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Effectiveness of a Guided Internet- and Mobile-Based Intervention for Patients with Chronic Back Pain and Depression (WARD-BP): A Multicenter, Pragmatic Randomized Controlled Trial

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Keywords
Depression · Chronic back pain · Comorbidity · eHealth · Internet-delivered CBT

Abstract
Introduction: There is neither strong evidence on effective treatments for patients with chronic back pain (CBP) and depressive disorder nor sufficiently available mental health care offers. ***Objective:*** The aim is to assess the effectiveness of internet- and mobile-based interventions (IMI) as a scalable approach for treating depression in a routine care setting. ***Methods:*** This is an observer-masked, multicenter, pragmatic randomized controlled trial with a randomization ratio of 1:1. Patients with CBP and diagnosed depressive disorder (mild to moderate severity) were recruited from 82 orthopedic rehabilitation clinics across Germany. The intervention group (IG) received a guided depression IMI tailored to CBP next to treatment-as-usual (TAU; including medication), while the control group (CG) received TAU. The primary outcome was observer-masked clinician-rated Hamilton depression severity (9-week follow-up). The secondary outcomes were: further depression outcomes, pain-related outcomes, health-related quality of life, and work capacity. Biostatistician blinded analyses using regression models were conducted by intention-to-treat and per protocol analysis. ***Results:*** Between October 2015 and July 2017, we randomly assigned 210 participants (IG, $n = 105$; CG, $n = 105$), mostly with only a mild pain intensity but substantial pain disability. No statistically significant difference in depression severity between IG and CG was observed at the 9-week follow-up ($\beta = -0.19$, 95% CI −0.43 to 0.05). Explorative secondary depression (4/9) and pain-related (4/6) outcomes were in part significant ($p < 0.05$). Health-related quality of life was significantly higher in the IG. No differences were found in work capacity. ***Conclusion:*** The results indicate that an IMI for patients with CBP and depression in a routine care setting has limited impact on depression. Benefits in pain and health-related outcomes suggest that an IMI might still be a useful measure to improve routine care.

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Introduction

Cognitive behavioral therapy (CBT) is regarded as effective in treating depression in complex patients with chronic back pain (CBP) and comorbid depression [1], given its effectiveness in other comorbid depression and somatic disease entities [2–4] as well as its probable effectiveness in individuals with CBP [5–7]. However, the challenge of limited availability and accessibility of evidence-based psychotherapeutic interventions for this patient group remains unsolved [8]. The absence of "easy to prescribe" evidence-based interventions, apart from antidepressant drugs that are neither indicated for nor preferred by all patients [9, 10] might be one of the reasons that (somatic) health care professionals struggle with the adequate referral of patients with comorbid depression.

Internet- and mobile-based interventions (IMI) have been suggested as promising approaches to further close this gap in mental health provision [10–12]. IMI proved to be highly efficacious for people with clinical depression [13], and they might also work for patients with somatic conditions [11, 14, 15]. Implemented into routine CBP care, they may provide an innovative way of lowering the disease burden of patients with both CBP and depression, as suggested by a small IMI trial in people with CBP and emotional distress [16]. However, evidence to date stems mostly from efficacy trials based on general population samples. It remains to be seen whether results can be replicated when IMI are integrated into routine health care [17].

The aim of the present study is to evaluate whether eSano BackCare-D, an IMI specially developed for CBP patients with depression, is effective: (1) in reducing depression severity, (2) in terms of depression remission and reliable change, health-related quality of life, pain intensity, pain-related disability, self-efficacy, and work capacity, and (3) as well as safe in terms of adverse events and side effects in patients with CBP and a depressive disorder compared to treatment as usual (TAU).

Materials and Methods

Study Design and Participants

This parallel, two-group, observer-blinded, multicenter randomized controlled trial was conducted to evaluate the effectiveness and cost-effectiveness of eSano BackCare-D in addition to TAU (intervention group, IG) compared with TAU alone (control group, CG). The present paper reports the effectiveness results. The trial was registered at the WHO International Clinical Trials Registry: DRKS00009272, was approved by the local ethics authorities (REC No. 8022-6-BW-H-2015; No. 297/14_150513) and monitored by the Clinical Trial Unit Freiburg as well as by an independent Data Safety and Monitoring Board (DSMB, M.Ha., M.Hä., L.K.). All analyses are reported in accordance with the CONSORT 2010 Statement [18, 19] and the methodological recommendations for trials of psychological interventions [20]. Details are available in the study protocol [21]. Changes to the study protocol can be found in online supplementary eTable 1 (see www.karger.com/doi/10.1159/000511881 for all online suppl. material).

Study outcomes were assessed via telephone and online self-report at baseline (T0) and over a 9-week and 6-month follow-up period after randomization (T1, T2). Trial participants received EUR 15 per completed follow-up telephone assessment.

Participants were recruited by means of two recruitment strategies: personal recruitment by clinical staff in eight orthopedic rehabilitation clinics at patient discharge, and online recruitment after patient discharge using flyer and information letters distributed by 74 orthopedic rehabilitation clinics. Individuals had to score positive twice (≥5; highly sensitive score for potential depression [22]) out of three Patient Health Questionnaire-9 (PHQ-9) [23] screenings within a 3-month period. When informed consent was provided, they were invited for an online and telephone assessment including a telephone-administered structured clinical interview for mental disorders (Structured Clinical Interview for DSM-5, SCID) [24].

The inclusion criteria were: (1) age 18 years and older, (2) back pain (diagnosed by the treating physician/from the medical records) and pain chronicity of at least 6 months (reported by the patient), (3) meeting DSM-IV criteria for a mild-to-moderate depressive episode or persistent depressive disorder, (4) German language skills, and (5) internet and PC access. Patients were excluded if they: (1) had ongoing or planned psychotherapy within the forthcoming 3 months, (2) were currently suicidal or had had suicidal attempts within the past 5 years, or (3) had a severe depressive episode. Participants with severe depressive episodes were excluded due to request from the ethics committee. Participants without a DSM depression diagnosis at baseline (criterion 3) were considered for inclusion in a different, concomitantly running prevention trial [25, 26].

Randomization and Masking

Participants were randomly allocated to IG or CG (1:1 ratio, stratified by the center with eight [on-site recruitment in eight units] plus one [online recruitment] strata) with permuted block randomization [4, 6, 8] by an independent researcher not otherwise involved in this trial (S.S.), who used an automated web-based randomization program (https://www.sealedenvelope.com). The researchers who recruited and screened participants for eligibility and conducted the baseline assessments via telephone were kept blinded to the randomization status. The final part of the baseline assessment was performed using online self-reports. Telephone interviews with participants at T1 and T2 were conducted by independent interviewers to keep outcome assessors blinded to the randomization status. Participants and eCoaches in the online intervention could not be masked given the nature of the intervention. A biometrician (M.M.), who was blinded to group allocation and not otherwise involved in the study, conducted the statistical analysis.

