All transferred data are secured via www.minddistrict.com based on ISO27001 and guidelines NEN7510.

Intervention content

eSano BackCare-D provides six minimally guided sessions with an estimated proceeding duration of 45-60 minutes each, developed to be processed weekly. Three optional sessions with back pain specific topics (sleep, partnership and sexuality, returning to work) are available at the end of sessions 3 through 5. Two booster sessions following the intervention are offered to improve sustainability of intervention effects. Session-specific contents and homework assignments are shown in table 2.

Session 1 provides psychoeducational information on depression, the interaction between CBP and depression as well as pain acceptance. Participants define their depression- and CBP-related goals and get to know the mood diary as the homework assignment for the next week. In session 2, the concept of behavioural activation and the connection between pleasant activities and mood is introduced. Based on the principles of action planning and coping planning [43, 44], participants create an individual list and schedule for completion of pleasant activities in the next few days. The main focus in sessions 3 and 4 is on the six-step plan to handle solvable problems and to better manage emerging issues, comparable to other studies [37, 45–47]. In addition, techniques to reduce rumination on unsolvable problems and the concept of mindfulness are introduced. Session 5 includes information and exercises on physical activity [33], a mindfulness exercise and techniques to strengthen self-esteem. The sixth

session serves to assess intervention-related changes in mood and provides a list of additional treatment options. Participants are encouraged to create a plan for the future. At the end, they write a letter to themselves about specific goals for the next four weeks and choose the date of the next booster session (after two, four or six weeks) that are developed to review what the participants have learned in previous sessions and to provide motivation to maintain and expand learned skills in the future.

The sleep session builds on an evidence based IMI for insomnia, i.e: GET.ON Recovery [48, 49]. As insomnia is a predictor and symptom of depression [50], participants learn about the principles of sleep hygiene, sleep restriction and stimulus control [51]. The partnership and sexuality session provides communication skills and exercises for improving physical closeness and sexuality. In the returning to work session, participants receive information on self-management and interpersonal competences as well as exercises in problem-solving and physical relaxation.

- Table 2 about here –

Text message coach

The text message coach in eSano BackCare-D automatically sends one supportive text message per day for the duration of six weeks as text message prompts have been shown to increase efficacy and adherence of IMIs [52–54]. The contents include a) reminders to complete the weekly assignments, b) repetition of the content, and c) motivation enhancement components.

Guidance

Based on previous studies showing that guidance and reminders and strict deadlines seem to be important with regard to the respective primary outcomes and adherence in IMIs [15, 55–57] the feedback manual of eSano BackCare-D provides instructions to remind, set deadlines and formulate standardised feedback for each session. Trained and supervised eCoaches (psychologists) serve as contact person and provide feedback within two work days after each completed session. Feedbacks are adapted to the participants' assignments and include positive reinforcement for completion of assignments and encouragement to proceed with the time spent on guidance will be approximately 60-100 minutes per participant.

Control condition

Participants have unrestricted access to TAU. All types of medical/psychological help received during the last three month are tracked at T0 and T2 with the Trimbos/iMTA questionnaire for costs associated with psychiatric illness [58].

Proposed sample size/power calculations

The sample size calculation is based on the primary endpoint, the HAM-D score at post treatment. According to the results of trials on online interventions for depression [15], a treatment effect (pooled effect size) of d=0.39 would be of clinical interest and is considered feasible for the type of treatment. On the basis of a two-sample t-test at two-sided significance level of 0.05, the study is planned to detect this effect with 80% power. This requires a sample of 105 individuals in each arm.

Assessments

Depression screening. Depressive symptoms are assessed by the Patient Health Questionnaire (PHQ-9) which is a well validated depression screening instrument that has also been evaluated to be delivered as online-version [59], with a Cronbach's alpha of .89 and 88% sensitivity and 88% specificity for major depression [60].

Depression diagnosis. The 17-item HAM-D is the most widely used clinician-rated measure of depression severity and as such viewed as the gold standard for the assessment of depression severity. Additionally, we use the Quick Inventory of Depressive Symptomatology (QIDS [61]) which assesses the severity of depressive symptoms, covering all criterion symptom domains of the DSM-IV to diagnose a major depressive episode [61]. Moreover we use Section A (Affective Syndromes) of the Structured Clinical Interview (SCID; 62) as a comprehensive, structured interview designed to be used by trained interviewers for the assessment of mental disorders according to the definitions and criteria of DSM. It enables a reliable, valid and efficient assessment of depressive disorders [63]. As an add-on to the SCID for DSM-IV, we use a German translation of the SCID-V-RV to allow for DSM-V [64] diagnoses as well.

Interviewers are trained and weekly supervised by a psychologist (LS, EM) and are blinded to randomisation condition. After an initial training session, a supervisor and the interviewers assess the same participant together, with comparison of results as follows: The Inter-Rater Reliability (IRR) for the SCID, measured by *Cohen's kappa* and the *Intra-Class Correlation* for the HAM-D and QIDS. An almost perfect Cohen's kappa ≥ .81 [65] and an excellent ICC coefficient ≥ .75 [66] is considered as sufficient. Each interviewer is compared to trainers´

rating (LS, EM) until the sufficient IRR values are met. Afterwards, the interviewers are compared to each other on a random basis to assess the IRR.

Primary outcome

Depression severity. Depression severity is the core patient-relevant outcome in trials among depressed individuals [67, 68] and is assessed by means of the clinician-rated Hamilton Rating Scale for Depression (HAM-D-17; 69) (see table 1) at post-treatment (T1).

Secondary outcomes

Depression response and remission. HAM-D scores are used to determine depression response in accordance to the recommendations of Riedel and colleagues [70]. Depression remission are assessed with all measures to diagnose a major depressive episode (HAM-D /SCID/QIDS).

Health related quality of life (QoL). The AQoL-6D includes 20 items and six dimensions and is suitable for quality of life assessments and economic evaluations of health programs with good psychometric properties [71] and a Cronbach's alpha of .89 [72]. We additionally obtain the most widely used quality of life assessment EuroQol (EQ-5D-5L) as a basis for cost-utility analyses with five health domains of importance to quality of life [73].

Pain intensity. We use an 11-point numerical rating (0-10) of the worst, least and average pain during the last week as well as the current pain level and calculate the mean of the four scales. Additionally, we use a categorical rating of pain intensity (none, mild, moderate, severe).

Pain related disability. We obtain the Oswestry Disability Index (ODI) [74] as a reliable ($\alpha = .86$; [75]) and valid 10 item self-report questionnaire, sensitive to change in difficulties in completing activities of daily living [74].

Pain self-efficacy. The Pain Self-Efficacy Questionnaire (PSEQ) is a validated and reliable (internal consistency: $\alpha = 0.93$) 10 item instrument that assesses self-efficacy expectations related to pain [76].

Work capacity. The subjective prognostic employment scale (SPE) is a validated 3-item self-report questionnaire (sum score 0-3) with high internal consistency (rep (Guttman scaling) = .99; [77]).

Intervention adherence. The attrition rate (calculated using the percentage of individuals who no longer use the intervention, as assessed by their log in data) gives an estimate of the individuals' intervention adherence.

Patient satisfaction.

The Client Satisfaction Questionnaire (CSQ-8, German: ZUF-8), optimised for the assessment of client satisfaction in IMIs (CSIQ-8) [78] is a validated 8 item instrument with high internal consistency (α = 0.92) [79]. The adapted version for the assessment of client satisfaction in IMIs has shown to have high internal consistency in a range of studies (α = 0.92-0.94) [48, 80, 81] and to be associated with treatment adherence and outcome.

Negative effects of psychotherapy. We include different ways of monitoring serious adverse events (SAE) adapted from the National Institute for Health Research recommendations [82] and Horigian et al. [83] who give general principles and examples to help illustrate their definition of SAEs: participants´ responses in interviews, reported SAEs to the eCoach and SAEs assessed by means of the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) during the online assessments [84]. The INEP consists of 15 items assessing a range of common changes participants experienced in line with the intervention. Cronbach's alpha is α = 0.86 [84]. At the beginning of every session, participants are asked about adverse events and are also encouraged to report the events to their eCoach who monitors the SAEs and initiates further actions if needed.

Costs.
We use the German version of the Cost Questionnaire "Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness" (TiC-P; 58), adapted for the German health care system by Nobis and colleagues [30] and for CBP individuals by the present authors. The TiC-P allows assessment of all direct healthcare services received during the last three months. Moreover, direct non-medical costs (e.g. parking costs) and indirect costs are assessed, including the number of 'work loss' days (absenteeism), the number of 'work cut-back' days (presentism) and costs associated with domestic tasks.

Covariates. Demographic variables, prior depression treatments, and internet affinity level are assessed by patient self-report, see table 1. We use the German version of the Internet Affinity Scale (IAS) by Haase and colleagues [85] to assess familiarity with the Internet. Depression type (Major Depression yes/no), baseline severity and depression chronicity are assessed by the SCID, back pain type, severity and chronicity are extracted from medical records.

Statistical Analysis

Clinical analyses. The primary endpoint will be analysed with the HAM-D score at T1 as dependent variable and baseline value as covariates, adjusting for sex and age. Continuous

secondary outcomes will be analysed accordingly. Standardised mean differences and 95% confidence intervals will be calculated to measure the between-group effect size at post-treatment and follow-up. Additionally, clinical significance analyses, such as number needed to treat (NNT) will be conducted. All analyses will be performed on an intention-to-treat (ITT) principle with multiple imputations to replace missing data [86]. Completer analyses (per-protocol) will be conducted to investigate the influence of study attrition on study results. Rates of patient-reported adverse events will be compared.

Economic evaluation. We will conduct a cost-effectiveness analysis (CEA), a cost-utility analysis (CUA) and the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) after six months. A cost-effectiveness analysis with depression response, defined by Riedel and colleagues [70], as clinical outcome and a cost-utility analysis with quality-adjusted life-years (QALYs) will be conducted from a societal perspective including all direct and indirect costs. Bootstrapping methods will be applied to estimate nonparametric confidence intervals for mean differences in costs and outcomes between the groups. Further, we will calculate a cost-acceptability curve to test the likelihood that the intervention is cost-effective relative to TAU, given varying threshold for the willingness to pay for one depression response or gained QALY, respectively.

Quality assurance and safety

The Clinical Trials Unit Freiburg performs monitoring visits to the participating clinic centres before, during and after completion of the study to ensure that the study is conducted, recorded and reported according to the study protocol, relevant standard operating procedures (SOPs), and requirements of the sponsor and/or the Ethic Committees in accordance with ICH-GCP. Rigorous operating procedures for data management and safety have been implemented.

Furthermore, an independent Data Safety and Monitoring Board (DSMB) consisting of two experienced scientists and psychotherapists (MHä, MHa) and one statistician (LK) with long-standing experience in clinical trials has been established. The function of the DSMB is to monitor the course of the study and, if necessary, to give recommendations to the steering committee for discontinuation, modification or continuation of the study.

