Economic evaluation alongside a randomized controlled trial of blended cognitive-behavioral therapy for patients suffering from major depressive disorder

Astrid Langergaard [a], Kim Mathiasen [c,d,e], Jesper Søndergaard [a], Sabrina S. Sørensen [a], Sidsel L. Laursen [a], Alexander A.P. Xylander [f], Mia B. Lichtenstein [c,d], Lars H. Ehlers [a,b,*]

[a] Danish Center for Healthcare Improvements, Department of Clinical Medicine, Aalborg University, Denmark
[b] Nordic Institute of Health Economics A/S, Aarhus, Denmark
[c] Department of Clinical Research, University of Southern Denmark, Denmark
[d] Center for Telepsychiatry, Mental Health Services in the Region of Southern Denmark, Denmark
[e] Odense Patient Data Exploratory Network, Odense University Hospital, Denmark
[f] Medical Informatics, Department of Health Science and Technology, Aalborg University, Denmark

ARTICLE INFO

ABSTRACT

Objective: This study aimed to investigate the cost-effectiveness of blended cognitive-behavioral therapy (CBT) compared to standard CBT for adult patients suffering from major depressive disorder (MDD).

Design: A cost-utility analysis alongside the randomized controlled ENTER trial.

Setting: Center for Telepsychiatry, Mental Health Services in the Region of Southern Denmark, Denmark.

Participants: The study included 76 patients suffering from MDD.

Interventions: The patients in the intervention group received blended CBT treatment comprising a combination of online modules and face-to-face consultations with a psychologist. The patients in the control group received standard CBT treatment, that is, solely face-to-face consultations with a psychologist. The treatment period was 12 weeks.

Outcome measures: Cost-effectiveness was reported as incremental cost-effectiveness ratio. A micro-costing approach was applied to evaluate the savings derived. Changes in quality-adjusted life-years (QALYs) were estimated using the EuroQol 5-Dimensions 5-Levels questionnaire at the baseline and the six-month follow-up.

Results: Data for 74 patients were included in the primary analysis. The adjusted QALY difference between blended CBT and standard CBT was −0.0291 (95% CI: −0.0535 to −0.0047), and the adjusted difference in costs was -£226.32 (95% CI: −300.86 to −151.77). Blended CBT was estimated to have a 6.6% and 3.1% probability of being cost-effective based on thresholds of £20,000 and £30,000.

Conclusion: Compared to standard CBT, blended CBT represents a cost-saving but also a loss in QALYs for patients suffering from MDD. However, results should be carefully interpreted, given the small sample size. Future research involving larger replication studies focusing on other aspects of blended CBT with more patient involvement is advised.

Trial registration number: ClinicalTrial.gov: S-20150150.

---

1. Introduction

Depressive disorders are highly prevalent diseases and, according to the World Health Organization (WHO), unipolar depression is the third most burdensome disease globally and number one in high-income countries (World Health Organization, 2008). Internationally, major depressive disorder (MDD) is estimated to affect more than 160 million people (World Health Organization, 2008). In Denmark, the prevalence of MDD is estimated at 3%, which corresponds to approximately 162,000 people (Olsen et al., 2004; The Danish Health and Medicines Authority, 2005). The economic burden of psychiatric diseases in the country was estimated at €5.2 billion in 2015, of which depression accounted for €1.2 billion (Vestergaard et al., 2020).

Although effective treatment for depression exists, there are large gaps in the availability of sufficient treatment, with most people suffering from MDD not in treatment and less than half of depression cases diagnosed correctly in general practice (The Danish Health and Medicines Authority, 2005; Huhn et al., 2014; Shafran et al., 2009; Alonso et al., 2007).

Cognitive-behavioral therapy (CBT) is the most effective psychotherapeutic treatment approach for MDD, with internet-based CBT (iCBT) showing promising results in terms of effectiveness, potentially increasing the availability of CBT treatment (Andrews et al., 2018; Hedman et al., 2012; Arnberg et al., 2014). Considering control conditions such as waiting lists, no treatment, and treatment as usual (with psychologists and general practitioners), the potential effectiveness of iCBT is clear. However, it is a low-intensity treatment format that presupposes a high degree of patient engagement (Karyotaki et al., 2018). Combining iCBT with standard face-to-face consultations in a blended CBT (B-CBT) format presumably retains advantages from both iCBT and standard CBT (S-CBT) (Mathiasen et al., 2016; Mathiasen et al., submitted; Andersson et al., 2009). Thus, a therapist-guided B-CBT treatment might enhance the efficacy of iCBT to reach levels equal to S-CBT, potentially saving costs. Few studies have investigated the cost-effectiveness of combining iCBT with S-CBT, indicating the demand for more evidence regarding B-CBT's cost-effectiveness (Kooistra et al., 2019).

Accordingly, this economic evaluation investigates the cost-effectiveness of B-CBT compared to S-CBT for adult patients suffering from MDD in a public psychiatric clinic in Denmark.

