

BMJ Open Cost-effectiveness analysis of internet-mediated cognitive behavioural therapy for depression in the primary care setting: results based on a controlled trial

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ABSTRACT

Objective To perform a cost-effectiveness analysis of a randomised controlled trial of internet-mediated cognitive behavioural therapy (ICBT) compared with treatment as usual (TaU) for patients with mild to moderate depression in the Swedish primary care setting. In particular, the objective was to assess from a healthcare and societal perspective the incremental cost-effectiveness ratio (ICER) of ICBT versus TaU at 12 months follow-up.

Design A cost-effectiveness analysis alongside a pragmatic effectiveness trial.

Setting Sixteen primary care centres (PCCs) in south-west Sweden.

Participants Ninety patients diagnosed with mild to moderate depression at the PCCs.

Main outcome measure ICERs calculated as $(\text{Cost}_{\text{ICBT}} - \text{Cost}_{\text{TaU}}) / (\text{Health outcome}_{\text{ICBT}} - \text{Health outcome}_{\text{TaU}}) = \Delta\text{Cost} / \Delta\text{Health outcomes}$, the health outcomes being changes in the Beck Depression Inventory-II (BDI-II) score and quality-adjusted life-years (QALYs).

Results The total cost per patient for ICBT was 4044 Swedish kronor (SEK) (€426) (healthcare perspective) and SEK47 679 (€5028) (societal perspective). The total cost per patient for TaU was SEK4434 (€468) and SEK50 343 (€5308). In both groups, the largest cost was associated with productivity loss. The differences in cost per patient were not statistically significant. The mean reduction in BDI-II score was 13.4 and 13.8 units in the ICBT and TaU groups, respectively. The mean QALYs per patient was 0.74 and 0.79 in the ICBT and TaU groups, respectively. The differences in BDI-II score reduction and mean QALYs were not statistically significant. The uncertainty of the study estimates when assessed by bootstrapping indicated that no firm conclusion could be drawn as to whether ICBT treatment compared with TaU was the most cost-effective use of resources.

Conclusions ICBT was regarded to be as cost-effective as TaU as costs, health outcomes and cost-effectiveness were similar for ICBT and TaU, both from a healthcare and societal perspective.

Trial registration number ID NR 30511.

Strengths and limitations of this study

- A key strength of this study was that the patients were exclusively primary care patients. Somatic comorbidity was not an exclusion criterion, indicating that the study population represented typical primary care patients, who often suffer from both mental and physical health problems.
- An additional strength was the thorough scrutinising of electronic patient records for care consumption surveillance that provided legitimacy for the healthcare cost outcomes as these data are more reliable than patient-reported care consumption data.
- Missing data with regards to sick leave for some patients was a weakness as productivity loss from absenteeism constitutes the largest part of societal costs.

BACKGROUND

WHO reports that depression constitutes the largest global burden of disease.¹ Societal costs of depression are considerable. The total annual cost for mood disorders in Europe 2010 was estimated at approximately €113.4 billion, which corresponds to almost 1% of the Gross Domestic Product in the European Union.² The largest component of the costs for depression in Sweden 2004 consisted of productivity loss due to impaired work performance.³

Most of the patients with depression are diagnosed and treated within primary care.⁴ In Sweden, around 2.4%–4.7% of primary care patients are diagnosed with a mood disorder.^{5 6} Cognitive behavioural therapy (CBT), the leading evidence-supported form of psychological therapy for people with depression,⁷ has been shown to be as

effective as antidepressants for treating mild–moderate depression.⁸

However, the availability of CBT in primary care is low,⁴⁷ often due to a shortage of trained psychologists and/or psychotherapists (henceforth collectively referred to as ‘therapists’), and many patients therefore do not receive appropriate treatment.⁹

Internet-mediated CBT (ICBT) is described as a feasible, effective and acceptable online alternative to standard manualised face-to-face CBT and may provide increased opportunities to offer patients an appropriate treatment.¹⁰ ICBT is internationally accepted as a treatment for depression.^{11–14} Guided ICBT has shown effect sizes post treatment of Cohen’s $d=1.46$, after 3 years follow-up $d=1.78$.¹²

ICBT has been specified as the treatment of choice for mild depression by the National Board of Health and Welfare in Sweden and is one of the preferred treatments for moderate depression.¹⁵ Several studies of cost-effectiveness of ICBT as treatment for depression show promising results in favour of ICBT.^{16–19}

McCrone *et al* investigated the cost-effectiveness of ICBT compared with treatment as usual (TaU) in treating depression and anxiety in a randomised controlled trial (RCT) conducted in the primary care setting in UK in 2004.¹⁶ They found that ICBT was more effective than TaU by the primary care team at negligible additional cost and that ICBT resulted in a reduction in productivity loss due to lower levels of sick leave compared with TaU. The cost of ICBT per quality-adjusted life-year (QALY)²⁰ was assessed to be competitive with regards to other recommended interventions. For example, at a value per QALY (threshold) of GBP5000 (€5900), there was an 85% likelihood that ICBT was cost-effective compared with TaU.¹⁶