Discussion and conclusions

The present effectiveness and cost-effectiveness trial focusses on individuals with CBP and comorbid depression as two of the most frequent, most disabling health conditions with high associated economic burden [7, 87].

The WARD-BP trial is innovative in several ways: a) Studies examining the effectiveness of psychological depression interventions are regularly methodologically limited as they lack diagnostic clarification of depression status [15, 67, 88]. By carrying out the SCID and HAM-D prior to randomization and at follow-up assessments, the present trial will be the first trial on a psychological depression intervention for people with chronic pain with verified DSM diagnosis of depression. b) With a target sample of 210 participants, the study will be optimally powered, overcoming limitations of small scale trials on psychological depression interventions in the medically ill [12, 67, 88]. c) The eSano BackCare-D intervention is tailored to the special needs of the target group of chronic back pain patients. This has been discussed as having an uptake and adherence facilitating effect [89], likely to improve the effectiveness of online interventions. d) The implementation of the intervention into the health-care system overcomes one of the main criticisms regarding IMI trial being only representative for a selective online population [90, 91]. e) The current trial design will allow examination of the reach of this IMI and will provide valuable information about which CBP individuals are willing to utilise such interventions. With the use of two different recruitment strategies, we will be able to compare two different ways of implementing IMIs into clinical routine. This will allow for conclusions on feasible ways of improving the adherence and uptake of IMIs in respective target populations [92–94]. f) Finally, as one of still few clinical trials on psychological depression interventions the present trial comprises a cost-effectiveness analysis.

If the results of WARD-BP indicate that eSano BackCare-D is effective and cost-effective, its clinical impact on depression health care services could be substantial. When implemented as part of the standard health care, IMIs have the potential to reduce the “lost in transition phenomenon” caused by fragmented health care systems [21, 95, 96]. Engaging individuals in treatment at the interface of different health care sectors, as in the present (cost-)effectiveness trial, will contribute important information on potential approaches to improve the delivery of mental health care and at the same time provide insights on possible ways of implementing depression IMIs into chronic back pain care in order to exploit their full potential. The first results of WARD-BP are expected in 2018, which will be published in peer-reviewed journals and disseminated broadly to healthcare professionals, the public, and other relevant groups.

Authors' contributions

HB, DE, MB, OM and HR initiated this study. All authors contributed to the design of this study. HB, LS, SP, DE, SaS, DL, SN, JB, HR, MB and JL developed the intervention content or intervention content eSano BackCare-D is based on as well as the assessment. HB, LS, SP, SaS, DE, and JL are responsible for recruitment. SaS is responsible for randomisation and allocation as well as the administration of participants. JL wrote the draft of the manuscript. HB provided expertise on depression, CBP and psychological pain interventions. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

Conflict of interest

A committee of independent scientists has been formed (Data Safety and Monitoring Board (DSMB)) to supervise study-related decisions and prevent any influence of a potential conflict of interest.

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Table 1: Key variables and measurements

Variables	Measurement	Depression screenings			T0	T1	T2
		1	2	3			
Inclusion/exclusion criteria							
Chronic back pain	MR + TI	x			x		
Mild to moderate depression or dysthymia	PHQ-9/HAM-D/QIDS/SCID				x	x	x
Severe depression (ICD-10 F32.2/F32.3/F33.2/F33.3 diagnosis)	SCID				x	x	x
Suicidality	HAM-D/QIDS/SCID				x	x	x
	PHQ-9	x	x	x	x	x	x
Further inclusion and exclusion criteria 1, 4, 5 and 6	SRQ +TI	x			x		
Primary outcome							
Depression severity	HAM-D				x	x	x
Secondary outcomes							
Depression remission and response	HAM-D /SCID/QIDS				x	x	x
Quality of life	AQol-6D/ EQ-5D-5L				x	x	x
Pain intensity	Numerical Rating scale				x	x	x
Pain related disability	ODI				x	x	x
Pain self-efficacy	PSEQ				x	x	x
Work capacity	SPE				x	x	x
Measurements for the economic evaluation							
Costs	TiC-P				x		x
Quality of life	AQol-6D/ EQ-5D-5L				x	x	x
Covariates							
Demographic variables	SRQ/MR	x			x		
Depression type and chronicity	SCID				x	x	x
Prior depression treatment	TI				x	x	
Back Pain type and chronicity	MR	x			x		
Internet affinity	IAS				x	x	
Patient adherence *	attrition rate				x	x	
Patient satisfaction *	CSQ-8					x	
Negative effects of the intervention	INEP/SRQ/TI/SReC					x	

AQol-6D = Assessment of Quality of Life; CSQ-8 = Client Satisfaction Questionnaire; EQ-5D-5L = European Quality of Life scale; HAM-D = Hamilton Rating Scale for Depression ; IAS=Internet Affinity Scale; INEP = Inventory for the Assessment of Negative Effects of Psychotherapy; MR = Medical record; ODI= Oswestry Disability Index, PHQ-9= Patient Health Questionnaire-9; PSEQ= Pain Self-Efficacy Questionnaire; SCID = Structured Clinical Interview; SPE = Subjective Prognostic Employment scale; SReC = self-report during treatment to the eCoach; SRQ = self-report assessment questionnaire, TI = telephone interview; TiC-P=Trimbos/iMTA questionnaire for costs associated with psychiatric illness. * intervention group only

Table 2 Overview of the sessions

Session	Depression-specific topics	Back pain-specific topics	Assignments
1	Psychoeducational information about depression	Connection between back pain and depression Pain acceptance	To write down medical history and set goals Homework assignment: mood diary
2	Behavioural activation Information on connection between behaviour and mood	Worrying about back pain-related complications	To create an activity plan Homework assignment: to complete the activation plan.
3	Problem solving I Introduction in problem solving. Information on solvable and unsolvable problems		To work with the 6 problem solving steps based on own problems Homework assignment: to implement the problem solving steps during the week
4	Problem solving II Information about techniques to reduce rumination. Introduction to mindfulness	Rumination about back pain	To review the problem solving steps and implement a technique to stop rumination Homework assignment: to practise and track mindfulness exercises
5	Behavioural activation, focus on physical activity and self-esteem. Connection between mood and movement	Physical activity and back pain. Connection between back pain and physical rest	To raise awareness of successes and strengths. To learn to value oneself Homework assignment: to implement physical activity in daily life
6	Plan for the future Collection of pleasant activities	Conversation with a General Practitioner	To improve patient-physician relationship Homework assignment: to implement positive activities and create a future plan
Additional (optional) sessions			
a	Healthy sleep Information on sleep hygiene, sleep restriction and stimulus control		To implement the 10 rules for healthy sleep into daily life
b	Partnership and sexuality Information on communication skills, physical closeness and sexuality		To implement communication skills and massage exercises in daily life
c	Returning to the workplace Information on self-management and interpersonal competencies	Fitness exercises at the workplace	To set priorities, to implement the 6 steps for problem-solving at the workplace, and to review communication skills
Booster sessions (within 3 months after the regular sessions)			
7	Summary: behavioural activation; review; pleasant activities; problem solving		To reflect on positive changes and update the activity plan; to practice the 6 steps for problem -solving
8	Summary of the key elements, behavioural activation		Choice of the intervention topics (1-6 above)

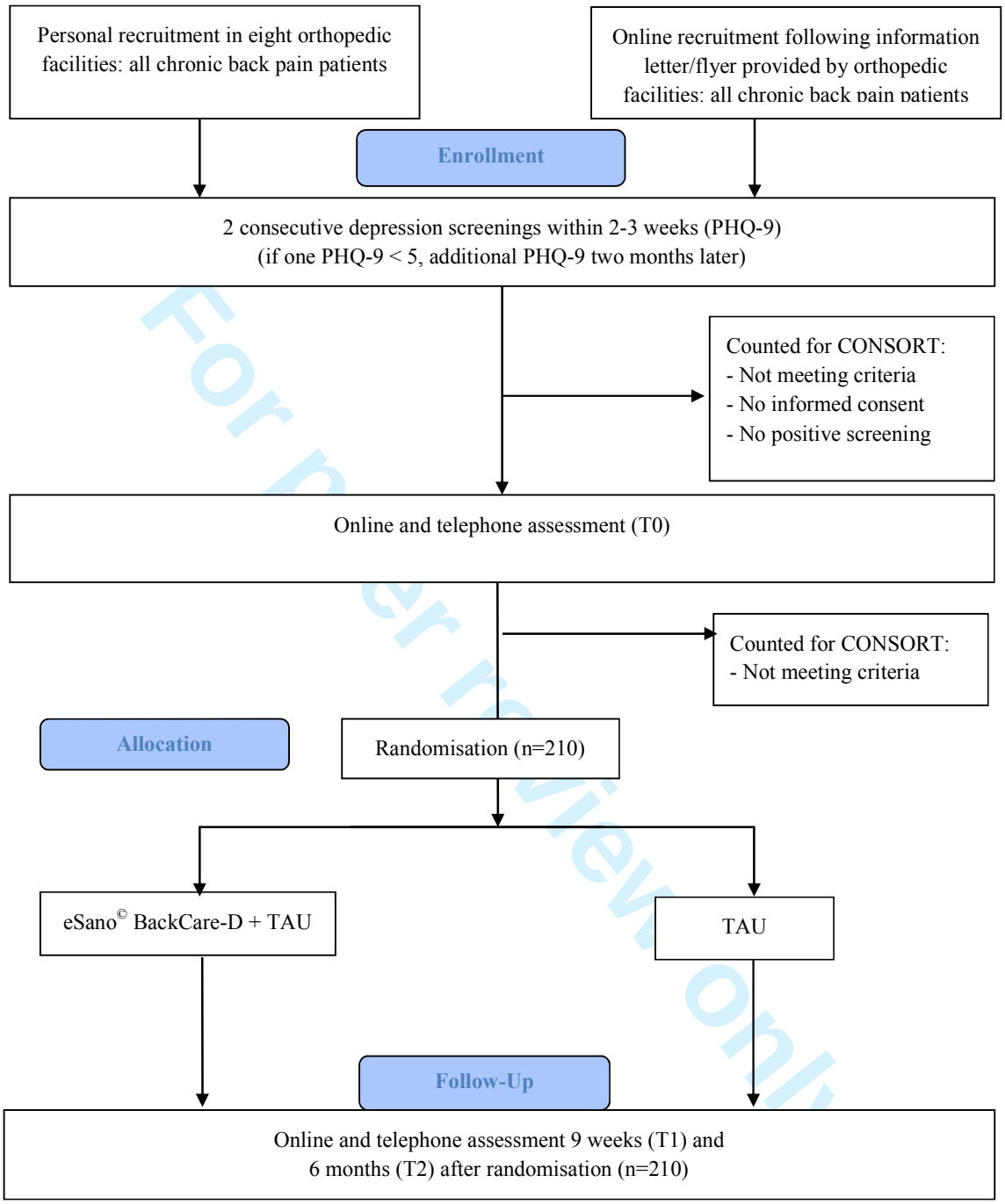

Figure 1. study flow

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

Section/item	Item No	Description	Page NO in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	(5/10)
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			6

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6,10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5,10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6-7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6-7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 / n.a.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	6
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

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

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Effectiveness and cost-effectiveness of a guided internet- and mobile-based depression intervention for in individuals with chronic back pain: protocol of a multi-centre randomised controlled trial

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Effectiveness and cost-effectiveness of a guided internet- and mobile-based depression intervention for individuals with chronic back pain: protocol of a multi-centre randomised controlled trial

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Abstract

Introduction: Depression often co-occurs with chronic back pain (CBP). Internet- and mobile-based interventions (IMIs) might be a promising approach for effectively treating depression in this patient group. In the present study, we will evaluate the effectiveness and cost-effectiveness of a guided depression IMI for individuals with CBP (eSano BackCare-D) integrated into orthopaedic health care.