2. Methods

A cost-utility analysis (CUA) was conducted in accordance with international guidelines for economic evaluations alongside clinical trials in the healthcare context (Ramsey et al., 2015; Faria et al., 2014; Drummond et al., 2015). The single-blinded two-arm randomized controlled non-inferiority trial comprised part of the E-Mental health research (ENTER) (ENTER - The Blended Care Project) located and co-ordinated from the Center for Telepsychiatry at the Mental Health Service of the Region of Southern Denmark. The ENTER trial protocol used in the study design and the clinical results of the trial are presented elsewhere (Mathiasen et al., 2016; Mathiasen et al., submitted). The costs were estimated using a case-mix approach that considered both micro-costs and mean costs based on diagnosis-related groups (Drummond et al., 2015). Only relevant costs were included, that is, costs that differed between the two alternatives. The cost data for 2015–2018 were adjusted to 2019 price levels using the Danish net price index and estimated by converting Danish Krone (DKK) to British Pounds Sterling (£) at the exchange rate of DKK 876.64 per £100 (from 30 December 2019) (Statistics Denmark; EUROinvestor, 2019). All clinical and cost data were collected alongside the ENTER trial and were not discounted due to a six-month time horizon.

2.1. Intervention and control group

The analyses considered B-CBT the intervention group and S-CBT the control group. Both groups received CBT as the treatment method; this approach featured the same core components but differed in terms of delivery format. The B-CBT participated in six individual face-to-face CBT consultations and six to eight online CBT modules. The face-to-face consultations were administered by a licensed clinical psychologist at the Center for Telepsychiatry in the Region of Southern Denmark. The online CBT modules comprised six mandatory modules involving psychoeducation, cognitive restructuring, behavioral activation, behavior experiments, and relapse prevention, along with two optional modules involving rumination coping techniques and restructuring of core beliefs. Thus, the participants receiving B-CBT were offered a total of 12–14 sessions over a period of 12 weeks.

Meanwhile, S-CBT participants received 12 individual face-to-face CBT consultations over a period of 12 weeks. The participants in both groups had access to the usual care from their general practitioner and medical treatment if they were able to keep it stable during the treatment period. Additionally, participants receiving B-CBT were monitored for symptoms of depression, suicidal thoughts, and treatment adherence between sessions and consultations. To encourage treatment adherence, participants received either or both automated SMS and e-mail reminders concerning homework assignments and questionnaires. Further e-mail or telephone contact was initiated if the participants receiving B-CBT were inactive. Additionally, their psychologist offered technical support during the treatment period.

2.2. Participants

The participants were recruited from the clinic "Internetpsykiatrien" at the Center for Telepsychiatry, which is located in a public mental health hospital (The Region of Southern Denmark). Recruitment was conducted using advertisements in local newspapers, social media accounts belonging to "Internetpsykiatrien", and brochures at local general practitioners, psychiatrists, psychologists, and job centers. Participants had to be ≥18 years of age, meet the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (O'Connor et al., 2009) criteria for MDD, and score ≥5 on a Patient Health Questionnaire-9 (PHQ-9) (Sun et al., 2020). The International Neuropsychiatric Interview version 5.0 (M.I.N.I.) (Sheehan et al., 1998) was used to confirm a depression diagnosis and determine the trial's feasibility for each patient. Participants were excluded if they met any of the following criteria: a) current high risk of suicide, b) inability to speak or write in Danish, c) no access to a computer with the Internet, d) concurrently receiving psychological treatment for depression, or e) a comorbid substance dependence, bipolar affective disorder, psychotic disorder, or obsessive-compulsive disorder. An independent researcher individually randomized participants to either B-CBT or S-CBT following eligibility and baseline assessment. Blinding of participants and clinicians was not possible, but the researcher and statisticians assessing the participants were blinded until the results interpretation stage. Participants were enrolled for the period between March 2016 and April 2018, and written informed consent was obtained from all participants before the trial began.

2.3. Intervention costs

The costs presented in this analysis are estimations of the expected costs of implementing B-CBT in a public psychiatric clinic in Denmark. Details of the cost estimates and intervention costs are presented in Appendix A. Intervention costs include technology costs, overhead costs, the education of healthcare professionals, and the costs of CBT sessions. Technology costs refer to the monthly license fee for the treatment program NoDep, which includes server space and technical support for psychologists and patients. Technology costs were allocated and

estimated according to the anticipated number of patients to be treated at the Center for Telepsychiatry over the 12-week treatment period. Overhead costs, including rental of office space, cleaning, and insurance, were estimated based on hourly costs and the number of face-to-face consultations. Regarding psychologist education, a parallel introduction to the program was provided, with one psychologist assumed to be a superuser of the program. The cost of educating psychologists was estimated as the annual cost based on the national hourly wage for psychologists and the time spent on education (Denmark, 2018). This cost was annuitized over three years with an annual discount rate of 4% in accordance with Danish capital accounting and calculated based on the number of patients treated by one psychologist per year (Drummond et al., 2015; Agency for Modernisation - Ministry of Finance, 2020; Finansministeriet, 2018). The cost of the CBT sessions and B-CBT-related contact was estimated from the time spent conducting CBT sessions, time spent contacting participants in the B-CBT group, and the national hourly wage of psychologists.