Procedure

eSano BackCare-D is a guided self-help IMI based on CBT with six regular and three optional sessions, including (homework) as-

signments, exercises, and two booster sessions following the intervention. eSano BackCare-D focusses on psychoeducation, behavior activation, and problem solving as well as including pain-specific content on psychoeducation, coping and acceptance, physical activity, and communication with health care professionals. Additional optional sessions target sleep, partnership and sexuality, and return to work. Individuals could choose to receive the booster sessions 2, 4, or 6 weeks after the last regular session. They aimed at encouraging participants to reflect on changes and to update and continually practice their intervention plans [21].

Participants were advised to complete one session per week and were given the option to receive motivating automated text messages. The mean completion time for one session was 54 min (SD 23.7). During the IMI, participants received semi-structured written feedback after each session from trained and supervised psychologists (eCoaches) plus contact on-demand. Feedback was based on a manual and provided semi-standardized. eCoaches sent reminders when session completion was overdue. eCoaches spent an average of 101 min (SD 38.4) on participants who completed at least all six core modules, and 79 min (SD 48.2) for all intervention participants. The intervention was provided using Minddistrict (www.minddistrict.com), a password protected, secured platform, available 24/7, for eHealth interventions.

For TAU, all participants had unrestricted access to the health care system. There was no specific TAU treatment schedule at place for this patient group. However, post hoc analysis of health care resource use following orthopedic rehabilitation shows that 89% of the population had at least one visit to a psychotherapist/psychiatrist and 74% received antidepressant medication (Table 2). Prior to this study, all CBP patients underwent an orthopedic rehabilitation that provided a bio-psycho-social treatment of 3 weeks' duration, aiming to improve patients' functional health and work capacity [27]. All patients fulfilled a depression diagnosis at the end of orthopedic rehabilitation, which comprises some mental health support, but is mainly focused on non-depression-specific exercise therapy, work capacity-related therapy, massage and relaxation training, (back) pain education courses, health behavior training, and social counselling [28]. Patients were randomized on average 75.1 days (SD 66.7) after their orthopedic rehabilitation.

Outcomes

The primary outcome was depression severity assessed via telephone with the clinician-rated structured Hamilton Depression Scale (HAM-D-17) [29–31] at T1. Clinician-rated secondary outcomes, via telephone assessment, were the HAM-D depression severity at T2 and clinician-rated Quick Inventory of Depressive Symptomatology (QIDS) [32] depression severity, depression remission (structured clinical interview for DSM-5 and SCID-V-RV, module A), conducted by trained and supervised psychologists, and reliable change of depression in the HAM-D-17 according to Jacobson and Truax [33]. All further secondary outcomes were based on self-report and collected using a secure, online-based assessment system (AES, 256-bit encrypted): depression severity (PHQ-9) [34], health-related quality of life (AQoL-6D) [35], pain intensity (a numerical rating scale from 0 "no pain" to 10 "extremely intense pain," and a rating scale with four categories from "none" to "severe"), pain-related disability (Oswestry Disability Index; ODI) [36], pain self-efficacy (Pain Self-Efficacy Questionnaire; PSEQ) [37], work capacity (Subjective Prognostic Employment Scale; SPE) [38], intervention adherence (average number of completed treatment sessions, overall attrition rate), and patient satisfaction (Client Satisfaction Questionnaire; CSQ-8) [39]. Health care resource utilization data were assessed using the German translation of the Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness (TiC-P) [40].

Adverse Events and Side Effects

Side effects and adverse events were investigated in five ways. Firstly, side effects of psychotherapy were identified using the Assessment of Negative Effects of Psychotherapy (INEP) [41] at T1. The INEP assesses negative effects in the areas intrapersonal change, relationship, friends and family, work, and stigma. Secondly, patients were asked to report special events including adverse events in a written form at the beginning of each intervention module. All written reports indicating possible adverse events were evaluated by L.B.S. and S.S. with regard to the presence of adverse events and their relation to the intervention. Thirdly, at the end of each telephone interview, when blinding of the clinician was removed, the clinician asked participants about (S)AEs. Fourthly, reliable deterioration based on HAM-D was calculated to assess possible negative changes in symptom severity [33].

Statistical Analysis

Prior trials of internet-based interventions for depression showed a pooled effect size of $d = 0.39$ at post-treatment [42]. The present study was powered to detect this standardized mean difference in the HAM-D with a two-sided significance level of 0.05 and a power of 80%.

Primary analyses were based on intention-to-treat (ITT). Per-protocol (PP) analyses investigated the influence of intervention adherence on outcomes. Participants who completed at least 80% of the intervention (at least five sessions) were defined as completers.

Group differences in continuous outcomes (e.g., HAM-D) were evaluated by linear regression models. Logistic regression was used for dichotomous outcomes (e.g., remission: yes/no). Group allocation, baseline values, recruitment center, sex, and age were defined as predictors in regression models [21].

Missing data was assumed to be missing at random [43]. Multivariate imputation by chained equations using predictive mean matching were performed to create 20 complete datasets [44, 45]. Imputation models were defined following the recommendations by van Buuren et al. [45, 46] with imputation models including outcome and auxiliary variables. Analyses were conducted for each imputed dataset and pooled using Rubin's rules [47, 48].

For all outcomes, the mean, standard deviation, standardized regression coefficient (odds ratio, respectively), and the corresponding 95% confidence interval (CI) were reported. The significance level was set to $p < 0.05$ for all analyses. The software R was used for all analyses [49].

Results

A total of 210 participants were randomized either to eSano BackCare-D + TAU (IG, $n = 105$) or to TAU alone (CG, $n = 105$) between October 2015 and July 2017