Methods and analysis: In this multicentre randomised controlled trial (RCT) of parallel design, the groups eSano BackCare-D vs. treatment as usual will be compared. 210 participants with CBP and diagnosed depression will be recruited subsequent to orthopedic rehabilitation care. Assessments will be conducted prior to randomisation and 9 weeks (posttreatment) and 6 months after randomisation. The primary outcome is depression severity (HAM-D-17). Secondary outcomes are depression remission and response, health related quality of life, pain intensity, pain related disability, self-efficacy and work capacity. Demographic and medical variables as well as internet affinity, intervention adherence, intervention satisfaction and negative effects will also be assessed. Data will be analysed on an intention-to-treat basis and an additional per-protocol analysis. Moreover, a cost-effectiveness and cost-utility analysis will be conducted from a societal perspective after 6 months.

Discussion

The innovative approach of using an IMI to treat depression in people with CBP will substantially increase the likelihood of psychological interventions being accessible in routine health care.

Ethics and dissemination: All procedures are approved by the ethics committee of the Albert- Ludwigs-University of Freiburg and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung). The results will be published in peer-reviewed journals and presented on international conferences.

Registration details: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): (DRKS00009272).

Keywords: Guided self-help; Internet-based; Chronic back pain; Depression; after care; Randomised controlled trial, effectiveness, cost-effectiveness

Strengths and limitations of this study

- This is a protocol for the first large scale, multi-centre RCT examining the effectiveness of a depression IMI for individuals with CBP and depression.
- This is the first trial examining the cost-effectiveness of a depression IMI for individuals with CBP and depression.
- The IMI will be implemented as integrated part of routine orthopaedic health care, thus overcoming the self-referral bias of most prior IMI trials.
- The IMI will take place after routine orthopaedic health care, examining the possibility to improve patients´ medical sector transitions by means of an e-mental-health offer.
- We use standardised interviews for the diagnosis and clinical rating scales for the assessment of the severity level of depression (SKID and HAMD/QIDS).

Introduction

The two widespread conditions chronic back pain (CBP) and depression belong to the top ten causes of years lived with disability (YLDs) worldwide [1]. The global one-month adult prevalence for low back pain is estimated to be 23.2% and a substantial increase during the next decades can be expected [2]. Depression has been shown to be the leading cause of burden of diseases in middle- to high-income countries with a lifetime prevalence of about 14.6% [3]. A strong association between depression and CBP has been frequently reported with prevalence rates for depression ranging from 21% to 50% in back pain and chronic low back pain individuals [4]. Several systematic reviews highlight a significant prognostic association between comorbid depression and increased morbidity of different somatic conditions and health care costs as well as diminished quality of life [5–7]. Moreover, depression is one of the core predictors of persistent pain symptoms, increased pain-related disability, and poor treatment outcomes in pain patients [4, 8, 9].

There is strong evidence for the efficacy of psychological interventions for chronic pain [10] and especially for chronic low back pain [11] aiming at pain intensity or disability/interference as primary outcomes. To the best of our knowledge however, there is no study that has examined the effects of psychological depression interventions in the population of CBP focussing on depression as the primary outcome [12]. Indeed, the evidence on depression treatments for patients with chronic pain and clinical depression is very limited, mostly relying on a few collaborative/stepped care trials conducted in the last two decades [13–15].

In order to improve health care for CBP individuals, internet- and mobile-based interventions (IMIs) are considered to be a promising approach [16, 17]. Among numerous meta-analyses

highlighting the efficacy of IMIs with regard to the reduction of depressive symptoms [18–21], one meta-analysis quantified the superiority of online depression interventions over waiting-list and treatment as usual (TAU) with standardised mean differences of d=-.68 (CI: -.85;-.52; n=8) and d=-.39 (CI:-.66;-.12; n=8) [20], albeit effect moderating factors of IMIs remain unclear [22]. As most trials used highly selective recruitment strategies, the evidence for the effectiveness of IMIs for depression (i.e., performance of an intervention when implemented within typical clinical practice, investigated by means of pragmatic trials) is far less conclusive [23] and many health systems have not included IMIs as an integrated treatment component. As an implemented part of a comprehensive care system, IMIs could reduce the deficiencies of most current health care systems in coordinating transitions of care, such as the transition from the inpatient to outpatient setting, where recommendations are regularly lost in transition [24–26].

The present WARD-BP study (**w**eb-based **a**ftercare depression intervention following **r**ehabilitation for individuals with **d**epression and chronic **b**ack **p**ain) aims to investigate the effectiveness and cost-effectiveness of the depression IMI "eSano BackCare-D" in a study population of CBP with a diagnosed depression in the aftermath of orthopaedic rehabilitation care. The primary research question is:

1) Is eSano BackCare-D effective in reducing depression in individuals with CBP and diagnosed depression compared to treatment as usual (TAU)?

Secondary research questions are:

2) Is eSano BackCare-D effective with regard to depression remission and response, health related quality of life, pain intensity, pain related disability, self-efficacy and work capacity in individuals with CBP and diagnosed depression compared to TAU?

3) Is eSano BackCare-D cost-effective in individuals with CBP and diagnosed depression compared to TAU from a societal perspective?

4) Which factors moderate and mediate the effects of eSano BackCare-D?

Methods and analysis

Study design

WARD-BP is a multi-centre pragmatic randomised controlled clinical trial (RCT) of parallel design. All participants receive TAU. We conduct assessments in both groups before randomisation (T0), nine weeks (T1= post treatment in case of regular IMI use) and six months (T2) after randomisation. Trial participants receive 15€ per completed post- and follow-up telephone assessment, see figure 1 for study flow.

- Figure 1 about here –

Randomisation

Randomisation and allocation of participants to the two groups (intervention or TAU) was prepared in advance by an independent researcher (SaS) by means of a web-based program (https://www.sealedenvelope.com/) using permuted block randomisation with variable block sizes of 4,6,8 (randomly arranged), ratio of 1:1. Participants are stratified by center. Centers are all eight orthopedic clinics where recruitment is conducted personally and a ninth (meta-)clinic, which includes all participants recruited by letter (see recruitment).The independent researcher (SaS) is responsible for the allocation of participants to trial arms as well as the administration of the trial and is blinded to the treatment process and assessments of the participants.

Recruitment

Recruitment has started in October 2015 and is planned to end in July 2017. While this study protocol has been submitted for publication after start of recruitment (due to usual writing-up, commenting and approving procedures by all co-authors), clinical trial registry took place a-priori to recruitment start.

Using the Patient Health Questionnaire (PHQ-9; [27]), we conduct two consecutive depression screenings within 2-3 weeks. In case of only one positive screening (PHQ $\geq$ 5), a third PHQ will be administered two months later via telephone interview. We recruit potential participants in orthopaedic rehabilitation units in Germany with two different recruitment strategies.

In the first recruitment setting (personal recruitment), patients with two positive screenings receive information on the intervention by clinic staff during their orthopedic care. Patients providing their informed consent are contacted by the study team in order to clarify further eligibility criteria by means of an online- and telephone assessment including a telephone administered clinical interview. The participating clinics are compensated for their recruitment efforts (i.e. selection of back pain patients, screening procedure, informed consent, documentation according to CONSORT, providing access to medical records) with 320€ per randomised participant. The second recruitment strategy (recruitment by letter) involves a letter with information flyers and study process for back pain patients after discharge from

orthopaedic rehabilitation units across Germany with a link to fill out an online PHQ-screening. Individuals screened positive, providing informed consent are contacted for the second PHQ-screening and a clinical interview via telephone equivalent to the first recruitment strategy.

Inclusion/exclusion criteria

We include patients if they fulfil the following inclusion criteria:

1) age 18 years or older

2) CBP assessed by physician for at least six months assessed during telephone interview

3) mild to moderate depression or dysthymia according to SCID assessment, assessed during telephone interview

4) sufficient knowledge of German language

5) Internet and PC access.

Patients are excluded in case of :

6) receiving ongoing psychotherapy or beginning psychotherapy within the next three months,

7) being currently suicidal or reporting suicidal attempts in the past five years assessed during telephone interview or

8) a current diagnosis of severe depression (ICD-10 F32.2/F32.3/F33.2/F33.3 diagnosis) assessed during telephone interview, see table 1.

The exclusion of individuals with severe depression is due to ethical concerns and based on ICD-10 criteria for severe depression according to the German treatment guidelines for depression [28]. A trained psychotherapist (HB, LS, EM or SaS) contacts the participant to initiate further actions when severe depression is classified. We invite participants with a depression severity of PHQ $\geq$ 5, who do not fulfil the criteria to participate, in a parallel conducted trial for CBP and subclinical depressive symptoms: eSano BackCare-DP [29].

Procedure on suicidal ideation

Participants who are currently suffering from suicidal ideation are identified by suicide screenings within the telephone interviews (SCID, HAM-D, QIDS) and questionnaires (PHQ-9). Following a suicide protocol adapted from prior trials [30–32] we send an email with detailed information on available health services and the advice to seek professional help if participants report low suicidal ideation (HAM-D, QIDS or PHQ-9 item score = 1). In case of moderate to high suicidal ideation during the assessments or any suicidal thoughts or intentions reported to an eCoach or the study administration, a trained psychotherapist from the study team (HB, LS, EM or SaS) contacts the participant and initiate further actions.