2.4. Healthcare and societal costs

Patient-specific costs of healthcare service use were retrieved from Danish registries and supplemented with additional resource use from the Treatment Inventory of Costs in Psychiatric Patients questionnaire (TiC-P) (Bouwmans et al., 2013; Timman et al., 2015). Demographic characteristics were retrieved from the Danish Civil Registration System (Sundhedsdatastyrelsen, n.d.-a; Schmidt et al., 2014). The costs of prescription medicine were valued at the reimbursed cost of the retail price, excluding value-added tax, and retrieved from the Danish National Prescription Registry (Sundhedsdatastyrelsen, n.d.-b). The costs associated with contact with general practitioners, psychologists, or other healthcare service providers in the primary sector were identified using the Danish National Health Insurance Service Register (Sundhedsdatastyrelsen, n.d.-c). The costs of inpatient, outpatient, and emergency hospitalizations in somatic and psychiatric wards were retrieved from the Danish National Patient Registry; these costs accounted for the diagnosis-related group (DRG) used for reimbursement, the procedure performed, and length of stay (Sundhedsdatastyrelsen, n.d.-d). Municipality costs covering home-care services were calculated based on the national hourly wage of a home-care nurse and the resource use retrieved from the TiC-P questionnaire (Bouwmans et al., 2013; Timman et al., 2015). The patient-paid costs included transportation and tax-excluded medicine costs. Costs of time for patients spent on transportation to and from the clinic were included in the societal perspective for patients with full-time employment only. In addition to participants' healthcare service use and costs for the study period, resource use and costs were also identified for the 12 months prior to the individual's trial start date to control for differences in healthcare utilization before the intervention.

2.5. Measure of effectiveness

Information concerning participants' health-related quality of life (HRQoL) was acquired using the validated EuroQol 5-Dimensions 5-levels questionnaire (EQ-5D-5L) (Herdman et al., 2011). The Danish weights for the EQ-5D-5L (Jensen et al., 2021) questionnaire were used to calculate the utility score at the following temporal collection points: baseline, 3-month follow-up, and 6-month follow-up. The quality-adjusted life-year (QALY) gain was estimated using linear interpolation of the utility scores from baseline to 6-month follow-up and used as this analysis' measure of effectiveness.

2.6. Statistical analyses

The cost-utility analyses were performed with an intention-to-treat principle, and multiple imputation was conducted to account for missing data under the assumption of data being missing at random

(Faria et al., 2014; Gupta, 2011). See Appendix B for a full description of the imputation approach.

The result of the CUA was expressed as the incremental cost-effectiveness ratio (ICER) = (ΔCost / ΔQALY), where ΔQALY refers to incremental QALY change, and ΔCost refers to incremental costs. The result was compared with an assumed cost-effectiveness threshold of £20,000–30,000 per QALY gained.

The primary analysis included only intervention costs. Then, three scenario analyses were performed, each including an extra cost layer, leading to a total of four analyses:

- Primary analysis with an intervention perspective;
- Scenario analysis I, including a disease-specific healthcare perspective;
- Scenario analysis II, including a general healthcare perspective;
- Scenario analysis III, including a restricted societal perspective.

The disease-specific healthcare perspective included the costs of psychiatric healthcare, visits to a general practitioner, consultations with psychologists, and prescription medicine for psychiatric diseases, such as anti-depressants. The healthcare perspective included all disease-specific costs as well as the costs of healthcare and prescription medicine, including costs incurred by hospital visits and admissions regardless of the cause. The restricted societal perspective included all healthcare perspective costs, municipality costs, and patient-paid costs, including prescription medicine costs, transportation costs, and travel-time costs. Given the uncertain association between the intervention and other healthcare and productivity costs, the successive inclusion of extra cost layers can be considered to represent the increasing levels of uncertainty. Both the primary analysis and the scenario analyses were performed using a probabilistic sensitivity analysis (PSA) based on 10,000 bootstrap samples drawn at random with replacement from estimated costs and QALYs.

Both the primary analysis and the sensitivity analyses were performed with and without adjustments for baseline imbalances between the groups, including adjustments of baseline differences in EQ-5D-5L. The incremental costs and QALYs for the primary analysis and scenario analyses were estimated using seemingly unrelated regression analysis (SUREG), an approach recommended for economic evaluations alongside clinical trials because it is a method that is robust to skewed data and allows for the calculation of correlations between costs and QALYs (Drummond et al., 2015). The estimates were performed using the *mi estimate, cmdok: sureg* command in Stata. All statistical analyses were performed using Stata, V.16.1.

Data are reported as means with standard error (SE) or number in each group with between-group differences presented as raw, unadjusted differences. p-Values for between-group differences were evaluated using a Student's *t*-test for continuous variables and a Pearson's χ^2 test for binary and multinomial variables. Statistical significance was assumed for p-values <0.05.

3. Results

A total of 76 participants were enrolled in the trial, with 38 participants in each group (Table 1). One participant in the intervention group was excluded due to no effectiveness data being reported at either the baseline, 3-month follow-up, or 6-month follow-up. Another participant in the intervention group was excluded from the analyses due to a somatic hospitalization evaluated as having no coherence with the interventions evaluated by the analyses. Thus, the analyses ultimately included 36 intervention-group participants and 38 control-group participants.

Although variables were missing in apparently equal numbers across both groups, the B-CBT group was missing more in the EQ-5D-5L outcome measure (two at the baseline, 10 at the 3-month follow-up, and 13 at the 6-month follow-up) compared to the S-CBT group (one

Table 1
Sample characteristics of participants at baseline.