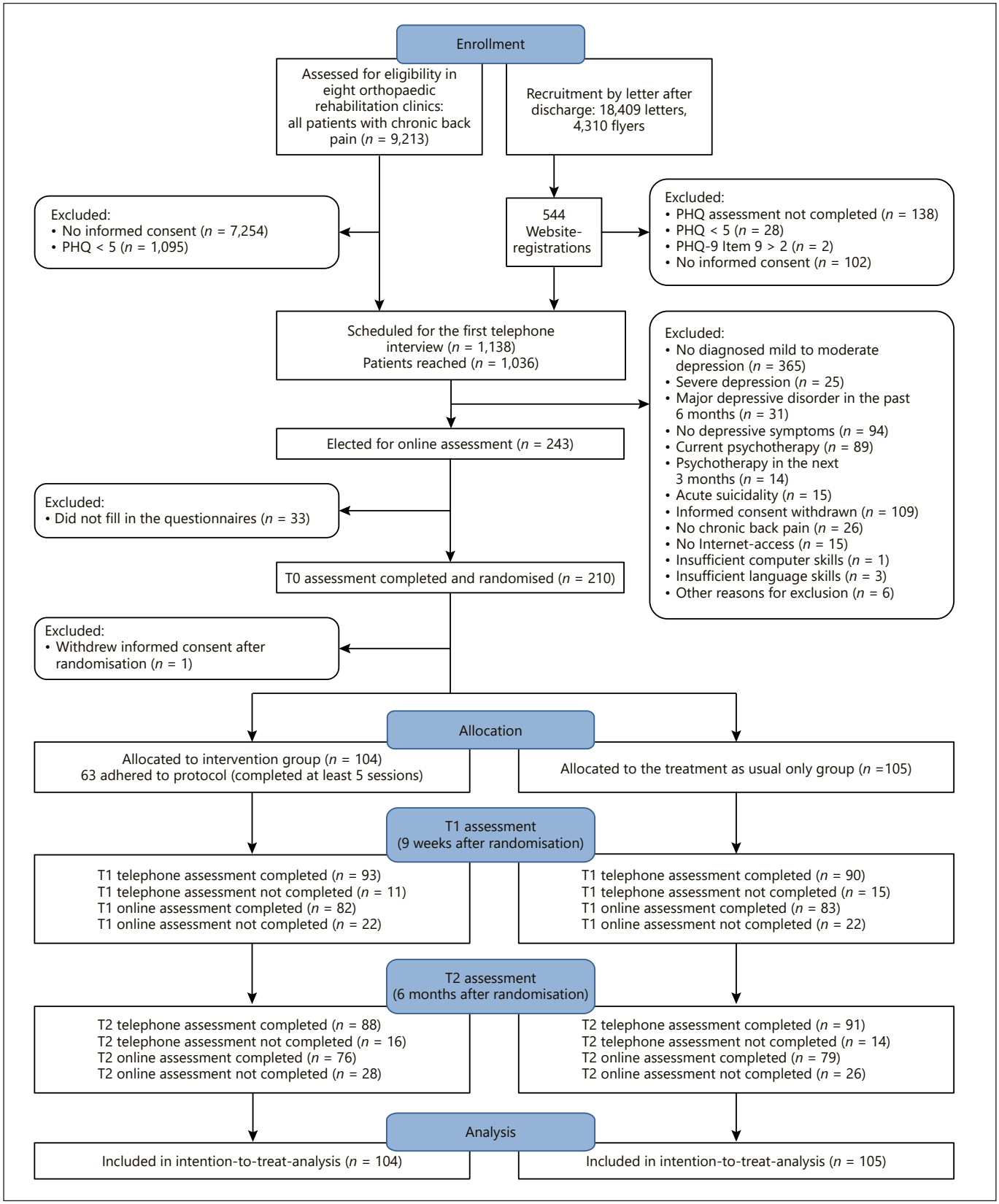

Fig. 1. Study flow chart. Digital depression and CBP intervention trial – WARD-BP.

(Fig. 1). The data of 1 participant in the IG who withdrew consent after randomization had to be removed from all analyses. Power with $n_{IG} = 104$ and $n_{CG} = 105$ remained approximately 80% for the assumed effect size. Participants in each trial arm showed comparable sociodemographic and medical characteristics at baseline (Table 1). Participants reported substantial pain disability while reporting only very low pain intensity (IG: 1.88, SD 0.71; CG: 1.78, SD 0.73). Almost all participants reported at least one visit to a psychotherapist/psychiatrist ($n = 198$, 95%; IG: $n = 101$, 97%; CG: $n = 97$, 92%) or receiving prescribed antidepressants at baseline ($n = 192$, 92%; IG: $n = 99$, 95%, CG: $n = 93$, 89%). The inter-rater reliability between outcome assessors and trainers was excellent ($\kappa = 0.96$, 95% CI 0.97 to 0.95, $p < 0.001$). Clinician ratings showed excellent intra-class correlation (ICC; HAM-D: ICC = 0.97, 95% CI 0.97 to 0.97; QIDS: ICC = 0.95, 95% CI 0.95 to 0.96).

In the IG, 87% of participants completed the introduction module. Adherence rates dropped over the course of six intervention modules: 78% completed the first, 71% the second, 65% the third, 63% the fourth, 58% the fifth, and 55% the final module. In addition to the six core modules, 37% completed the optional module on relationship, 26% on returning to work, and 50% on sleep. Treatment satisfaction was high (mean 24.12, SD 5.01). On average, 87% would "rather" or "strongly recommend" the treatment to a friend in need of help.

Primary Outcome

Depression severity measured by HAM-D was descriptively lower in the IG (mean 9.67, SD 6.41) than in the CG (mean 11.01, SD 7.26) 9 weeks after randomization (T1). However, this group difference was not significant (β = –0.19, 95% CI –0.43 to 0.05, $p = 0.124$; Table 2). Similarly, PP analysis showed a non-significant effect in the same direction (β = –0.27, 95% CI –0.56 to 0.02, $p = 0.071$; Table 3).

Secondary Outcomes

Further Depression Severity Outcomes

At the 6-month follow-up (T2), the IG showed non-significant lower depression severity measured by HAM-D compared to the CG (β = –0.14, 95% CI –0.40 to 0.12, $p = 0.283$). In the PP analysis, a significant difference favoring the IG was found at T2 (β = –0.33, 95% CI –0.63 to –0.04, $p = 0.026$).

Depression severity measured by the QIDS yielded a significant group difference favoring the IG at T1 (β = –0.27, 95% CI –0.52 to –0.01, $p = 0.038$) and a non-significant difference at T2 (β = –0.22, 95% CI –0.49 to 0.05, $p = 0.103$). PP analysis showed significant differences favoring IG at T1 (β = –0.33, 95% CI –0.64 to –0.03, $p = 0.033$) and T2 (β = –0.38, 95% CI –0.67 to –0.09, $p = 0.011$).

In contrast to depression severity rated by clinicians, self-reported depression severity (PHQ-9) was significantly lower in the IG across all measurement points in ITT and PP analyses (ITT at T1: β = –0.40, 95% CI –0.61 to –0.19, $p < 0.001$; T2: β = –0.25, 95% CI –0.49 to –0.00, $p = 0.047$; PP at T1: β = –0.46, 95% CI –0.70 to –0.22, $p < 0.001$; T2: β = –0.44, 95% CI –0.70 to –0.17, $p = 0.001$).