Table 1: Key variables and measurements

Variables	Measurement	Depression screenings			T0	T1	T2
		1	2	3			
Inclusion/exclusion criteria							
Chronic back pain	MR + TI	x			x		
Mild to moderate depression or dysthymia	PHQ-9/HAM-D/QIDS/SCID				x	x	x
Severe depression (ICD-10 F32.2/F32.3/F33.2/F33.3 diagnosis)	SCID				x	x	x
Suicidality	HAM-D/QIDS/SCID				x	x	x
	PHQ-9	x	x	x	x	x	x
Further inclusion and exclusion criteria 1, 4, 5 and 6	SRQ +TI	x			x		
Primary outcome							
Depression severity	HAM-D				x	x	x
Secondary outcomes							
Depression remission and response	HAM-D /SCID/QIDS				x	x	x
Quality of life	AQol-6D/ EQ-5D-5L				x	x	x
Pain intensity	Numerical Rating scale				x	x	x
Pain related disability	ODI				x	x	x
Pain self-efficacy	PSEQ				x	x	x
Work capacity	SPE				x	x	x
Measurements for the economic evaluation							
Costs	TiC-P				x		x
Quality of life	AQol-6D/ EQ-5D-5L				x	x	x
Covariates							
Demographic variables	SRQ/MR	x			x		
Depression type and chronicity	SCID				x	x	x
Prior depression treatment	TI				x	x	
Back Pain type and chronicity	MR	x			x		
Internet affinity	IAS				x	x	
Patient adherence *	attrition rate				x	x	
Patient satisfaction *	CSQ-8					x	
Negative effects of the intervention	INEP/SRQ/TI/SReC					x	

AQol-6D = Assessment of Quality of Life; CSQ-8 = Client Satisfaction Questionnaire; EQ-5D-5L = European Quality of Life scale; HAM-D = Hamilton Rating Scale for Depression ; IAS=Internet Affinity Scale; INEP = Inventory for the Assessment of Negative Effects of Psychotherapy; MR = Medical record; ODI= Oswestry Disability Index, PHQ-9= Patient Health Questionnaire-9; PSEQ= Pain Self-Efficacy Questionnaire; SCID = Structured Clinical Interview; SPE = Subjective Prognostic Employment scale; SReC = self-report during treatment to the eCoach; SRQ = self-report assessment questionnaire, TI = telephone interview; TiC-P=Trimbos/iMTA questionnaire for costs associated with psychiatric illness. * intervention group only

Intervention development

eSano BackCare-D is based on cognitive behaviour therapy (CBT), systematic behavioural activation [33–35] and problem solving [36]. The depression-specific components are based upon a prior IMI "GET.ON Mood Enhancer", that has been evaluated in numerous RCTs in different samples [30, 37, 38] and shown to be effective in lowering depressive symptoms in individuals with diabetes mellitus type 1 and 2 with an intention to treat (ITT) effect size of d=0.89 at two-months post treatment [38] and d=0.83 at 6 months follow up [39]. We added CBP-relevant information, videos and audio clips, based on existing literature on psychological back pain treatment [40, 41], our clinical experience, and an existing IMI for chronic pain individuals based on acceptance and commitment therapy [42, 43]. Think-aloud interviews with five persons with CBP helped us to pilot validate the intervention and further improve its feasibility and acceptability before recruitment start. Access to the platform proceeds through a unique username password combination and is available on a 24/7 basis from all devices with internet access, however, optimized for PCs, notebooks and (large-screen) tablets. It is not possible to assess which device will be used by individual participants. Additionally, a text message coach is provided in eSano BackCare-D that is described below. All transferred data are secured via www.minddistrict.com based on ISO27001 and guidelines NEN7510.

Intervention content

eSano BackCare-D provides six minimally guided sessions with an estimated proceeding duration of 45-60 minutes each, developed to be processed weekly. Three optional sessions with back pain specific topics (sleep, partnership and sexuality, returning to work) are available at the end of sessions 3 through 5. Two booster sessions following the intervention are offered to improve sustainability of intervention effects. Session-specific contents and homework assignments are shown in table 2.

Session 1 provides psychoeducational information on depression, the interaction between CBP and depression as well as pain acceptance. Participants define their depression- and CBP-related goals and get to know the mood diary as the homework assignment for the next week. In session 2, the concept of behavioural activation and the connection between pleasant activities and mood is introduced. Based on the principles of action planning and coping planning [44, 45], participants create an individual list and schedule for completion of pleasant activities in the next few days. The main focus in sessions 3 and 4 is on the six-step plan to handle solvable problems and to better manage emerging issues, comparable to other studies [38, 46–48]. In addition, techniques to reduce rumination on unsolvable problems and the concept of mindfulness are introduced. Session 5 includes information and exercises on phys-

ical activity [35], a mindfulness exercise and techniques to strengthen self-esteem. The sixth session serves to assess intervention-related changes in mood and provides a list of additional treatment options. Participants are encouraged to create a plan for the future. At the end, they write a letter to themselves about specific goals for the next four weeks and choose the date of the next booster session (after two, four or six weeks) that are developed to review what the participants have learned in previous sessions and to provide motivation to maintain and expand learned skills in the future.

The sleep session builds on an evidence based IMI for insomnia, i.e: GET.ON Recovery [49, 50]. As insomnia is a predictor and symptom of depression [51], participants learn about the principles of sleep hygiene, sleep restriction and stimulus control [52]. The partnership and sexuality session provides communication skills and exercises for improving physical closeness and sexuality. In the returning to work session, participants receive information on self-management and interpersonal competences as well as exercises in problem-solving and physical relaxation.

Table 2 Overview of the sessions

Session	Depression-specific topics	Back pain-specific topics	Assignments
1	Psychoeducational information about depression	Connection between back pain and depression Pain acceptance	To write down medical history and set goals Homework assignment: mood diary
2	Behavioural activation Information on connection between behaviour and mood	Worrying about back pain-related complications	To create an activity plan Homework assignment: to complete the activation plan.
3	Problem solving I Introduction in problem solving. Information on solvable and unsolvable problems		To work with the 6 problem solving steps based on own problems Homework assignment: to implement the problem solving steps during the week
4	Problem solving II Information about techniques to reduce rumination. Introduction to mindfulness	Rumination about back pain	To review the problem solving steps and implement a technique to stop rumination Homework assignment: to practise and track mindfulness exercises
5	Behavioural activation, focus on physical activity and self-esteem. Connection between mood and movement	Physical activity and back pain. Connection between back pain and physical rest	To raise awareness of successes and strengths. To learn to value oneself Homework assignment: to implement physical activity in daily life
6	Plan for the future Collection of pleasant activities	Conversation with a General Practitioner	To improve patient-physician relationship Homework assignment: to implement positive activities and create a future plan
Additional (optional) sessions			
a	Healthy sleep Information on sleep hygiene, sleep restriction and stimulus control		To implement the 10 rules for healthy sleep into daily life
b	Partnership and sexuality Information on communication skills, physical closeness and sexuality		To implement communication skills and massage exercises in daily life

c	Returning to the workplace Information on self-management and interpersonal competencies	Fitness exercises at the workplace	To set priorities, to implement the 6 steps for problem-solving at the workplace, and to review communication skills
Booster sessions (within 3 months after the regular sessions)			
7	Summary: behavioural activation; review; pleasant activities; problem solving		To reflect on positive changes and update the activity plan; to practice the 6 steps for problem -solving
8	Summary of the key elements, behavioural activation		Choice of the intervention topics (1-6 above)

Text message coach

The text message coach in eSano BackCare-D automatically sends one supportive text message per day for the duration of six weeks as text message prompts have been shown to increase efficacy and adherence of IMIs [53–55]. The contents include a) reminders to complete the weekly assignments, b) repetition of the content, and c) motivation enhancement components.

Guidance

Based on previous studies showing that guidance and reminders and strict deadlines seem to be important with regard to the respective primary outcomes and adherence in IMIs [20, 56–58] the feedback manual of eSano BackCare-D provides instructions to remind, set deadlines and formulate standardised feedback for each session. Trained and supervised eCoaches (psychologists) serve as contact person and provide feedback within two work days after each completed session. Feedbacks are adapted to the participants' assignments and include positive reinforcement for completion of assignments and encouragement to proceed with the time spent on guidance will be approximately 60-100 minutes per participant.

Control condition

Participants have unrestricted access to TAU. All types of medical/psychological help received during the last three month are tracked at T0 and T2 with the Trimbos/iMTA questionnaire for costs associated with psychiatric illness [59].

Proposed sample size/power calculations

The sample size calculation is based on the primary endpoint, the HAM-D score at post treatment. According to the results of trials on online interventions for depression [20], a treatment effect (pooled effect size) of d=0.39 would be of clinical interest and is considered feasible for the type of treatment. On the basis of a two-sample t-test at two-sided significance

level of 0.05, the study is planned to detect this effect with 80% power. This requires a sample of 105 individuals in each arm.

Assessments

Depression screening. Depressive symptoms are assessed by the Patient Health Questionnaire (PHQ-9) which is a well validated depression screening instrument that has also been evaluated to be delivered as online-version [60], with a Cronbach's alpha of .89 and 88% sensitivity and 88% specificity for major depression [61].

Depression diagnosis. The 17-item HAM-D is the most widely used clinician-rated measure of depression severity and as such viewed as the gold standard for the assessment of depression severity. Additionally, we use the Quick Inventory of Depressive Symptomatology (QIDS [62]) which assesses the severity of depressive symptoms, covering all criterion symptom domains of the DSM-IV to diagnose a major depressive episode [62]. Moreover we use Section A (Affective Syndromes) of the Structured Clinical Interview (SCID; [63]) as a comprehensive, structured interview designed to be used by trained interviewers for the assessment of mental disorders according to the definitions and criteria of DSM. It enables a reliable, valid and efficient assessment of depressive disorders [64]. As an add-on to the SCID for DSM-IV, we use a German translation of the SCID-V-RV to allow for DSM-V [65] diagnoses as well.

Interviewers are trained and weekly supervised by a psychologist (LS, EM) and are blinded to randomisation condition. At the beginning of each interview, participants and interviewers will be reminded to keep blinding throughout the assessment. After an initial training session, a supervisor and the interviewers assess the same participant together, with comparison of results as follows: The Inter-Rater Reliability (IRR) for the SCID, measured by *Cohen's kappa* and the *Intra-Class Correlation* for the HAM-D and QIDS. An almost perfect Cohen's kappa ≥ .81 [66] and an excellent ICC coefficient ≥ .75 [67] is considered as sufficient. Each interviewer is compared to trainers´ rating (LS, EM) until the sufficient IRR values are met. Afterwards, the interviewers are compared to each other on a random basis to assess the IRR.

Primary outcome

Depression severity. Depression severity is the core patient-relevant outcome in trials among depressed individuals [68, 69] and is assessed by means of the clinician-rated Hamilton Rating Scale for Depression (HAM-D-17; [70]) (see table 1) at post-treatment (T1) as part of the telephone interview. Inter-rater reliability of the SCID was reported to be high for inter-rater reliability comparing telephone and face-to-face interviews [71].