Study population	B-CBT (n = 38)	S-CBT (n = 38)
Age, median, years (IQR)[a]	29.75 (24.25–45.87)	30.19 (22.96–47.10)
Sex, female, n (%)[a]	28 (73.6)	30 (79)
Cohabitation status, n (%)[a]		
Living with somebody	16 (42.1)	19 (50)
Living alone	22 (57.9)	19 (50)
Education, n (%)		
Missing	1 (2.6)	1 (2.6)
Education < 3 years[b]	21 (55.3)	20 (52.6)
Education ≥ 3 years[c]	16 (42.1)	17 (44.7)
Employment, n (%)		
Missing	4 (10.5)	2 (5.3)
In employment	13 (34.2)	14 (36.8)
Not in employment	21 (55.3)	22 (57.9)
Depression severity (PHQ-9), median (IQR)	14.42 (12–18)	16.05 (14–18)
Missing, n (%)	2 (5.3)	1 (2.6)
Utility score (EQ-5D-5L), median (IQR)	0.68 (0.518–0.756)	0.57 (0.472–0.682)
Missing, n (%)	2 (5.3)	1 (2.6)
Costs, £, mean (SE)		
Healthcare costs		
Disease specific	627.50 (57.27)	678.72 (44.72)
Non-disease specific	736.48 (248.81)	1170.52 (333.35)
Municipality costs	0	53.75 (53.75)
Missing, n (%)	1 (2.70)	1 (2.63)
Patient costs	143.38 (32.36)	142.99 (29.27)
Total costs	1507.36 (293.50)	2045.98 (335.62)

£, British Pounds Sterling; B-CBT, blended cognitive-behavioral therapy; EQ-5D-5L, EuroQol-5-Dimensions 5-Levels; IQR, Interquartile range; PHQ-9, Patient Health Questionnaire 9-items; S-CBT, standard cognitive-behavioral therapy.

[a] Variables with no missing values.

[b] Participants with the highest education level of public school, high school, further education <3 years, or apprenticeship.

[c] Participants with further education ≥3 years.

missing at the baseline, four at the 3-month follow-up, and eight at the 6-month follow-up).

The primary analysis revealed a total raw difference between the two groups of -£215.5, mainly due to CBT consultations and feedback (B-CBT £343.5 vs. S-CBT £589.78, p-value = 0.00) (Table 2). When healthcare costs, municipality costs, and patient-paid costs were incorporated, the B-CBT group consistently used fewer resources than the S-CBT group, with a total raw difference of -£828.37 (including intervention costs). This difference was primarily driven by disease-specific healthcare costs (B-CBT £376.19 vs. S-CBT £632.58, p-value = 0.00) and patient costs (B-CBT £71.08 vs. S-CBT £406.14, p-value = 0.00).

Both groups demonstrated consistent increases in utility scores over the research period (Table 3). The utility scores are presented as unadjusted imputed means. Compared to the S-CBT group, the B-CBT group recorded a significantly smaller QALY gain (B-CBT 0.0290 vs. S-CBT 0.0834) and consistently lower utility scores for all measurement points except at baseline.

In the primary analysis, the adjusted QALY difference between B-CBT and S-CBT was −0.0291 (95% CI: −0.0535 to −0.0047), and the adjusted difference in costs was -£226.32 (95% CI: −300.86 to −151.77), indicating both an HRQoL decrease and a small per-patient cost-saving for patients receiving B-CBT rather than S-CBT (Table 4). This indicates that B-CBT features a 6.6% probability of being cost-effective at the £20,000 per QALY threshold and a 3.1% probability at the £30,000 threshold.

The subsequent scenario analyses similarly demonstrated lower costs but decreased HRQoL for patients in the B-CBT group (Fig. 1). The iterations from all scenario analyses are located in the southwest quadrant of the scatterplot, with a few samples in the southeast quadrant. Based on an assumed cost-effectiveness threshold of £30,000 cost-saving per QALY, neither the primary analysis nor the scenario analyses were cost-

Table 2
Unadjusted mean costs per participant at the 6-month follow-up. (Data were complete for all costs except municipality costs, which contained 10 missing values.)

Costs	Mean (SE), £		Raw between-group difference, £	p-Value
	B-CBT (n = 36)	S-CBT (n = 38)		
Primary analysis				
Consultations and feedback	343.50 (14.45)	589.78 (33.13)	−246.28	<0.00
Basic operation costs, including rent, cleaning, insurance, and administration.	14.05 (0.71)	25.71 (1.44)	−11.66	<0.00
Education of healthcare professionals[a]	1.02 (0)	0	1.02	–
Operational costs, including license fee and technical support.	41.43 (0)	0	41.43	–
Total intervention costs	400.00 (15.15)	615.49 (34.57)	−215.49	<0.00
Sensitivity analyses				
Healthcare costs				
Disease specific	376.19 (57.48)	632.58 (68.53)	−256.39	<0.00
Non-disease specific	232.90 (78.98)	246.47 (67.08)	−13.57	0.90
Municipality costs	38.28 (38.28)	46.13 (37.51)	−7.85	0.88
Patient costs	71.08 (17.83)	406.14 (25.41)	−335.06	<0.00
Total costs (including intervention costs)	1118.44 (128.61)	1946.81 (136.06)	−828.37	<0.00

£, British Pounds Sterling; B-CBT, blended cognitive-behavioral therapy; S-CBT, standard cognitive-behavioral therapy.

[a] Annuitized over a 3-year period with a discount rate of 4%.

Table 3
Unadjusted imputed utility scores at baseline, 3-month follow-up, and 6-month follow-up, including total QALY gains during the 6-month follow-up period.