Depression Remission

Structured clinical interviews (SCID) were conducted to assess effects on depression diagnosis and remission. Remission rates in the IG (T1, 72%; T2, 76%) and the CG (T1, 64%; T2, 63%) were both high. No difference in the odds for remission of depression were present at T1 (OR 1.49, 95% CI 0.82 to 2.72, $p = 0.192$). At the 6-month follow-up, the odds for remission were significantly increased in the IG by 97% (OR 1.97, 95% CI 1.05 to 3.68, $p = 0.035$; Table 2). On average NNT (number needed to treat), 7.63 (95% CI 3.99 to 166) subjects needed to be treated to gain 1 additional remission at T2. In the PP analysis, the group difference at T1 was not significant. At T2, the odds for remission were significantly increased by 133% in the IG (OR 2.33, 95% CI 1.08 to 4.97, $p = 0.031$). The NNT was 6.06 (95% CI 3.44 to 47.64).

Reliable Change in Depression

The reliable change index was calculated to further investigate meaningful improvement in depression. Logistic regression analysis yielded no significant differences in the odds for reliable change in clinician-rated depression severity (HAM-D; IG vs. CG: T1, $n = 37$, 36% vs. $n = 33$, 31%; T2, $n = 38$, 37% vs. $n = 34$, 32%; Table 2).

Pain

The IG showed significantly lower pain intensity (β = –0.32, 95% CI –0.57 to –0.06, $p = 0.013$), pain-related disability (ODI; β = –0.31, 95% CI –0.47 to –0.15, $p < 0.001$), and significantly higher pain self-efficacy (β = 0.33, 95% CI 0.15 to 0.51, $p < 0.001$) at T1. Positive effects on pain self-efficacy persisted at T2 (β = 0.24, 95% CI 0.02 to 0.46, $p = 0.032$). No significant group differences in pain intensity and pain-related disability were present at T2 (Table 2).

Table 1. Baseline characteristics

	IG (n = 104)	CG (n = 105)	All (n = 209)
Trial characteristics			
Method of recruitment			
On-site	68 (65)	66 (63)	134 (64)
Online	36 (35)	39 (37)	75 (36)
Patient characteristics			
Patient characteristics			
Age	50.3±9.39	49.6±9.36	49.9±9.36
Sex			
Male	44 (42)	40 (38)	84 (40)
Female	60 (58)	65 (62)	125 (60)
Education level[a]			
Low	69 (66)	63 (60)	132 (63)
Medium	20 (19)	27 (26)	47 (22)
High	15 (14)	15 (14)	30 (14)
Marital status			
Single	12 (12)	10 (10)	22 (11)
Relationship/married	70 (67)	74 (70)	144 (69)
Divorced, separated, or widowed	21 (20)	21 (20)	43 (20)
Number of children			
0	21 (20)	18 (17)	39 (19)
≥1	83 (80)	87 (83)	170 (81)
Social support[b]	1.91±1.00	2.02±1.08	1.97±1.04
Internet affinity[c]			
Low	69 (66)	77 (73)	146 (71)
Medium	31 (30)	20 (19)	51 (24)
High	4 (4)	8 (8)	12 (6)
Diagnosis (SCID-5)			
Chronic MDD	0 (0)	1 (1)	1 (<1)
Chronic MDD + PDD	3 (3)	5 (5)	8 (4)
Chronic MDE + PDD	18 (17)	18 (17)	36 (17)
Chronic MDE without PDD	0 (0)	1 (1)	1 (<1)
MDE	76 (73)	74 (70)	150 (72)
PDD	2 (2)	1 (1)	3 (1)
PDD with intermittent MDE and current episode	2 (2)	5 (5)	7 (3)
PDD (dysthymic syndrome)	3 (3)	0 (0)	3 (1)
Time of first onset			
Early onset (age <21 years)	23 (22)	17 (16)	40 (19)
Late onset (age ≥21 years)	81 (78)	88 (84)	169 (81)
Prior treatment experience[d]			
Only psychotherapy	22 (21)	23 (22)	45 (22)
Only pharmacotherapy	15 (14)	8 (8)	23 (11)
Both	28 (27)	28 (27)	56 (27)
None	65 (63)	71 (68)	136 (65)
Baseline resource use[e]			
At least one visit to psychotherapist/psychiatrist	101 (97)	97 (92)	198 (95)
Receiving prescribed antidepressants	99 (95)	93 (89)	192 (92)
None of both	0 (0)	4 (4)	4 (2)
Post-treatment resource use[e]			
At least one visit to psychotherapist/psychiatrist	65 (86)	72 (89)	139 (89)
Receiving prescribed antidepressants	59 (78)	55 (69)	116 (74)
None of both	5 (6)	5 (5)	10 (6)

Data are observed data, presented as n (%) or the mean ± SD. MDE, major depressive episode; PDD, persistent depressive disorder; MDD, major depressive disorder.

[a] Education level is based on the International Standard Classification of Education (ISCED) 2011 (low: level 1–2, medium: level 3–4, high: level 5+).

[b] Social support was rated from 0 (no support) to 4 (very good support).

[c] Internet affinity (low: 5–11, medium: 12–18, high: 19–25).

[d] Assessed at T0 via telephone.

[e] Assessed with the Tic-P. Percentage of patients causing expenditure for contact (at least one) to a psychotherapist/psychiatrist or for antidepressants within 3 months before baseline or T2.

Table 2. Outcomes at T1 and T2 (ITT)

	IG (n = 104)	CG (n = 105)	Effect size β/OR (95% CI)[a]	p
Primary outcome				
Hamilton				
T0	14.40±5.45	14.61±5.32		
T1	9.67±6.41	11.14±7.26	−0.19 (−0.43 to 0.05)	0.124
Secondary outcomes				
Depression				
Hamilton				
T2	8.97±6.44	9.95±7.13	−0.14 (−0.40 to 0.12)	0.283
QIDS				
T0	12.12±3.79	12.24±3.80		
T1	7.29±4.27	8.56±4.78	−0.27 (−0.52 to −0.01)	0.038
T2	6.68±4.56	7.79±4.97	−0.22 (−0.49 to 0.05)	0.103
PHQ-9				
T0	12.69±4.18	13.00±4.33		
T1	8.92±4.71	11.29±5.82	−0.40 (−0.61 to −0.19)	<0.001
T2	8.63±5.24	10.08±5.69	−0.25 (−0.49 to −0.00)	0.047
Remission (SCID-5)				
T1	75 (72)	67 (64)	1.49 (0.82 to 2.72)	0.192
T2	79 (76)	66 (63)	1.97 (1.05 to 3.68)	0.035
Reliable change (Hamilton)				
T1	37 (36)	33 (31)	1.20 (0.65 to 2.24)	0.557
T2	38 (37)	34 (32)	1.24 (0.69 to 2.21)	0.475
Reliable deterioration (Hamilton)				
T1	3 (3)	7 (7)	0.44 (0.11 to 1.87)	0.270
T2	7 (7)	5 (5)	1.48 (0.44 to 5.00)	0.527
Pain				
Pain intensity (NRS)				
T0	1.88±0.71	1.78±0.73		
T1	1.43±0.79	1.63±0.74	−0.32 (−0.57 to −0.06)	0.013
T2	1.62±0.76	1.67±0.81	−0.14 (−0.43 to 0.15)	0.329
Pain-related disability (ODI)				
T0	36.83±15.86	33.85±14.03		
T1	30.22±15.64	32.36±15.54	−0.31 (−0.47 to −0.15)	<0.001
T2	31.38±16.84	31.42±16.32	−0.17 (−0.35 to 0.01)	0.064
Pain self-efficacy (PSEQ)				
T0	28.08±12.48	32.38±13.01		
T1	35.74±13.77	35.04±14.03	0.33 (0.15 to 0.51)	<0.001
T2	35.59±14.23	35.59±13.75	0.25 (0.04 to 0.46)	0.020
Quality of Life				
AQoL-6D				
T0	54.90±8.62	54.04±7.90		
T1	48.32±9.85	51.20±11.23	−0.36 (−0.55 to −0.18)	<0.001
T2	47.45±10.93	49.50±11.44	−0.28 (−0.47 to −0.08)	0.006
Work capacity				
SPE				
T0	1.70±1.08	1.76±1.07		
T1	1.77±1.19	1.62±1.16	0.15 (−0.08 to 0.38)	0.197
T2	1.59±1.16	1.68±1.17	−0.05 (−0.33 to 0.23)	0.709