Secondary outcomes

Depression response and remission. HAM-D scores are used to determine depression response in accordance to the recommendations of Jacobson and Truax [72]. Depression remission is assessed by means of the SCID as part of the telephone interviews.

Health related quality of life (QoL). The AQoL-6D includes 20 items and six dimensions and is suitable for quality of life assessments and economic evaluations of health programs with good psychometric properties [73] and a Cronbach's alpha of .89 [74]. We additionally obtain the most widely used quality of life assessment EuroQol (EQ-5D-5L) as a basis for-cost-utility analyses with five health domains of importance to quality of life [75].

Pain intensity. We use an 11-point numerical rating (0-10) of the worst, least and average pain during the last week and calculate the mean of the three scales. Additionally, we use a categorical rating of pain intensity (none, mild, moderate, severe).

Pain related disability. We obtain the Oswestry Disability Index (ODI) [76] as a reliable ($\alpha = .86$; [77]) and valid 10 item self-report questionnaire, sensitive to change in difficulties in completing activities of daily living [76].

Pain self-efficacy. The Pain Self-Efficacy Questionnaire (PSEQ) is a validated and reliable (internal consistency: $\alpha = 0.93$) 10 item instrument that assesses self-efficacy expectations related to pain [78].

Work capacity. The subjective prognostic employment scale (SPE) is a validated 3-item self-report questionnaire (sum score 0-3) with high internal consistency (rep (Guttman scaling) = .99; [79]).

Intervention adherence. The attrition rate (calculated using the percentage of individuals who no longer use the intervention, as assessed by their log in data) gives an estimate of the individuals' intervention adherence.

Patient satisfaction.

The Client Satisfaction Questionnaire (CSQ-8, German: ZUF-8), optimised for the assessment of client satisfaction in IMIs (CSIQ-8) [80] is a validated 8 item instrument with high internal consistency ($\alpha = 0.92$) [81]. The adapted version for the assessment of client satisfaction in IMIs has shown to have high internal consistency in a range of studies ($\alpha = 0.92$-0.94) [50, 82, 83] and to be associated with treatment adherence and outcome.

Negative effects of psychotherapy. We include different ways of monitoring serious adverse events (SAE) adapted from the National Institute for Health Research recommendations [84] and Horigian et al. [85] who give general principles and examples to help illustrate their defi-

nition of SAEs: participants´ responses in interviews, reported SAEs to the eCoach and SAEs assessed by means of the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) during the online assessments [86]. The INEP consists of 15 items assessing a range of common changes participants experienced in line with the intervention. Cronbach's alpha is $\alpha = 0.86$ [86]. At the beginning of every session, participants are asked about adverse events and are also encouraged to report the events to their eCoach who monitors the SAEs and initiates further actions if needed.

Costs.
We use the German version of the Cost Questionnaire "Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness" (TiC-P; 59), adapted for the German health care system by Nobis and colleagues [32] and for CBP individuals by the present authors. The TiC-P allows assessment of all direct healthcare services received during the last three months. Moreover, direct non-medical costs (e.g. travel costs) and indirect costs are assessed, including the number of 'work loss' days (absenteeism), the number of 'work cut-back' days (presentism) and costs associated with domestic tasks.

Covariates. Demographic variables, prior depression treatments, and internet affinity level are assessed by patient self-report, see table 1. We use the German version of the Internet Affinity Scale (IAS) by Haase and colleagues [87] to assess familiarity with the Internet. Depression type (Major Depression yes/no), baseline severity and depression chronicity are assessed by the SCID, back pain type, severity and chronicity are extracted from medical records.

Statistical Analysis

Clinical analyses. The primary endpoint will be analysed with the HAM-D score at T1 as dependent variable and baseline value as covariates, adjusting for sex and age. Continuous secondary outcomes will be analysed accordingly. Standardised mean differences and 95% confidence intervals will be calculated to measure the between-group effect size at post-treatment and follow-up. Additionally, clinical significance analyses, such as number needed to treat (NNT) will be conducted. All analyses will be performed on an intention-to-treat (ITT) principle with multiple imputations to replace missing data [88]. Completer analyses (per-protocol) will be conducted to investigate the influence of study attrition on study results. Rates of patient-reported adverse events will be compared.

Economic evaluation. We will conduct a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). Outcome estimates will be the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) after six months. A cost-effectiveness analysis with depression response as clinical outcome will be conducted. The generic outcome for the cost-utility analysis will be quality-adjusted life-years (QALYs), that will be based on the AQoL-6D [73] and in a sensitivity analysis based on the EQ-5D-5L [75]. Both analyses will be conducted from a societal perspective including all direct and indirect costs. Nonparametric bootstrapping will be used to take into account stochastic uncertainty of the ICER. Further, we will calculate a cost-acceptability curve to test the likelihood that the intervention is cost-effective relative to TAU, given varying threshold for the willingness to pay for one depression response or QALY gained, respectively.

Ethics and dissemination

All procedures are approved by the ethics committee of the Albert- Ludwigs-University of Freiburg and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung). The trial has been registered prior to recruitment start at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): (DRKS00009272).

We conduct and report the RCT in accordance with the CONSORT 2010 Statement [89], the supplement of the CONSORT statement for pragmatic effectiveness trials [89, 90] and current guidelines for executing and reporting Internet intervention research [91]. The results will be published in peer-reviewed journals and presented on international conferences.

Quality assurance and safety

The Clinical Trials Unit Freiburg performs monitoring visits to the participating clinic centres before, during and after completion of the study to ensure that the study is conducted, recorded and reported according to the study protocol, relevant standard operating procedures (SOPs), and requirements of the sponsor and/or the Ethic Committees in accordance with ICH-GCP. Rigorous operating procedures for data management and safety have been implemented.

Furthermore, an independent Data Safety and Monitoring Board (DSMB) consisting of two experienced scientists and psychotherapists (MHä, MHa) and one statistician (LK) with long-standing experience in clinical trials has been established. The function of the DSMB is to monitor the course of the study and, if necessary, to give recommendations to the steering committee for discontinuation, modification or continuation of the study.

Discussion and conclusions

The present effectiveness and cost-effectiveness trial focusses on individuals with CBP and comorbid depression as two of the most frequent, most disabling health conditions with high associated economic burden [5, 92].

The WARD-BP trial is innovative in several ways: a) Studies examining the effectiveness of psychological depression interventions are regularly methodologically limited as they lack diagnostic clarification of depression status [20, 69, 93]. By carrying out the SCID and HAM-D prior to randomization and at follow-up assessments, the present trial will be the first trial on a psychological depression intervention for people with chronic pain with verified DSM diagnosis of depression. b) With a target sample of 210 participants, the study will be optimally powered, overcoming limitations of small scale trials on psychological depression interventions in the medically ill [12, 69, 93]. c) The eSano BackCare-D intervention is tailored to the special needs of the target group of chronic back pain patients. This has been discussed as having an uptake and adherence facilitating effect [94], likely to improve the effectiveness of online interventions. d) The implementation of the intervention into the health-care system overcomes one of the main criticisms regarding IMI trial being only representative for a selective online population [95, 96]. e) The current trial design will allow examination of the reach of this IMI and will provide valuable information about which CBP individuals are willing to utilise such interventions. With the use of two different recruitment strategies, we will be able to compare two different ways of implementing IMIs into clinical routine. This will allow for conclusions on feasible ways of improving the adherence and uptake of IMIs in respective target populations [97–99]. f) Finally, as one of still few clinical trials on psychological depression interventions the present trial comprises a cost-effectiveness analysis.

If the results of WARD-BP indicate that eSano BackCare-D is effective and cost-effective, its clinical impact on depression health care services could be substantial. When implemented as part of the standard health care, IMIs have the potential to reduce the “lost in transition phenomenon” caused by fragmented health care systems [26, 100, 101]. Engaging individuals in treatment at the interface of different health care sectors, as in the present (cost-)effectiveness trial, will contribute important information on potential approaches to improve the delivery of mental health care and at the same time provide insights on possible ways of implementing depression IMIs into chronic back pain care in order to exploit their full potential. The first results of WARD-BP are expected in 2018.

Authors' contributions

HB, DE, MB, OM and HR initiated this study. All authors contributed to the design of this study. HB, LS, SP, DE, SaS, DL, SN, JB, HR, MB and JL developed the intervention content or intervention content eSano BackCare-D is based on as well as the assessment. HB, LS, SP, SaS, DE, and JL are responsible for recruitment. SaS is responsible for randomisation and allocation as well as the administration of participants. JL wrote the draft of the manuscript. HB provided expertise on depression, CBP and psychological pain interventions. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

Conflict of interest

JL, LS, SP, SS, JB, SN, OM, HR and HB report no conflict of interest. DE, MB, and DL are stakeholders of the "Institute for Online Health Trainings", a company aiming to transfer scientific knowledge related to the present research into routine health care. A committee of independent scientists has been formed (Data Safety and Monitoring Board (DSMB)) to supervise study-related decisions and prevent any influence of a potential conflict of interest.

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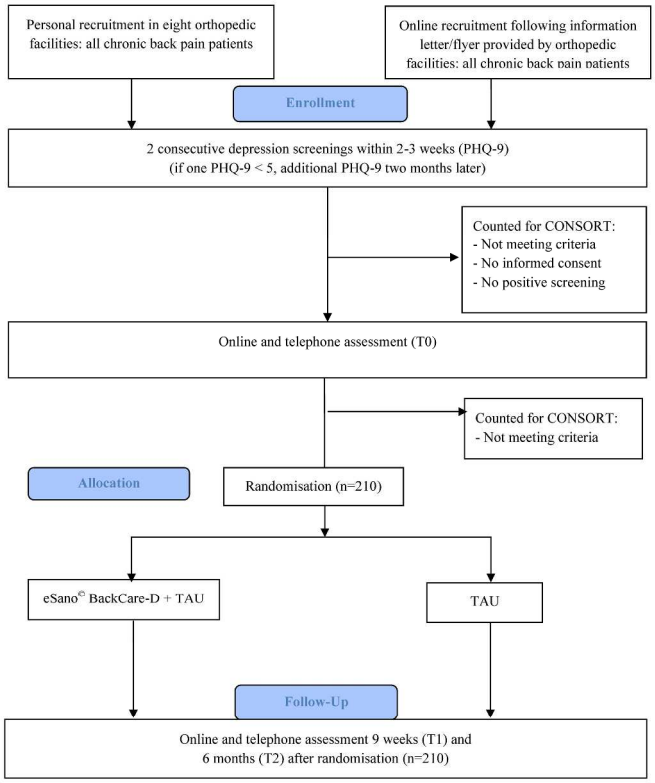

Figure 1. study flow

Flow Chart

297x420mm (300 x 300 DPI)

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

Section/item	Item No	Description	Page NO in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	(5/10)
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			6

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6,10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5,10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6-7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6-7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	15 / n.a.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	6
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

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

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Effectiveness and cost-effectiveness of a guided internet- and mobile-based depression intervention for individuals with chronic back pain: protocol of a multi-centre randomised controlled trial

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Effectiveness and cost-effectiveness of a guided internet- and mobile-based depression intervention for individuals with chronic back pain: protocol of a multi-centre randomised controlled trial

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Abstract

Introduction: Depression often co-occurs with chronic back pain (CBP). Internet- and mobile-based interventions (IMIs) might be a promising approach for effectively treating depression in this patient group. In the present study, we will evaluate the effectiveness and cost-effectiveness of a guided depression IMI for individuals with CBP (eSano BackCare-D) integrated into orthopaedic health care.