Utility	EQ-5D-5L, mean (SE)		Raw between-group difference (p-value)
	B-CBT (n = 36)	S-CBT (n = 38)	
Baseline	0.6401 (0.0315)	0.5392 (0.0409)	0.1009
3-month follow-up	0.6914 (0.0355)	0.7525 (0.0235)	−0.0611
6-month follow-up	0.7696 (0.0424)	0.7800 (0.0330)	−0.0104
QALY gain	0.0290 (0.0122)	0.0834 (0.0141)	−0.0544 (0.003)

B-CBT, blended cognitive-behavioral therapy; EQ-5D-5L, EuroQol-5-Dimensions 5-Levels; S-CBT, standard cognitive-behavioral therapy; QALY, quality-adjusted life year.

effective. However, B-CBT showed a 74.71% probability of being cost-effective from a threshold of £20,000 in scenario analysis III.

4. Discussion

This study's principal findings suggest that, in a public psychiatric hospital setting, B-CBT is not a cost-effective treatment option for patients suffering from MDD compared to high-quality S-CBT. The probability of B-CBT being cost-effective ranged from 3% to 75% depending on the assumptions of the scenarios and the choice of cost-effectiveness threshold.

However, despite not being cost-effective in a cost-utility sense, B-CBT could still be attractive in a public healthcare system. This trial has demonstrated that introducing Internet-based treatment significantly

Table 4
Incremental costs and QALYs at the 6-month follow-up.

Scenarios	Incremental costs, £ (95% CI)	Incremental QALYs (95% CI)	Probability of cost-effectiveness, %		ICER, £ saved per QALY lost[a]
			£20,000 threshold	£30,000 threshold	
Primary analysis, adjusted	−226.32 (−300.86 to −151.77)	−0.0291 (−0.0535 to −0.0047)	6.57	3.08	7767.50
Primary analysis, unadjusted	−215.49 (−289.87 to −141.12)	−0.0544 (−0.0902 to −0.0186)	−		3961.13
Scenario analysis I					
Disease-specific healthcare perspective, adjusted	−477.92 (−693.61 to −262.24)	−0.0291 (−0.0535 to −0.0047)	33.61	13.60	16,403.08
Disease-specific healthcare perspective, unadjusted	−471.88 (−688.40 to −255.36)	−0.0544 (−0.0902 to −0.0186)	−		8674.00
Scenario analysis II					
Healthcare perspective, adjusted	−459.88 (−759.26 to −160.51)	−0.0291 (−0.0535 to −0.0047)	32.41	13.47	15,783.93
Healthcare perspective, unadjusted	−495.28 (−816.35 to −174.20)	−0.0544 (−0.0902 to −0.0186)	−		9104.09
Scenario analysis III:					
Restricted societal perspective, adjusted	−786.48 (−1117.55 to −455.41)	−0.0291 (−0.0535 to −0.0047)	74.71	41.21	26,993.22
Restricted societal perspective, unadjusted	−830.33 (−1189.87 to −470.80)	−0.0544 (−0.0902 to −0.0186)	−		15,263.09

£, British Pounds Sterling; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

[a] The ICER represents savings per QALY lost, thus in order for the intervention to be cost-effective, a minimum cost-saving of £20,000–30,000 per QALY lost needs to be achieved.
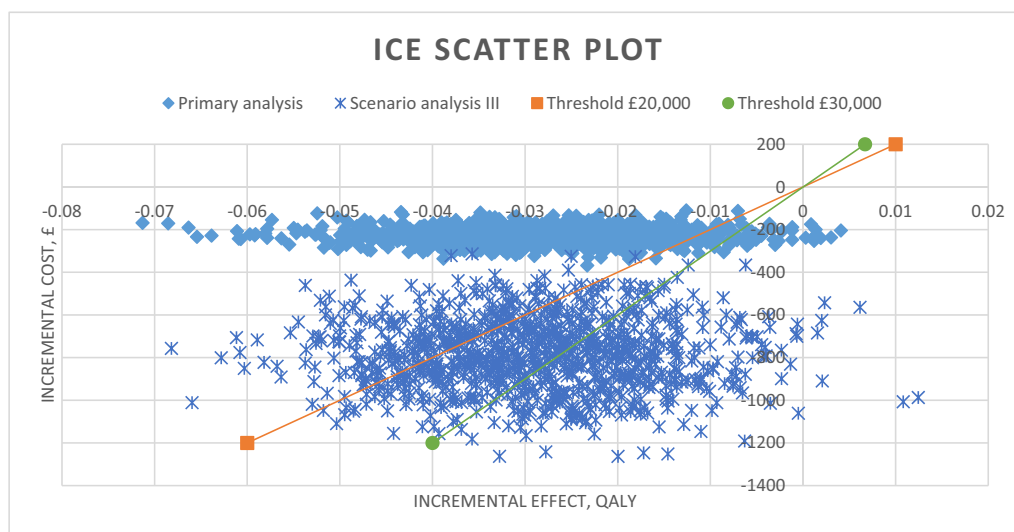
Fig. 1. An incremental cost-effectiveness scatterplot of the probabilistic sensitivity analysis. The figure includes iterations from the adjusted primary analysis (diamond bullets) and adjusted scenario analysis III (cross bullets). The orange line and green line indicate cost-effectiveness thresholds of £20,000 and £30,000 per quality-adjusted life-year (QALY).

reduced public healthcare costs compared to S-CBT. Considering that S-CBT has not been fully implemented in Denmark or most other countries—that is, there are variations in its application—B-CBT could be considered a relatively "cheap" intervention and an attractive way of increasing the supply of MDD treatment in healthcare systems with limited resources. Thus, the possibility of offering B-CBT as a treatment option might increase the number of patients offered treatment because therapists could potentially treat more patients and reduce the waiting time for treatment (Knowles et al., 2014).