Data are based on multiple imputations, presented as the mean ± SD or n (%), unless otherwise indicated. T1, 9-week follow-up; T2, 6-month follow-up. Confidence intervals are based on robust standard errors.

[a] Adjusted between group differences provided as the standardized regression estimate (β; or OR for remission [SCID-5] and reliable change [Hamilton]) adjusted for trial center, age, sex, and baseline.

Table 3. Outcomes at T1 and T2 (PP)

	IG (n = 63)	CG (n = 105)	Adjusted between group differences (95% CI)[a]	p
Secondary outcomes				
Depression				
Hamilton				
T0	14.90±5.57	14.61±5.32		
T1	9.17±6.81	11.14±7.26	−0.27 (−0.56 to 0.23)	0.071
T2	7.95±6.01	9.95±7.13	−0.33 (−0.63 to −0.04)	0.026
QIDS				
T0	12.37±3.95	12.24±3.80		
T1	6.75±4.36	8.56±4.78	−0.33 (−0.64 to −0.03)	0.033
T2	5.95±4.06	7.79±4.97	−0.38 (−0.67 to −0.09)	0.011
PHQ-9				
T0	12.87±4.44	13.00±4.33		
T1	8.44±4.50	11.29±5.82	−0.46 (−0.70 to −0.22)	<0.001
T2	7.61±4.65	10.08±5.69	−0.44 (−0.70 to −0.17)	0.001
Remission (SCID-5)				
T1	45 (71)	67 (64)	1.41 (0.70 to 2.83)	0.341
T2	50 (79)	66 (63)	2.33 (1.09 to 4.97)	0.031
Reliable change (Hamilton)				
T1	29 (46)	33 (31)	2.07 (1.02 to 4.19)	0.046
T2	31 (49)	34 (32)	2.31 (1.17 to 4.58)	0.017
Reliable deterioration (Hamilton)				
T1	1 (2)	7 (7)	0.25 (0.03 to 2.2)	0.218
T2	2 (3)	5 (5)	0.52 (0.08 to 3.26)	0.490
Pain				
Pain intensity (NRS)				
T0	1.90±0.67	1.78±0.73		
T1	1.41±0.81	1.59±0.73	−0.41 (−0.68 to −0.14)	0.003
T2	1.56±0.70	1.68±0.81	−0.24 (−0.52 to 0.03)	0.085
Pain-related disability (ODI)				
T0	36.32±16.17	33.85±14.03		
T1	29.80±16.08	32.32±15.55	−0.32 (−0.51 to −0.14)	<0.001
T2	29.52±16.84	31.25±16.33	−0.28 (−0.49 to −0.08)	0.007
Pain self-efficacy (PSEQ)				
T0	27.97±12.74	32.38±13.01		
T1	38.13±13.82	34.88±14.06	0.49 (0.27 to 0.70)	<0.001
T2	37.57±14.80	35.54±13.78	0.35 (0.10 to 0.60)	0.007
Quality of Life				
AQoL-6D				
T0	54.89±8.66	54.04±7.90		
T1	47.32±9.92	51.19±11.25	−0.44 (−0.66 to −0.23)	<0.001
T2	45.21±10.47	49.49±11.44	−0.48 (−0.70 to −0.26)	<0.001
Work capacity				
SPE				
T0	1.71±1.12	1.76±1.07		
T1	1.50±1.23	1.63±1.16	−0.11 (−0.35 to 0.13)	0.372
T2	1.50±1.20	1.68±1.17	−0.15 (−0.41 to 0.11)	0.252

PP data are imputed data, presented as the mean ± SD or n (%), unless otherwise indicated. T1, 9-week follow-up; T2, 6-month follow-up. Confidence intervals are based on robust standard errors.

[a] Adjusted between group differences provided as the standardized regression estimate (β; or OR for remission [SCID-5] and reliable change [Hamilton]) adjusted for trial center, age, sex, and baseline.

Table 4. Summary of side effects based on the INEP questionnaire

	Negative change		No change		Positive change	
	n	IMI assoc.	*n*	IMI assoc.	*n*	IMI assoc.
Intrapersonal change						
Improvement/worsening of symptoms	5	1	19	3	58	45
More/less trusting of others	0	0	42	5	40	31
Suffering from past experiences/events	4	1	25	4	53	47
Difficulties to make decisions alone	8	2	74	20	–	–
Feeling dependent on eCoach	3	2	79	36	–	–
Longer periods of feeling bad	26	1	56	20	–	–
As a human being changed to the negative	3	1	79	33	–	–
Thoughts/plans to commit first-time suicide	2	0	80	25	–	–
Relationship						
More/less arguments in relationship	6	5	32	2	30	23
Partner jealous with therapeutic relationship	0	0	66	17	–	–
Friends and family						
Worsened/improved family relationship	2	2	36	5	44	32
Worsened/improved friends relationship	3	0	42	8	37	29
Work						
More/less arguments with colleagues/superiors	3	1	79	36	–	–
Stigma						
Worries about insurance fees	5	1	77	25	–	–
Financial worries	15	0	67	18	–	–

Data are observed data of the IG (n = 104). IMI assoc., events attributed to the IMI.

Effects were higher for adherent participants. All pain outcomes except pain intensity at T2 significantly favored the IG compared to the CG at T1 and T2 in the PP analyses (Table 3).