Methods and analysis: In this multicentre randomised controlled trial (RCT) of parallel design, the groups eSano BackCare-D vs. treatment as usual will be compared. 210 participants with CBP and diagnosed depression will be recruited subsequent to orthopedic rehabilitation care. Assessments will be conducted prior to randomisation and 9 weeks (posttreatment) and 6 months after randomisation. The primary outcome is depression severity (HAM-D-17). Secondary outcomes are depression remission and response, health related quality of life, pain intensity, pain related disability, self-efficacy and work capacity. Demographic and medical variables as well as internet affinity, intervention adherence, intervention satisfaction and negative effects will also be assessed. Data will be analysed on an intention-to-treat basis and an additional per-protocol analysis. Moreover, a cost-effectiveness and cost-utility analysis will be conducted from a societal perspective after 6 months.

Ethics and dissemination: All procedures are approved by the ethics committee of the Albert- Ludwigs-University of Freiburg and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung). The results will be published in peer-reviewed journals and presented on international conferences.

Registration details: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): (DRKS00009272).

Keywords: Guided self-help; Internet-based; Chronic back pain; Depression; after care; Randomised controlled trial, effectiveness, cost-effectiveness

Strengths and limitations of this study

- This is a protocol for the first large scale, multi-centre RCT examining the effectiveness of a depression IMI for individuals with CBP and depression.
- This is the first trial examining the cost-effectiveness of a depression IMI for individuals with CBP and depression.
- The IMI will be implemented as integrated part of routine orthopaedic health care, thus overcoming the self-referral bias of most prior IMI trials, examining the possibility to improve patients´ medical sector transitions by means of an e-mental-health offer.
- We use standardised interviews for the diagnosis and clinical rating scales for the assessment of the severity level of depression (SKID and HAMD/QIDS).
- Findings will be limited to patients with back pain and depression receiving a depression IMI as aftercare intervention of a bio-psycho-social focused orthopaedic inpatient treatment, which might limit the (incremental) effectiveness of the intervention.

Introduction

The two widespread conditions chronic back pain (CBP) and depression belong to the top ten causes of years lived with disability (YLDs) worldwide [1]. The global one-month adult prevalence for low back pain is estimated to be 23.2% and a substantial increase during the next decades can be expected [2]. Depression has been shown to be the leading cause of burden of diseases in middle- to high-income countries with a lifetime prevalence of about 14.6% [3]. A strong association between depression and CBP has been frequently reported with prevalence rates for depression ranging from 21% to 50% in back pain and chronic low back pain individuals [4]. Several systematic reviews highlight a significant prognostic association between comorbid depression and increased morbidity of different somatic conditions and health care costs as well as diminished quality of life [5–7]. Moreover, depression is one of the core predictors of persistent pain symptoms, increased pain-related disability, and poor treatment outcomes in pain patients [4, 8, 9].

There is strong evidence for the efficacy of psychological interventions for chronic pain [10] and especially for chronic low back pain [11] aiming at pain intensity or disability/interference as primary outcomes. To the best of our knowledge however, there is no study that has examined the effects of psychological depression interventions in the population of CBP focussing on depression as the primary outcome [12]. Indeed, the evidence on depres-

sion treatments for patients with chronic pain and clinical depression is very limited, mostly relying on a few collaborative/stepped care trials conducted in the last two decades [13–15].

In order to improve health care for CBP individuals, internet- and mobile-based interventions (IMIs) are considered to be a promising approach [16, 17]. Among numerous meta-analyses highlighting the efficacy of IMIs with regard to the reduction of depressive symptoms [18–21], one meta-analysis quantified the superiority of online depression interventions over waiting-list and treatment as usual (TAU) with standardised mean differences of d=-.68 (CI: -.85;-.52; n=8) and d=-.39 (CI:-.66;-.12; n=8) [20], albeit effect moderating factors of IMIs remain unclear [22]. As most trials used highly selective recruitment strategies, the evidence for the effectiveness of IMIs for depression (i.e., performance of an intervention when implemented within typical clinical practice, investigated by means of pragmatic trials) is far less conclusive [23] and many health systems have not included IMIs as an integrated treatment component. As an implemented part of a comprehensive care system, IMIs could reduce the deficiencies of most current health care systems in coordinating transitions of care, such as the transition from the inpatient to outpatient setting, where recommendations are regularly lost in transition [24–26].

The present WARD-BP study (**w**eb-based **a**ftercare depression intervention following **r**ehabilitation for individuals with **d**epression and chronic **b**ack **p**ain) aims to investigate the effectiveness and cost-effectiveness of the depression IMI "eSano BackCare-D" in a study population of CBP with a diagnosed depression in the aftermath of orthopaedic rehabilitation care. The primary research question is:

1) Is eSano BackCare-D effective in reducing depression in individuals with CBP and diagnosed depression compared to treatment as usual (TAU)?

Secondary research questions are:

2) Is eSano BackCare-D effective with regard to depression remission and response, health related quality of life, pain intensity, pain related disability, self-efficacy and work capacity in individuals with CBP and diagnosed depression compared to TAU?

3) Is eSano BackCare-D cost-effective in individuals with CBP and diagnosed depression compared to TAU from a societal perspective?

4) Which factors moderate and mediate the effects of eSano BackCare-D?

Methods and analysis

Study design

WARD-BP is a multi-centre pragmatic randomised controlled clinical trial (RCT) of parallel design. All participants receive TAU. We conduct assessments in both groups before randomisation (T0), nine weeks (T1= post treatment in case of regular IMI use) and six months (T2) after randomisation. Trial participants receive 15€ per completed post- and follow-up telephone assessment, see figure 1 for study flow.

- Figure 1 about here –

Randomisation

Randomisation and allocation of participants to the two groups (intervention or TAU) was prepared in advance by an independent researcher (SaS) by means of a web-based program (https://www.sealedenvelope.com/) using permuted block randomisation with variable block sizes of 4,6,8 (randomly arranged), ratio of 1:1. Participants are stratified by center. Centers are all eight orthopedic clinics where recruitment is conducted personally and a ninth (meta-)clinic, which includes all participants recruited by letter (see recruitment).The independent researcher (SaS) is responsible for the allocation of participants to trial arms as well as the administration of the trial and is blinded to the treatment process and assessments of the participants.

Recruitment

Recruitment has started in October 2015 and is planned to end in July 2017. While this study protocol has been submitted for publication after start of recruitment (due to usual writing-up, commenting and approving procedures by all co-authors), clinical trial registry took place prior to recruitment start.

Using the Patient Health Questionnaire (PHQ-9; [27]), we conduct two consecutive depression screenings within 2-3 weeks. In case of only one positive screening (PHQ $\geq$ 5), a third PHQ will be administered two months later via telephone interview. We recruit potential participants in orthopaedic rehabilitation units in Germany with two different recruitment strategies.

In the first recruitment setting (personal recruitment), patients with two positive screenings receive information on the intervention by clinic staff during their orthopedic care. Patients

providing their informed consent to the clinical trial study team (exemplary informed consent form see supplementary material) are contacted by the study team in order to clarify further eligibility criteria by means of an online- and telephone assessment including a telephone administered clinical interview. The participating clinics are compensated for their recruitment efforts (i.e. selection of back pain patients, screening procedure, informed consent, documentation according to CONSORT, providing access to medical records) with 320€ per randomised participant. The second recruitment strategy (recruitment by letter) involves a letter with information flyers and study process for back pain patients after discharge from orthopaedic rehabilitation units across Germany with a link to fill out an online PHQ-screening. Individuals screened positive, providing informed consent are contacted for the second PHQ-screening and a clinical interview via telephone equivalent to the first recruitment strategy.

Inclusion/exclusion criteria

We include patients if they fulfil the following inclusion criteria:

1) age 18 years or older

2) CBP assessed by physician for at least six months assessed during telephone interview

3) mild to moderate depression or dysthymia according to SCID assessment, assessed during telephone interview

4) sufficient knowledge of German language

5) Internet and PC access.

Patients are excluded in case of :

6) receiving ongoing psychotherapy or beginning psychotherapy within the next three months,

7) being currently suicidal or reporting suicidal attempts in the past five years assessed during telephone interview or

8) a current diagnosis of severe depression (ICD-10 F32.2/F32.3/F33.2/F33.3 diagnosis) assessed during telephone interview, see table 1.

The exclusion of individuals with severe depression is due to ethical concerns and based on ICD-10 criteria for severe depression according to the German treatment guidelines for depression [28]. A trained psychotherapist (HB, LS, EM or SaS) contacts the participant to initiate further actions when severe depression is classified. We invite participants with a depression severity of PHQ $\geq$ 5, who do not fulfil the criteria to participate, in a parallel conducted trial for CBP and subclinical depressive symptoms: eSano BackCare-DP [29].

Procedure on suicidal ideation

Participants who are currently suffering from suicidal ideation are identified by suicide screenings within the telephone interviews (SCID, HAM-D, QIDS) and questionnaires (PHQ-9) and potentially through communication with the eCoach or the study administration. Following a suicide protocol adapted from prior trials [30–32] we send an email with detailed information on available health services and the advice to seek professional help if participants report low suicidal ideation (HAM-D, QIDS or PHQ-9 item score = 1). In case of moderate to high suicidal ideation during the assessments or any suicidal thoughts or intentions reported to an eCoach or the study administration, a trained psychotherapist from the study team (HB, LS, EM or SaS) contacts the participant and initiate further actions. In the case of suicidal ideation communicated to the eCoach, unblinding is regarded as permissible.