This study's strength is its strict adherence to international guidelines for economic evaluation alongside clinical trials. Furthermore, the patient-specific resource consumptions retrieved from the Danish registries enabled the calculation of treatment costs with high validity and minimal missing data. The study's main limitations are the small sample size, the short-term follow-up period, and no accounting for a "learning

curve" (Drummond et al., 2009), that is, the possibility of the organization improving the quality of B-CBT over time.

The standard cost-utility framework applied in this study does not attempt to quantify all possible benefits of Internet-based treatment modalities for either patients or the organization. From a patient perspective, B-CBT might provide flexibility and easy access, potentially reducing stigmatization and increasing treatment adherence (Knowles et al., 2014). The online B-CBT component enables electronic monitoring of patient progress and activity with potential for treatment optimization and research (Laursen et al., 2021). Additionally, geographical distance to a psychiatrist or psychologist might be a barrier to treatment and lead some patients to prefer Internet-based treatment. These aspects all emphasize the possible relevance of B-CBT as an S-CBT substitute, despite the lack of cost-effectiveness.

It is worth noting that QALYs is an important outcome measure in

clinical trials because it facilitates comparisons across disease areas, with evidence suggesting that EQ-5D-5L is responsive in most populations with depression (Drummond et al., 2015). In this trial, we also found a similar small, but significant difference between groups in the disease specific outcome measure PHQ-9 (data presented elsewhere (Mathiasen et al., submitted)). The correlation between EQ-5D-5L and PHQ-9 was 0.56, which seems to support the assumption of EQ-5D-5L being a responsive instrument in this patient group. However, this trial was not powered to find statistically significant differences in QALYs, and it would be inappropriate to conclude that the lack of a statistically significant difference is synonymous with no treatment effect. Health economic guidelines suggest using estimation of cost-effectiveness rather than hypothesis testing because the purpose of an economic evaluation is to provide decision-makers with insights concerning resource allocation rather than make statistical inferences about QALYs and costs (Ramsey et al., 2015; Drummond et al., 2015).

In general, it is difficult to compare telehealthcare interventions for patients suffering from depression due to heterogeneous interventions and the various study designs used for evaluation (Arnberg et al., 2014; Ahern et al., 2018). Notably, Ahern et al. observed therapist-guided iCBT to be as effective as S-CBT in terms of improving symptoms but not necessarily in terms of improving quality of life (Ahern et al., 2018). Elsewhere, Donker et al. recognized therapist-guided iCBT as cost-effective in comparison to control conditions, such as waiting lists, unguided iCBT, and treatment-as-usual, but made no comparisons with S-CBT (Donker et al., 2015). Additionally, that study found promising results concerning guided iCBT reducing service demand in the healthcare sector for psychiatric diseases, improving quality of life, and saving costs (Donker et al., 2015). Thus, despite promising results for telehealthcare interventions similar to B-CBT, the heterogeneity of these interventions and the variety of methodical approaches produce inconsistencies concerning the potential impact on the HRQoL of patients with depression, emphasizing the difficulties of evaluating and comparing the cost-effectiveness of telehealthcare interventions.

To the best of the researchers' knowledge, only one pilot study has investigated the cost-effectiveness of B-CBT compared to S-CBT (Kooistra et al., 2019). .That study by Kooistra et al. found B-CBT to be cost-effective from a healthcare sector perspective but not from a societal perspective, reporting that baseline imbalances between the groups were a limitation, and cost-effectiveness was only observed after statistically controlling for that limitation (Kooistra et al., 2019). That study also differed from this study by the broad inclusion of the time costs associated with using the online treatment program, which apparently reduced the economic advantages of blended care from a societal perspective (presumably) because patients spend more time on the online treatment platform. This study included only patient productivity costs—that is, time taken off from work to receive treatment—rather than all patient time costs (Scenario analysis III). Thus, although Internet-based treatment outside of normal business hours could provide cost savings from a restricted societal perspective, blended care is still not considered to be cost-effective.

Future research should investigate ways of improving the cost-effectiveness of B-CBT to capture the full potential of the treatment format. Furthermore, blended care solutions should be investigated in other populations, such as patients with less severe depression or adolescents or children with MDD, especially given increased prevalence of psychiatric diseases has been observed within the younger population (Andersen et al., 2020).

Ultimately, this study suggests that B-CBT cannot be considered a cost-effective treatment option for patients suffering from MDD compared to high-quality S-CBT. Although B-CBT is likely to generate cost-savings at the healthcare-system level and at the patient level—by reduced transportation and waiting time—it also seems to decrease QALYs in comparison to best practice.

Ethics approval and consent to participate

This study was approved by the Regional Scientific Ethical Committees for Southern Denmark and performed in accordance with the Declaration of Helsinki. The study has been registered with ClinicalTrial.gov, including all items from the WHO Trial Registration Data Set version 1.2 (Registration number is S-20150150, https://clinicaltrials.gov/ct2/show/NCT02796573?id=S-20150150&draw=2&rank=1). Participant registration occurred between March 2016 and April 2018. All adult participants provided written informed consent regarding their participation in this study.

Data availability statement

The datasets generated and analyzed for this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

AL was primarily responsible for the economic evaluation. LHE developed the economic evaluation's design, and SSS and KM were responsible for data collection. AL, JS, SLL, SSS, and LHE developed the analytic plan. AL and SLL analyzed the data. AL, JS, SLL, SSS, and LHE participated in data interpretation. AL drafted the first version of the article. All authors provided critical feedback, helped shape both the analysis and the manuscript, and approved submission. Cambridge Proofreading & Editing was used for proofreading of the article.