Health-Related Quality of Life

Significant differences between groups in health-related quality of life (AQoL-6D) favoring the IG were found at T1 (β = –0.36, 95% CI –0.55 to –0.18, $p < 0.001$) and T2 (β = –0.28, 95% CI –0.47 to –0.08, $p = 0.006$; Table 2). Beneficial effects on health-related quality of life were higher for adherent participants (T1: β = –0.44, 95% CI –0.66 to –0.23, $p < 0.001$; T2: β = –0.48, 95% CI –0.70 to –0.26, $p < 0.001$; Table 3).

Work Capacity

Differences in work capacity were non-significant at T1 and T2 (Table 2). PP analysis showed similar results (Table 3).

Adverse Events and Side Effects

In the IG, a total of 49 adverse events were reported at T1 and 48 at T2. No participant reported an adverse event caused by the intervention. In the CG, 42 and 44 adverse events occurred at T1 and T2, respectively. No significant differences in the frequency of adverse events were found (T1: $\chi^2_{(1,\, n = 209)}$ 0.806, $p = 0.369$; T2: $\chi^2_{(1,\, n = 209)}$ 0.230, $p = 0.632$). A total of 33 participants self-reported an adverse event over the course of the intervention, assessed at the beginning of each session. None of these events were attributed to the intervention.

Based on the INEP self-report questionnaire, participants of the IG reported 262 positive, 853 neutral (no change), and 85 negative side effects. Of the 85 negative side effects, 17 (20%) were attributed to the intervention (Table 4).

Finally, reliable deterioration in depression (HAM-D) was not significantly influenced by group at T1 ($n_{IG} = 3$, $n_{CG} = 7$, OR 0.44, 95% CI 0.11 to 1.87, $p = 0.270$) and T2 ($n_{IG} = 7$, $n_{CG} = 5$, OR 1.48, 95% CI 0.44 to 5.00, $p = 0.527$; Table 2). The PP analysis showed similar results (Table 3).

Discussion

The primary outcome, observer-masked HAM-D, suggests that eSano BackCare-D as a depression IMI for patients with comorbid CBP and a depressive disorder is not significantly superior over usual care alone when implemented following routine orthopedic rehabilitation care. While self-reported depression severity and remission rates at the 6-month follow-up improved significantly in the IG compared to the CG, reliable changes on the HAM-D were not significant (please note the explorative nature of all secondary outcomes). Results for secondary endpoints other than depression suggest that eSano BackCare-D might be effective in reducing pain-related outcomes and improving health-related quality of life with low to moderate effects. In health care policy, digitalization has become a key concept meant to overcome mental health care gaps. Whereas research mostly support this viewpoint [13, 50, 51], the present study argues to temper expectations and to look closely at ways of implementation in different settings.

Methodological differences might explain the low effect sizes in the present trial. Higher effect sizes in prior trials [13, 52] might be a function of using self-reported rather than clinician-diagnosed depression outcomes, not blinding outcome assessors and biostatisticians, and using waiting list CGs instead of TAU as control conditions [42, 53, 54]. Thus, the results of this study might just reflect a more conservative estimate of the true effect size of depression interventions examined in methodologically rigorous conducted trials, regardless of the online or face-to-face provision of the intervention.

The nature of the trial population and the setting might constitute further reasons for the non-significant small primary outcome effect. Participants with comorbid CBP and a mild to moderate depressive disorder were recruited. The findings of the present trial might suggest added complexity in the treatment of depression in this population; however, there is little research indicating depression to be more difficult to treat in CBP patients compared to other somatically ill patients. The findings could be further moderated by the representative case mix of substantially male, older, and less educated CBP participants that we managed to recruit. Studies on moderators of IMI, however, suggest none of these variables as a predictor for smaller between group treatment effects [13, 52].

Finally, the specific setting might be of relevance when interpreting the findings. Unlike most other trials of depression IMI [52], we recruited in routine care. Thus, the present population represents a sample of patients who were willing to access on-site health care for their medical health conditions. IMI might work differently in samples recruited from the general population through different online/offline advertisement strategies or from routine health care settings. Our recruitment strategy may have resulted in a different case mix with different prior treatment experience. In contrast to prior trials, the present study was conducted as an aftercare trial following orthopedic rehabilitation. Orthopedic rehabilitation in Germany comprises insufficient mental health resources to adequately treat depression and all included patients fulfilled the criteria for a depressive disorder at discharge. Still, patients might have profited from unspecific psycho-social treatment strategies (e.g. patient education groups, walking classes, and relaxation sessions) within the rehabilitation setting. These elements alone might have reduced depression severity in the long term, as was evidenced by the high remission rate in the CG (64% at the 9-week follow-up). This suggests an already effective and sustainable routine care, in which an impressive 95 and 89% of participants reported at least one visit to a psychotherapist or psychiatrist at baseline, respectively, 3–6 months after randomization as part of usual care following orthopedic rehabilitation. In this respect, our findings are similar to a trial reported by Gilbody et al. [17], who examined the adjunct effects of IMI provided by general practitioners. They also reported a non-significant finding, arguing for a tempered view on effect sizes of IMI integrated into existing routine care.

Therefore, integrating IMI as innovative interventions into existing health care requires distinguishing between stand-alone and add-on solutions. It needs to be defined where these approaches can: (a) complement or (b) replace existing offers, and (c) where IMI do not provide additional benefit. Further research should focus on both the effectiveness and reach of these interventions [10, 53–57] to help define the public health relevance of e-mental health innovations.

There are limitations to consider. First, due to the nature of the intervention participants could not be blinded to their assigned condition. Expectancy effects and biases based on the absence of blinding might have occurred. However, expectancy effects are common in routine care and do not necessarily constitute a flaw of naturalistic trials, even allowing a more realistic evaluation in routine care [58–60]. Second, participants needed to pass through an intensive informed consent and assessment process in order to take part in this study. This research bias of se-

lecting the resilient part of a population, which is inherent to all RCTs, might have led to a sample non-representative of the CBP population with a depressive disorder. Third, patients had only mild to moderate baseline depression severity on average, thus limiting the potential for improvement [61]. However, as IMI are suggested as a low-intensity approach for mild to moderate depression [61], the present effectiveness trial highlights that this recommendation needs further specification. A depression IMI for patients with a depressive disorder might not work in routine care as it does in general population samples [13], at least not if provided adjunct to usual care. Fourth, the present effectiveness trial builds on routine care which varies substantially across countries. Hence, effects might differ substantially if implemented into routine care settings of other countries, probably with higher effects if implemented in resource-poor health care settings. Fifth, participants reported only mild pain intensity at baseline despite their diagnosed CBP disorder and substantial pain disability. As such, the present sample might not be generalizable to patient samples with intensive acute pain conditions.