Table 1: Key variables and measurements

Variables	Measurement	Depression screenings			T0	T1	T2
		1	2	3			
Inclusion/exclusion criteria							
Chronic back pain	MR + TI	x			x		
Mild to moderate depression or dysthymia	PHQ-9/HAM-D/QIDS/SCID				x	x	x
Severe depression (ICD-10 F32.2/F32.3/F33.2/F33.3 diagnosis)	SCID				x	x	x
Suicidality	HAM-D/QIDS/SCID				x	x	x
	PHQ-9	x	x	x	x	x	x
Further inclusion and exclusion criteria 1, 4, 5 and 6	SRQ +TI	x			x		
Primary outcome							
Depression severity	HAM-D				x	x	x
Secondary outcomes							
Depression remission and response	HAM-D /SCID/QIDS				x	x	x
Quality of life	AQol-6D/ EQ-5D-5L				x	x	x
Pain intensity	Numerical Rating scale				x	x	x
Pain related disability	ODI				x	x	x
Pain self-efficacy	PSEQ				x	x	x
Work capacity	SPE				x	x	x
Measurements for the economic evaluation							
Costs	TiC-P				x		x
Quality of life	AQol-6D/ EQ-5D-5L				x	x	x
Covariates							
Demographic variables	SRQ/MR	x			x		
Depression type and chronicity	SCID				x	x	x
Prior depression treatment	TI				x	x	
Back Pain type and chronicity	MR	x			x		

Internet affinity	IAS	x	x
Patient adherence *	attrition rate	x	x
Patient satisfaction *	CSQ-8		x
Negative effects of the intervention	INEP/SRQ/TI/SReC		x

AQol-6D = Assessment of Quality of Life; CSQ-8 = Client Satisfaction Questionnaire; EQ-5D-5L = European Quality of Life scale; HAM-D = Hamilton Rating Scale for Depression ; IAS=Internet Affinity Scale; INEP = Inventory for the Assessment of Negative Effects of Psychotherapy; MR = Medical record; ODI= Oswestry Disability Index, PHQ-9= Patient Health Questionnaire-9; PSEQ= Pain Self-Efficacy Questionnaire; SCID = Structured Clinical Interview; SPE = Subjective Prognostic Employment scale; SReC = self-report during treatment to the eCoach; SRQ = self-report assessment questionnaire, TI = telephone interview; TiC-P=Trimbos/iMTA questionnaire for costs associated with psychiatric illness. * intervention group only

Intervention development

eSano BackCare-D is based on cognitive behaviour therapy (CBT), systematic behavioural activation [33–35] and problem solving [36]. The depression-specific components are based upon a prior IMI "GET.ON Mood Enhancer", that has been evaluated in numerous RCTs in different samples [30, 37, 38] and shown to be effective in lowering depressive symptoms in individuals with diabetes mellitus type 1 and 2 with an intention to treat (ITT) effect size of d=0.89 at two-months post treatment [38] and d=0.83 at 6 months follow up [39]. We added CBP-relevant information, videos and audio clips, based on existing literature on psychological back pain treatment [40, 41], our clinical experience, and an existing IMI for chronic pain individuals based on acceptance and commitment therapy [42, 43]. Think-aloud interviews with five persons with CBP helped us to pilot validate the intervention and further improve its feasibility and acceptability before recruitment start. Access to the platform proceeds through a unique username password combination and is available on a 24/7 basis from all devices with internet access, however, optimized for PCs, notebooks and (large-screen) tablets. It is not possible to assess which device will be used by individual participants. Additionally, a text message coach is provided in eSano BackCare-D that is described below. All transferred data are secured via www.minddistrict.com based on ISO27001 and guidelines NEN7510.

Intervention content

eSano BackCare-D provides six minimally guided sessions with an estimated proceeding duration of 45-60 minutes each, developed to be processed weekly. Three optional sessions with back pain specific topics (sleep, partnership and sexuality, returning to work) are available at the end of sessions 3 through 5. Two booster sessions following the intervention are offered to

improve sustainability of intervention effects. Session-specific contents and homework assignments are shown in table 2.

Session 1 provides psychoeducational information on depression, the interaction between CBP and depression as well as pain acceptance. Participants define their depression- and CBP-related goals and get to know the mood diary as the homework assignment for the next week. In session 2, the concept of behavioural activation and the connection between pleasant activities and mood is introduced. Based on the principles of action planning and coping planning [44, 45], participants create an individual list and schedule for completion of pleasant activities in the next few days. The main focus in sessions 3 and 4 is on the six-step plan to handle solvable problems and to better manage emerging issues, comparable to other studies [38, 46–48]. In addition, techniques to reduce rumination on unsolvable problems and the concept of mindfulness are introduced. Session 5 includes information and exercises on physical activity [35], a mindfulness exercise and techniques to strengthen self-esteem. The sixth session serves to assess intervention-related changes in mood and provides a list of additional treatment options. Participants are encouraged to create a plan for the future. At the end, they write a letter to themselves about specific goals for the next four weeks and choose the date of the next booster session (after two, four or six weeks) that are developed to review what the participants have learned in previous sessions and to provide motivation to maintain and expand learned skills in the future.

The sleep session builds on an evidence based IMI for insomnia, i.e: GET.ON Recovery [49, 50]. As insomnia is a predictor and symptom of depression [51], participants learn about the principles of sleep hygiene, sleep restriction and stimulus control [52]. The partnership and sexuality session provides communication skills and exercises for improving physical closeness and sexuality. In the returning to work session, participants receive information on self-management and interpersonal competences as well as exercises in problem-solving and physical relaxation.

Table 2 Overview of the sessions

Session	Depression-specific topics	Back pain-specific topics	Assignments
1	Psychoeducational information about depression	Connection between back pain and depression Pain acceptance	To write down medical history and set goals Homework assignment: mood diary
2	Behavioural activation Information on connection between behaviour and mood	Worrying about back pain-related complications	To create an activity plan Homework assignment: to complete the activation plan.

3	Problem solving I Introduction in problem solving. Information on solvable and unsolvable problems		To work with the 6 problem solving steps based on own problems Homework assignment: to implement the problem solving steps during the week
4	Problem solving II Information about techniques to reduce rumination. Introduction to mindfulness	Rumination about back pain	To review the problem solving steps and implement a technique to stop rumination Homework assignment: to practise and track mindfulness exercises
5	Behavioural activation, focus on physical activity and self-esteem. Connection between mood and movement	Physical activity and back pain. Connection between back pain and physical rest	To raise awareness of successes and strengths. To learn to value oneself Homework assignment: to implement physical activity in daily life
6	Plan for the future Collection of pleasant activities	Conversation with a General Practitioner	To improve patient-physician relationship Homework assignment: to implement positive activities and create a future plan
Additional (optional) sessions			
a	Healthy sleep Information on sleep hygiene, sleep restriction and stimulus control		To implement the 10 rules for healthy sleep into daily life
b	Partnership and sexuality Information on communication skills, physical closeness and sexuality		To implement communication skills and massage exercises in daily life
c	Returning to the workplace Information on self-management and interpersonal competencies	Fitness exercises at the workplace	To set priorities, to implement the 6 steps for problem-solving at the workplace, and to review communication skills
Booster sessions (within 3 months after the regular sessions)			
7	Summary: behavioural activation; review; pleasant activities; problem solving		To reflect on positive changes and update the activity plan; to practice the 6 steps for problem -solving
8	Summary of the key elements, behavioural activation		Choice of the intervention topics (1-6 above)

Text message coach

The text message coach in eSano BackCare-D automatically sends one supportive text message per day for the duration of six weeks as text message prompts have been shown to increase efficacy and adherence of IMIs [53–55]. The contents include a) reminders to complete the weekly assignments, b) repetition of the content, and c) motivation enhancement components.

Guidance

Based on previous studies showing that guidance and reminders and strict deadlines seem to be important with regard to the respective primary outcomes and adherence in IMIs [20, 56–58] the feedback manual of eSano BackCare-D provides instructions to remind, set deadlines and formulate standardised feedback for each session. Trained and supervised eCoaches (psychologists) serve as contact person and provide feedback within two work days after each completed session. Feedbacks are adapted to the participants' assignments and include posi-

tive reinforcement for completion of assignments and encouragement to proceed with the time spent on guidance will be approximately 60-100 minutes per participant.

Control condition

Participants have unrestricted access to TAU. All types of medical/psychological help received during the last three month are tracked at T0 and T2 with the Trimbos/iMTA questionnaire for costs associated with psychiatric illness [59].

Proposed sample size/power calculations

The sample size calculation is based on the primary endpoint, the HAM-D score at post treatment. According to the results of trials on online interventions for depression [20], a treatment effect (pooled effect size) of d=0.39 would be of clinical interest and is considered feasible for the type of treatment. On the basis of a two-sample t-test at two-sided significance level of 0.05, the study is planned to detect this effect with 80% power. This requires a sample of 105 individuals in each arm.

Assessments

Depression screening. Depressive symptoms are assessed by the Patient Health Questionnaire (PHQ-9) which is a well validated depression screening instrument that has also been evaluated to be delivered as online-version [60], with a Cronbach's alpha of .89 and 88% sensitivity and 88% specificity for major depression [61].

Depression diagnosis. The 17-item HAM-D is the most widely used clinician-rated measure of depression severity and as such viewed as the gold standard for the assessment of depression severity. Additionally, we use the Quick Inventory of Depressive Symptomatology (QIDS [62]) which assesses the severity of depressive symptoms, covering all criterion symptom domains of the DSM-IV to diagnose a major depressive episode [62]. Moreover we use Section A (Affective Syndromes) of the Structured Clinical Interview (SCID; [63]) as a comprehensive, structured interview designed to be used by trained interviewers for the assessment of mental disorders according to the definitions and criteria of DSM. It enables a reliable, valid and efficient assessment of depressive disorders [64]. As an add-on to the SCID for DSM-IV, we use a German translation of the SCID-V-RV to allow for DSM-V [65] diagnoses as well.

Interviewers are trained and weekly supervised by a psychologist (LS, EM) and are blinded to randomisation condition. At the beginning of each interview, participants and interviewers will be reminded to keep blinding throughout the assessment. After an initial training session, a supervisor and the interviewers assess the same participant together, with comparison of

results as follows: The Inter-Rater Reliability (IRR) for the SCID, measured by *Cohen's kappa* and the *Intra-Class Correlation* for the HAM-D and QIDS. An almost perfect Cohen's kappa ≥ .81 [66] and an excellent ICC coefficient ≥ .75 [67] is considered as sufficient. Each interviewer is compared to trainers´ rating (LS, EM) until the sufficient IRR values are met. Afterwards, the interviewers are compared to each other on a random basis to assess the IRR.

Primary outcome

Depression severity. Depression severity is the core patient-relevant outcome in trials among depressed individuals [68, 69] and is assessed by means of the clinician-rated Hamilton Rating Scale for Depression (HAM-D-17; [70]) (see table 1) at post-treatment (T1) as part of the telephone interview. Inter-rater reliability of the SCID was reported to be high for inter-rater reliability comparing telephone and face-to-face interviews [71].

Secondary outcomes

Depression response and remission. HAM-D scores are used to determine depression response in accordance to the recommendations of Jacobson and Truax [72]. Depression remission is assessed by means of the SCID as part of the telephone interviews.