Declaration of competing interest

The software NoDep was developed jointly by the Region of Southern Denmark and the private partner Context Consulting. Kim Mathiasen participated in the development process as a representative of the public partner Region of Southern Denmark. Kim Mathiasen has no affiliation with any of the private vendors involved in the project, including Context Consulting, and obtains no financial benefit from the sale of licenses. The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.invent.2022.100513.

References

Agency for Modernisation - Ministry of Finance, 2020. Levetider (Service lives). https://oes.dk/oekonomi/oeav/regnskabsregler/generelle-bogfoeringsbestemmelser/levetider/. (Accessed 30 March 2021).

Ahern, E., Kinsella, S., Semkovska, M., 2018. Clinical efficacy and economic evaluation of online cognitive behavioral therapy for major depressive disorder: a systematic

review and meta-analysis. Expert Rev. Pharmacoecon. Outcomes Res. 18 (1), 25–41. https://doi.org/10.1080/14737167.2018.1407245.

Alonso, J., Codony, M., Kovess, V., Angermeyer, M.C., Katz, S.J., 2007. Population level of unmet need for mental population level of unmet need for mental healthcare in Europe. Br. J. Psychiatry 190, 299–306. https://doi.org/10.1192/bjp.bp.106.022004.

Andersen, S.H., Ladenburg, J., Dyssegaard, P.S., 2020. The mental health of Danes. Development, background, and consequences.. In: Danskernes mentale sundhed. Udvikling, baggrund og konsekvenser, pp. 1–55.

Andersson, G., Carlbring, P., Berger, T., Almlöv, J., Cuijpers, P., 2009. In: What Makes Internet Therapy Work?, 38. Taylor & Francis, pp. 55–60. https://doi.org/10.1080/16506070902916400.

Andrews, G., Basu, A., Cuijpers, P., et al., 2018. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. J. Anxiety Disord. 55 (January), 70–78. https://doi.org/10.1016/j.janxdis.2018.01.001.

Arnberg, F.K., Linton, S.J., Hultcrantz, M., Heintz, E., Jonsson, U., 2014. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. PLoS One. 9 (5), 745–764. https://doi.org/10.1371/journal.pone.0098118.

Bouwmans, C., De Jong, K., Timman, R., et al., 2013. 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. 1–9 https://doi.org/10.1186/1472-6963-13-217.

Denmark, Statistics, 2018. Statistikbanken - LONS20: Løn efter arbejdsfunktion, sektor, aflønningsform, lønmodtagergruppe, lønkomponent og køn (Statistikbanken - LONS20: Wages estimated on job function, sector, payment form, employment group, wage component and gender). http://statistikbanken.dk/statbank5a/default.asp?w=1920. (Accessed 30 March 2021).

Donker, T., Blankers, M., Hedman, E., Ljotsson, B., Petrie, K., Christensen, H., 2015. Economic evaluations of internet interventions for mental health: a systematic review. Psychol. Med. 45 (16), 3357–3376. https://doi.org/10.1017/S0033291715001427.

Drummond, M., Griffin, A., Tarricone, R., 2009. Economic evaluation for devices and drugs-same or different? Value Heal. 12, 402–404. https://doi.org/10.1111/j.1524-4733.2008.00476.x.

Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L., Torrance, G.W., 2015. Methods for the Economic Evaluation of Health Care Programmes, 4th ed. Oxford University Press, Oxford, England.

ENTER - The Blended Care Project. https://www.ementalhealthresearch.dk/28-blendedcare.html. Accessed January 15, 2021.

EUROinvestor, 2019. Exchange Rates "Valutakurser". https://www.valutakurser.dk/. (Accessed 30 March 2021).

Faria, R., Gomes, M., Epstein, D., White, I.R., 2014. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. PharmacoEconomics 32 (12), 1157–1170. https://doi.org/10.1007/s40273-014-0193-3.

Finansministeriet, 2018. In: Den Samfundsøkonomiske Diskonteringsrente, November, p. 1. https://fm.dk/media/10174/dokumentationsnotat-_-den-samfundsoekonomiske-diskonteringsrente.pdf.

Gupta, S.K., 2011. Intention to treat concept: a review. Perspect. Clin. Res. 3, 109–112. https://doi.org/10.4103/2229-3485.83221.

Health, The Danish, Authority, Medicines, 2005. Sundhedsstyrelsen. In: Treatment of depression. Behandling Af Depressionssygdomme. http://www.sst.dk. (Accessed 30 March 2021).

Hedman, E., Ljótsson, B., Lindefors, N., 2012. Cognitive behavior therapy via the internet: a systematic review of applications, clinical efficacy and cost–effectiveness expert. Expert Rev. https://doi.org/10.1586/ERP.12.67.

Herdman, M., Gudex, C., Lloyd, A., et al., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res. 20, 1727–1736. https://doi.org/10.1007/s11136-011-9903-x.

Huhn, M., Tardy, M., Spineli, L.M., et al., 2014. Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic overview of meta-analyses. JAMA Psychiatry. 71 (6), 706–715. https://doi.org/10.1001/jamapsychiatry.2014.112.

Jensen, C.E., Sørensen, S.S., Gudex, C., Jensen, M.B., Pedersen, K.M., Ehlers, L.H., 2021. The danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. Appl. Health Econ. Health Policy (February), 1–13. https://doi.org/10.1007/s40258-021-00639-3.