Conclusion

IMI for CBP patients with a depressive disorder may have limited impact in routine clinical care, at least when routine care already comprises further active treatments such as medication and psychotherapy. Future studies should therefore explore for whom IMI work best and how and at what point of the disease and treatment course they should be provided either as stand-alone, in a stepped-care framework, or as combination therapy. Positive secondary depression, pain, and health-related quality of life outcomes of the present trial argue for the potential of such an intervention, particularly in more resource-poor populations not already sufficiently treated.

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Statement of Ethics

All patients gave their written informed consent. All procedures were approved by the ethics committee of the Albert-Ludwigs University of Freiburg, Germany (No. 8022-6-BW-H-2015; No. 297/14_160939) and the data security committee of the German Pension Insurance (Deutsche Rentenversicherung; 8022-6-BW).

Conflict of Interest Statement

Authors of the manuscript were partly involved in the development of eSano BackCare-BP or its predecessor versions. A committee of independent scientists has been formed (DSMB) to supervise study-related decisions and prevent any influence of potential conflicts of interest.

L.B.S. and S.S. have received payments for workshops on e-mental-health. H.B. received consultancy fees, reimbursement of congress attendance and travel costs as well as payments for lectures from Psychotherapy and Psychiatry Associations as well as Psychotherapy Training Institutes in the context of E-Mental-Health topics. He has been the beneficiary of study support (third-party funding) from several public funding organizations. D.D.E. and D.L. possess shares in the GET.On Institut GmbH, which works to transfer research findings on internet- and mobile-phone-based health interventions into routine care. D.D.E. has received payments from several companies and health insurance providers for advice on the use of Internet-based interventions. He has received payments for lectures from Psychotherapy and Psychiatry Associations and has been the beneficiary of third-party funding from health insurance providers. J.B. is a member of the committee on E-Mental Health in the Association of Psychotherapists (Landespsychotherapeutenkammer Baden-Württemberg).

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Author Contributions

H.B. is the overall guarantor of this report and takes responsibility for the content, including the data and analysis. H.B. designed the trial, acquired funding and ethics approval, is the chief investigator of the trial, coordinated trial management, developed the intervention, collected data, and wrote and revised the manuscript. S.P. acquired ethics approval, coordinated the clinical trial, developed the intervention, collected data, and wrote and revised the manuscript. L.B.S. and J.L. acquired ethics approval, coordinated the clinical trial, developed the intervention, collected data and revised the manuscript. S.S. coordinated the randomization, allocation, and assessment procedure, collected data, provided intervention development support, and revised the manuscript. Y.T. provided methodological and statistical support and wrote and revised the manuscript. M.M. conducted the independent data analysis and revised the manuscript. J.B. was co-investigator at the University of Freiburg and revised the manuscript. D.L. provided intervention development support and revised the manuscript. D.D.E. designed the trial, acquired funding, coordinated trial management, provided intervention development support, and wrote and revised the manuscript. All authors read and approved the final report.

References

1 Campbell LC, Clauw DJ, Keefe FJ. Persistent pain and depression: a biopsychosocial perspective. Biol Psychiatry. 2003 Aug;54(3):399–409.
2 Thom R, Silbersweig DA, Boland RJ. Major depressive disorder in medical illness: a review of assessment, prevalence, and treatment options. Psychosom Med. 2019 Apr;81(3):246–55.
3 Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. Cochrane Database Syst Rev. 2012 Dec;12:CD008381.
4 Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Cochrane Database Syst Rev. 2011 Sep;9(9):CD008012.
5 Vitoula K, Venneri A, Varrassi G, Paladini A, Sykioti P, Adewusi J, et al. Behavioral therapy approaches for the management of low back pain: an up-to-date systematic review. Pain Ther. 2018 Jun;7(1):1–12.
6 Broderick JE, Keefe FJ, Schneider S, Junghaenel DU, Bruckenthal P, Schwartz JE, et al. Cognitive behavioral therapy for chronic pain is effective, but for whom? Pain. 2016 Sep;157(9):2115–23.
7 Dixon KE, Keefe FJ, Scipio CD, Perri LM, Abernethy AP. Psychological interventions for arthritis pain management in adults: a meta-analysis. Health Psychol. 2007 May;26(3):241–50.
8 Saxena S, Thornicroft G, Knapp M, Whiteford H. Resources for mental health: scarcity, inequity, and inefficiency. Lancet. 2007 Sep;370(9590):878–89.
9 Pilling S, Anderson I, Goldberg D, Meader N, Taylor C; Two Guideline Development Groups. Depression in adults, including those with a chronic physical health problem: summary of NICE guidance. BMJ. 2009 Oct;339:b4108.
10 Ebert DD, Van Daele T, Nordgreen T, Karekla M, Compare A, Zarbo C, et al. Internet- and Mobile-based psychological interventions: applications, efficacy, and potential for improving mental health. Eur Psychol. 2018;23(2):167–87.
11 Bendig E, Bauereiss N, Ebert DD, Snoek F, Andersson G, Baumeister H. Internet-based interventions in chronic somatic disease. Dtsch Arztebl Int. 2018 Nov;115(40):659–65.
12 Wright JH, Caudill R. Remote treatment delivery in response to the COVID-19 Pandemic. Psychother Psychosom. 2020;89(3):130–2.
13 Josephine K, Josefine L, Philipp D, David E, Harald B. Internet- and mobile-based depression interventions for people with diagnosed depression: a systematic review and meta-analysis. J Affect Disord. 2017 Dec;223:28–40.
14 van Beugen S, Ferwerda M, Hoeve D, Rovers MM, Spillekom-van Koulil S, van Middendorp H, et al. Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review. J Med Internet Res. 2014 Mar;16(3):e88.