Health related quality of life (QoL). The AQoL-6D includes 20 items and six dimensions and is suitable for quality of life assessments and economic evaluations of health programs with good psychometric properties [73] and a Cronbach's alpha of .89 [74]. We additionally obtain the most widely used quality of life assessment EuroQol (EQ-5D-5L) as a basis for cost-utility analyses with five health domains of importance to quality of life [75].

Pain intensity. We use an 11-point numerical rating (0-10) of the worst, least and average pain during the last week and calculate the mean of the three scales. Additionally, we use a categorical rating of pain intensity (none, mild, moderate, severe).

Pain related disability. We obtain the Oswestry Disability Index (ODI) [76] as a reliable (α = .86; [77]) and valid 10 item self-report questionnaire, sensitive to change in difficulties in completing activities of daily living [76].

Pain self-efficacy. The Pain Self-Efficacy Questionnaire (PSEQ) is a validated and reliable (internal consistency: $\alpha = 0.93$) 10 item instrument that assesses self-efficacy expectations related to pain [78].

Work capacity. The subjective prognostic employment scale (SPE) is a validated 3-item self-report questionnaire (sum score 0-3) with high internal consistency (rep (Guttman scaling) = .99; [79]).

Intervention adherence. The attrition rate (calculated using the percentage of individuals who no longer use the intervention, as assessed by their log in data) gives an estimate of the individuals' intervention adherence.

Patient satisfaction.

The Client Satisfaction Questionnaire (CSQ-8, German: ZUF-8), optimised for the assessment of client satisfaction in IMIs (CSIQ-8) [80] is a validated 8 item instrument with high internal consistency (α = 0.92) [81]. The adapted version for the assessment of client satisfaction in IMIs has shown to have high internal consistency in a range of studies (α = 0.92-0.94) [50, 82, 83] and to be associated with treatment adherence and outcome.

Negative effects of psychotherapy. We include different ways of monitoring serious adverse events (SAE) adapted from the National Institute for Health Research recommendations [84] and Horigian et al. [85] who give general principles and examples to help illustrate their definition of SAEs: participants´ responses in interviews, reported SAEs to the eCoach and SAEs assessed by means of the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP) during the online assessments [86]. The INEP consists of 15 items assessing a range of common changes participants experienced in line with the intervention. Cronbach's alpha is α = 0.86 [86]. At the beginning of every session, participants are asked about adverse events and are also encouraged to report the events to their eCoach who monitors the SAEs and initiates further actions if needed.

Costs.

We use the German version of the Cost Questionnaire "Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness" (TiC-P; 59), adapted for the German health care system by Nobis and colleagues [32] and for CBP individuals by the present authors. The TiC-P allows assessment of all direct healthcare services received during the last three months. Moreover, direct non-medical costs (e.g. travel costs) and indirect costs are assessed, including the number of 'work loss' days (absenteeism), the number of 'work cut-back' days (presentism) and costs associated with domestic tasks.

Covariates. Demographic variables, prior depression treatments, and internet affinity level are assessed by patient self-report, see table 1. We use the German version of the Internet Affinity Scale (IAS) by Haase and colleagues [87] to assess familiarity with the Internet. Depression type (Major Depression yes/no), baseline severity and depression chronicity are assessed by the SCID, back pain type, severity and chronicity are extracted from medical records.

Statistical Analysis

Clinical analyses. The primary endpoint will be analysed with the HAM-D score at T1 as dependent variable and baseline value as covariates, adjusting for sex and age. Continuous secondary outcomes will be analysed accordingly. Standardised mean differences and 95% confidence intervals will be calculated to measure the between-group effect size at post-treatment and follow-up. Additionally, clinical significance analyses, such as number needed to treat (NNT) will be conducted. All analyses will be performed on an intention-to-treat (ITT) principle with multiple imputations to replace missing data [88]. Completer analyses (per-protocol) will be conducted to investigate the influence of study attrition on study results. Rates of patient-reported adverse events will be compared.

Economic evaluation. We will conduct a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). Outcome estimates will be the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) after six months. A cost-effectiveness analysis with depression response as clinical outcome will be conducted. The generic outcome for the cost-utility analysis will be quality-adjusted life-years (QALYs), that will be based on the AQoL-6D [73] and in a sensitivity analysis based on the EQ-5D-5L [75]. Both analyses will be conducted from a societal perspective including all direct and indirect costs. Nonparametric bootstrapping will be used to take into account stochastic uncertainty of the ICER. Further, we will calculate a cost-acceptability curve to test the likelihood that the intervention is cost-effective relative to TAU, given varying threshold for the willingness to pay for one depression response or QALY gained, respectively.

Ethics and dissemination

All procedures are approved by the ethics committee of the Albert- Ludwigs-University of Freiburg and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung). The trial has been registered prior to recruitment start at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): (DRKS00009272).

We conduct and report the RCT in accordance with the CONSORT 2010 Statement [89], the supplement of the CONSORT statement for pragmatic effectiveness trials [89, 90] and current guidelines for executing and reporting Internet intervention research [91]. The results will be published in peer-reviewed journals and presented on international conferences.

Quality assurance and safety

The Clinical Trials Unit Freiburg performs monitoring visits to the participating clinic centres before, during and after completion of the study to ensure that the study is conducted, recorded and reported according to the study protocol, relevant standard operating procedures (SOPs), and requirements of the sponsor and/or the Ethic Committees in accordance with ICH-GCP. Rigorous operating procedures for data management and safety have been implemented. The principal investigator and the research assistants have access to the source data that will be kept for as long as the study takes until 10 years after completion.

Furthermore, an independent Data Safety and Monitoring Board (DSMB) consisting of two experienced scientists and psychotherapists (MHä, MHa) and one statistician (LK) with long-standing experience in clinical trials has been established. The function of the DSMB is to monitor the course of the study and, if necessary, to give recommendations to the steering committee for discontinuation, modification or continuation of the study.

Discussion

The present effectiveness and cost-effectiveness trial focusses on individuals with CBP and comorbid depression as two of the most frequent, most disabling health conditions with high associated economic burden [5, 92].

The WARD-BP trial is innovative in several ways: a) Studies examining the effectiveness of psychological depression interventions are regularly methodologically limited as they lack diagnostic clarification of depression status [20, 69, 93]. By carrying out the SCID and HAM-D prior to randomization and at follow-up assessments, the present trial will be the first trial on a psychological depression intervention for people with chronic pain with verified DSM diagnosis of depression. b) With a target sample of 210 participants, the study will be optimally powered, overcoming limitations of small scale trials on psychological depression interventions in the medically ill [12, 69, 93]. c) The eSano BackCare-D intervention is tailored to the special needs of the target group of chronic back pain patients. This has been discussed to have an uptake and adherence facilitating effect [94], likely to improve the effectiveness of online interventions. d) The implementation of the intervention into the health-care system overcomes one of the main criticisms regarding IMI trial being only representative for a selective online population [95, 96]. e) The current trial design will allow examination of the reach of this IMI and will provide valuable information about which CBP individuals are willing to utilise such interventions. With the use of two different recruitment strategies, we will be able to compare two different ways of implementing IMIs into clinical routine. This will allow for conclusions on feasible ways of improving the adherence and uptake of IMIs in respective

target populations [97–99]. f) Finally, as one of still few clinical trials on psychological depression interventions the present trial comprises a cost-effectiveness analysis.

If the results of WARD-BP indicate that eSano BackCare-D is effective and cost-effective, its clinical impact on depression health care services could be substantial. When implemented as part of the standard health care, IMIs have the potential to reduce the "lost in transition phenomenon" caused by fragmented health care systems [26, 100, 101]. Engaging individuals in treatment at the interface of different health care sectors, as in the present (cost-)effectiveness trial, will contribute important information on potential approaches to improve the delivery of mental health care and at the same time provide insights on possible ways of implementing depression IMIs into chronic back pain care in order to exploit their full potential. The first results of WARD-BP are expected in 2018.

Authors' contributions

HB, DE, MB, OM and HR initiated this study. All authors contributed to the design of this study. HB, LS, SP, DE, SaS, DL, SN, JB, HR, MB and JL developed the intervention content or intervention content eSano BackCare-D is based on as well as the assessment. HB, LS, SP, SaS, DE, and JL are responsible for recruitment. SaS is responsible for randomisation and allocation as well as the administration of participants. JL wrote the draft of the manuscript. HB provided expertise on depression, CBP and psychological pain interventions. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

Conflict of interest

JL, LS, SP, SS, JB, SN, OM, HR and HB report no conflict of interest. DE, MB, and DL are stakeholders of the "Institute for Online Health Trainings", a company aiming to transfer scientific knowledge related to the present research into routine health care. A committee of independent scientists has been formed (Data Safety and Monitoring Board (DSMB)) to supervise study-related decisions and prevent any influence of a potential conflict of interest.

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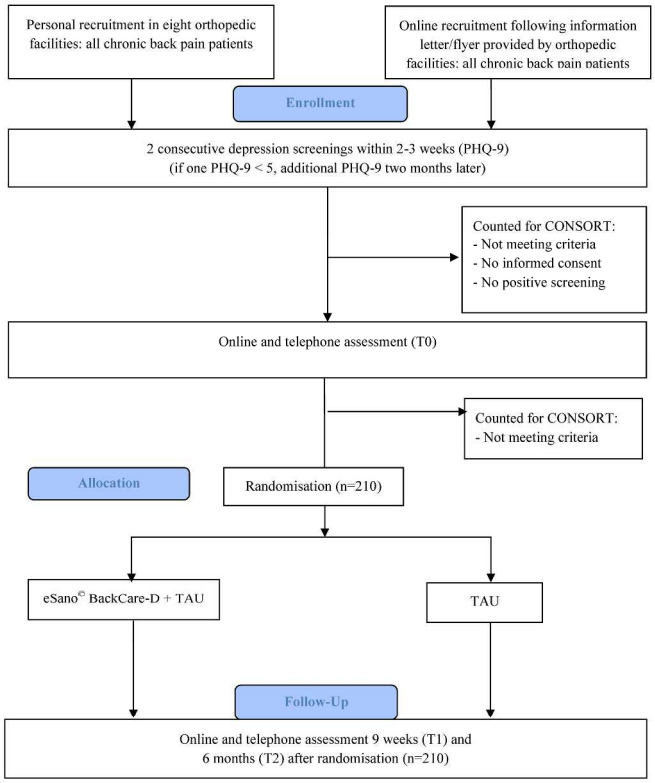

Figure 1. study flow

Flow Chart

297x420mm (300 x 300 DPI)

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

Section/item	Item No	Description	Page NO in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	(5/11)
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11,16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 10-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			6

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6,12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7-8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5,Figure 1, 7-8. 12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5-6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15-16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15-16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	See informed consent attached
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15-16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	17 / n.a.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

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