Karyotaki, E., Kemmeren, L., Riper, H., et al., 2018. Is self-guided internet-based cognitive behavioural therapy (iCBT) harmful? An individual participant data meta-analysis. Psychol. Med. 48 (15), 2456–2466. https://doi.org/10.1017/S0033291718000648.

KM Mathiasen TE Andersen MB Lichtenstein LH Ehlers H Riper AM Kleiboer KK Roessler . (Submitted). Clinical Effectiveness of Blended CBT Compared vs Face-to-Face CBT for Adult Depression: A Randomised Controlled Non-inferiority Trial.

Knowles, S.E., Toms, G., Sanders, C., et al., 2014. Qualitative meta-synthesis of user experience of computerised therapy for depression and anxiety. PLoS One 9 (1). https://doi.org/10.1371/journal.pone.0084323.

Kooistra, L.C., Wiersma, J.E., Ruwaard, J., et al., 2019. Cost and effectiveness of blended versus standard cognitive behavioral therapy for outpatients with depression in routine specialized mental health care: pilot randomized controlled trial. J. Med. Internet Res. 21 (10), 1–13. https://doi.org/10.2196/14261.

Laursen, S.L., Helweg-Jørgensen, S., Langergaard, A., et al., 2021. Economic evaluation: A mobile diary app versus parper-based diary cards for patients with borderline personality disorder. JMIR 23 (11), 1–12. https://doi.org/10.2196/28874.

Mathiasen, K., Riper, H., Ehlers, L.H., Valentin, J.B., Rosenberg, N.K., 2016. Internet-based CBT for social phobia and panic disorder in a specialised anxiety clinic in routine care: results of a pilot randomised controlled trial. Internet Interv. 4, 92–98. https://doi.org/10.1016/j.invent.2016.03.001.

O'Connor, E.A., Whitlock, E.P., Gaynes, B., Beil, T.L., 2009:s.43.. Table 1. Primary DSM-IV depression disorders, criteria for adults. In: Screening for Depression in Adults and Older Adults in Primary Care: An Updated Systematic Review. Agency for Healthcare Research and Quality.

Olsen, L.R., Mortensen, E.L., Bech, P., 2004. Prevalence of major depression and stress indicators in the danish general population. Acta Psychiatr. Scand. 109 (2), 96–103. https://doi.org/10.1046/j.0001-690X.2003.00231.x.

Ramsey, S.D., Willke, R.J., Glick, H., et al., 2015. Cost-effectiveness analysis alongside clinical trials II - an ISPOR good research practices task force report. Value Health 18 (2), 161–172. https://doi.org/10.1016/j.jval.2015.02.001.

Schmidt, M., Pedersen, L., Sørensen, H.T., 2014. The danish civil registration system as a tool in epidemiology. Eur. J. Epidemiol. 29 (8), 541–549. https://doi.org/10.1007/s10654-014-9930-3.

Shafran, R., Clark, D.M., Fairburn, C.G., et al., 2009. Mind the gap: improving the dissemination of CBT. Behav. Res. Ther. 47 (11), 902–909. https://doi.org/10.1016/j.brat.2009.07.003.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., et al., 1998. The MINI-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry. 59 (20), 22–33.

Statistics Denmark - Net Price Index "Nettoprisindeks". https://www.dst.dk/da/Statistik/emner/priser-og-forbrug/forbrugerpriser/nettoprisindeks. Accessed March 30, 2021.

Sun, Y., Fu, Z., Bo, Q., Mao, Z., Ma, X., Wang, C., 2020. The reliability and validity of PHQ-9 in patients with major depressive disorder in psychiatric hospital. BMC Psychiatry 20 (1), 1–7. https://doi.org/10.1186/s12888-020-02885-6.

Sundhedsdatastyrelsen. Det Centrale Personregister (CPR) (The Danish Civil Registration System). https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/personoplysninger-og-sundhedsfaglig-beskaeftigelse/cpr-registeret. (Accessed 30 March 2021).

Sundhedsdatastyrelsen. Lægemiddelstatistikregistret (LSR) (The Danish National Prescription Registry). https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/laegemiddelstatistikregisteret. (Accessed 30 March 2021).

Sundhedsdatastyrelsen. Sygesikringsregistret (SSR) (The Danish National Health Insurance Service Register). https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sundhedsoekonomi-og-finansiering/sygesikringsregisteret. (Accessed 30 March 2021).

Sundhedsdatastyrelsen. Landspatientregisteret (LPR) (The Danish National Patient Registry). https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/landspatientregisteret. (Accessed 30 March 2021).

The Region of Southern Denmark. The Center for Tele-Psychiatry "Internetpsykiatrien". https://www.internetpsykiatrien.dk/wm507341. Accessed March 30, 2021.

Timman, R., Bouwmans, C., Busschbach, J.J.V., Hakkaart-Van, Roijen L., 2015. Development of the treatment inventory of costs in psychiatric patients: TIC-P mini and midi. Value Health 18 (8), 994–999. https://doi.org/10.1016/j.jval.2015.07.006.

Vestergaard, S.V., Rasmussen, T.B., Stallknecht, S., et al., 2020. Occurrence, mortality and cost of brain disorders in Denmark: a population-based cohort study. BMJ Open 10 (11), 1–9. https://doi.org/10.1136/bmjopen-2020-037564.

World Health Organization N, 2008. The Global Burden of Disease: 2004 Update. https://doi.org/10.1038/npp.2011.85.