15 Garg S, Garg D, Turin TC, Chowdhury MF. Web-based interventions for chronic back pain: a systematic review. J Med Internet Res. 2016 Jul;18(7):e139.
16 Buhrman M, Syk M, Burvall O, Hartig T, Gordh T, Andersson G. Individualized guided internet-delivered cognitive-behavior therapy for chronic pain patients with comorbid depression and anxiety: a randomized controlled trial. Clin J Pain. 2015 Jun;31(6):504–16.
17 Gilbody S, Littlewood E, Hewitt C, Brierley G, Tharmanathan P, Araya R, et al.; REEACT Team. Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. BMJ. 2015 Nov;351:h5627.
18 Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar;340:c869.
19 Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al.; CONSORT group; Pragmatic Trials in Healthcare (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ. 2008 Nov;337:a2390.
20 Guidi J, Brakemeier EL, Bockting CL, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological recommendations for trials of psychological interventions. Psychother Psychosom. 2018;87(5):276–84.
21 Lin J, Sander L, Paganini S, Schlicker S, Ebert D, Berking M, et al. 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. BMJ Open. 2017 Dec;7(12):e015226.
22 He C, Levis B, Riehm KE, Saadat N, Levis AW, Azar M, et al. The accuracy of the Patient Health Questionnaire-9 algorithm for screening to detect major depression: an individual participant data meta-analysis. Psychother Psychosom. 2020;89(1):25–37.
23 Löwe B, Kroenke K, Herzog W, Gräfe K. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord. 2004 Jul;81(1):61–6.
24 Wittchen HU, Zaudig M, Fydrich T. Strukturiertes Klinisches Interview für DSM-IV. Göttingen: Hogrefe; 1997.
25 Sander L, Paganini S, Lin J, Schlicker S, Ebert DD, Buntrock C, et al. Effectiveness and cost-effectiveness of a guided Internet- and mobile-based intervention for the indicated prevention of major depression in patients with chronic back pain-study protocol of the PROD-BP multicenter pragmatic RCT. BMC Psychiatry. 2017 Jan;17(1):36.
26 Sander LB, Paganini S, Terhorst Y, Schlicker S, Lin J, Spanhel K, et al. Effectiveness of a guided web-based self-help intervention to prevent depression in patients with persistent back pain: the PROD-BP randomized clinical trial. JAMA Psychiatry. 2020 May;77(10):1001.
27 Vogel H, Zdrahal-Urbanek J. Rehabilitation in Germany: new challenges of a structured social security scheme. Int J Rehabil Res. 2004 Jun;27(2):93–8.
28 Jäckel W, Gülich M. Reha-Therapiestandards Chronischer Rückenschmerzen. Berlin: Deutsche Rentenversicherung Bund; 2011.
29 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960 Feb;23(1):56–62.
30 Carrozzino D, Patierno C, Fava GA, Guidi J. The Hamilton Rating Scales for Depression: A critical review of clinimetric properties of different versions. Psychother Psychosom. 2020;89(3):133–50.
31 Potts MK, Daniels M, Burnam MA, Wells KB. A structured interview version of the Hamilton Depression Rating Scale: evidence of reliability and versatility of administration. J Psychiatr Res. 1990;24(4):335–50.
32 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003 Sep;54(5):573–83.
33 Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991 Feb;59(1):12–9.
34 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606–13.
35 Richardson JR, Peacock SJ, Hawthorne G, Iezzi A, Elsworth G, Day NA. Construction of the descriptive system for the Assessment of Quality of Life AQoL-6D utility instrument. Health Qual Life Outcomes. 2012 Apr;10(1):38.
36 Mannion AF, Junge A, Grob D, Dvorak J, Fairbank JC. Development of a German version of the Oswestry Disability Index. Part 2: sensitivity to change after spinal surgery. Eur Spine J. 2006 Jan;15(1):66–73.
37 Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. Eur J Pain. 2007 Feb;11(2):153–63.
38 Mittag O, Raspe H. A brief scale for measuring subjective prognosis of gainful employment: findings of a study of 4279 statutory pension insurees concerning reliability (Guttman scaling) and validity of the scale. Rehabilitation. 2003 Jun;42(3):169–74. German.
39 Boß L, Lehr D, Reis D, Vis C, Riper H, Berking M, et al. Reliability and validity of assessing user satisfaction with web-based health interventions. J Med Internet Res. 2016 Aug;18(8):e234.
40 Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van der Feltz-Cornelis C, Tan Swan S, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Serv Res. 2013 Jun;13(1):217.
41 Ladwig I, Rief W, Nestoriuc Y. What are the risks and side effects of psychotherapy? – Development of an inventory for the assessment of negative effects of psychotherapy (INEP). Verhaltenstherapie. 2014;24(4):252–63.
42 Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. Clin Psychol Rev. 2012 Jun;32(4):329–42.
43 Enders CK. Applied missing data analysis. New York: Guilford Press; 2010.
44 Little RJ. Missing-data adjustments in large surveys. J Bus Econ Stat. 1988;6(3):287–96.
45 van Buuren S, Groothuis-Oudshoorn K. Mice : multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3)1–67. https://doi.org/10.18637/jss.v045.i03.
46 van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999 Mar;18(6):681–94.
47 Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley Sons; 1987. https://doi.org/10.1002/9780470316696.
48 Rubin DB. Multiple Imputation after 18+ years. J Am Stat Assoc. 1996;91(434):473–89.
49 R Core Team [Internet]. R: a language and environment for statistical computing. Vienna: R foundation for statistical computing; 2018 [cited 2020 Sep 24th]. Available from: https://www.R-project.org/.
50 Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther. 2018 Jan;47(1):1–18.
51 Paganini S, Teigelkötter W, Buntrock C, Baumeister H. Economic evaluations of internet- and mobile-based interventions for the treatment and prevention of depression: a systematic review. J Affect Disord. 2018 Jan;225:733–55.
52 Karyotaki E, Kemmeren L, Riper H, Twisk J, Hoogendoorn A, Kleiboer A, et al. Is self-guided internet-based cognitive behavioural therapy (iCBT) harmful? An individual participant data meta-analysis. Psychol Med. 2018 Nov;48(15):2456–66.
53 Hempel S, Suttorp MJ, Miles JN, Wang Z, Maglione M, Morton S, et al. Empirical evidence of associations between trial quality and effect size. Rockville: Agency for Healthcare Research and Quality; 2011.
54 Zhang Z, Xu X, Ni H. Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. Crit Care. 2013 Jan;17(1):R2.

55 Baumeister H, Seifferth H, Lin J, Nowoczin L, Lüking M, Ebert D. Impact of an acceptance facilitating intervention on patients' acceptance of Internet-based pain interventions. Clin J Pain. 2015 Jun;31(6):528–35.
56 Ebert DD, Berking M, Cuijpers P, Lehr D, Pörtner M, Baumeister H. Increasing the acceptance of internet-based mental health interventions in primary care patients with depressive symptoms. A randomized controlled trial. J Affect Disord. 2015 May;176:9–17.
57 Baumeister H, Terhorst Y, Grässle C, Freudenstein M, Nübling R, Ebert DD. Impact of an acceptance facilitating intervention on psychotherapists' acceptance of blended therapy. PLoS One. 2020 Aug;15(8):e0236995.
58 Rutherford BR, Wager TD, Roose SP. Experimental methodology and effects on patient outcome. Curr Psychiatry Rev. 2010 Feb;6(1):1–10.
59 Meyer B, Pilkonis PA, Krupnick JL, Egan MK, Simmens SJ, Sotsky SM. Treatment expectancies, patient alliance, and outcome: further analyses from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol. 2002 Aug;70(4):1051–5.
60 Greenberg RP, Constantino MJ, Bruce N. Are patient expectations still relevant for psychotherapy process and outcome? Clin Psychol Rev. 2006 Oct;26(6):657–78.
61 Bower P, Kontopantelis E, Sutton A, Kendrick T, Richards DA, Gilbody S, et al. Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. BMJ. 2013 Feb;346:f540.