However, recently, Gilbody *et al* conducted the REEACT trial, an RCT concerning two different ICBT programmes for depression in primary care in the UK. No substantial improvement in depression outcomes could be seen compared with usual general practitioner (GP) care alone.²¹ The trial based cost-effectiveness analyses suggested that none of the ICBT programmes were cost-effective compared with usual GP care alone. Usual GP care alone was the intervention most likely to be cost-effective at an assumed GBP20 000 (€23 600) per QALY threshold.²² This was the first large-scale pragmatic primary care RCT that studied the effectiveness of treatment of well-defined depression with ICBT compared with usual primary care, and not combined with anxiety as in McCrone *et al*.¹⁶

Most research on the effectiveness of ICBT for depression has been conducted in the general population, with participants recruited through advertisement, or in clinical settings, most often with waiting list patients as control group.⁹ There are very few studies of ICBT as treatment for depression in the primary care setting with the clinically most relevant comparison group. We performed an ICBT pragmatic effectiveness trial in Swedish primary care (PRIM-NET), where the intervention—ICBT

treatment—was comparable with TaU in general practice concerning depression, quality of life and sick leave results in a 3-month and 12-month evaluation.^{23 24} It is generally acknowledged that pragmatic effectiveness studies are the most informative for economic and cost-effectiveness conclusions.²⁵

OBJECTIVE

The objective of this study was to perform an economic evaluation of ICBT compared with TaU as treatment for mild to moderate depression in the primary care setting, based on a pragmatic effectiveness trial performed in Swedish primary care, initially a 3-month RCT²³ with further 9 months of follow-up as a controlled trial.²⁴ In particular, the objective was to assess the incremental cost-effectiveness ratio (ICER) of ICBT versus TaU at 12 months follow-up, from a healthcare and a societal perspective.

METHOD

The current cost-effectiveness study is part of the PRIM-NET pragmatic effectiveness trial conducted in the southwestern region of Sweden (Västra Götaland) in 2010–2014. A detailed protocol has been presented previously.^{23 24}

Patient involvement statement

Patients were not involved.

Practice and participant recruitment

All primary care centres (PCCs) in the region of Västra Götaland (with about 1.6 million inhabitants) with access to a therapist with CBT competence were invited by the primary care research network to participate in the study, of which 16 accepted and were engaged.²³ Of the PCCs 4 were privately and 12 were publicly run; 12 were urban and 4 rural.

GPs and nurses at the PCCs were instructed to invite to the study all patients aged ≥ 18 years with a probable diagnosis of mild to moderate depression and positive to ICBT as a treatment alternative. Mild and moderate depression was based on Diagnostic and Statistical Manual of Mental Disorders IV criteria and the Montgomery Åsberg Depression Rating Scale—self rating version (MADRS-S).²⁶ Patients had to have a MADRS-S score < 35 , which is the cut-off point for severe depression.²⁶ To be included in the study, patients also had to have access to a computer with speakers or headphones. For patients on antidepressant maintenance treatment, no dosage change should have taken place during the last four weeks. We excluded patients with earlier suicide attempt or present risk of suicide, substance dependence or alcohol abuse, bipolar, psychotic or other severe psychiatric disorder, and those with cognitive disability or insufficient knowledge of the Swedish language. All included patients gave informed consent before taking part in the study.

After receiving oral information about the study and the intervention by their GP or nurse, the patients who agreed to participate met a licensed psychologist or psychotherapist for an approximately 1 hour diagnostic assessment within 2 weeks. The assessment was based on the Mini International Neuropsychiatric Interview Swedish V.6.0.0b.²⁷ Patients who met the inclusion criteria also received written information and signed consent to participation, and then met a registered nurse for randomisation and to fill out study protocols including background data.

Sample size calculation

The study was designed for detecting a possible significant difference in effect size of approximately 10% between the ICBT group and the TaU group regarding the summary scores obtained in the completed instruments of the Beck Depression Inventory-II (BDI-II)^{28 29} and EuroQol EQ-5D-3L.³⁰ The significance level was set at 0.05 and the power estimate at 0.80, which required 71 participants in each group. The assumed effect sizes were chosen based on findings reported in a study by Proudfoot *et al.*¹¹ and on the study group's empirical expectations.^{15 23}

The intervention

A secure email service was used for contact between patient and healthcare provider. Patients randomised to TaU received the treatment typically provided at the specific PCC. TaU could consist of visits to a GP (58%), nurse (18%), antidepressants (50%), face-to-face psychotherapy (39%), sick leave certification (32%) or combinations of these.^{23 24}

Patients randomised to ICBT received access to a commercially available ICBT treatment programme (Depressionshjälpen) based on CBT techniques, consisting of seven modules accessible for 12 weeks. The modules were completely self-help. The support from the therapists was concentrated on validating the patient, reinforcing progress and encouraging the patient to continue working with the programme. The contacts were around 15 min per week via secure email or by telephone. The patients were recommended to work through the modules within 8 weeks. The treatment period was defined as 12 weeks. The ICBT patients could also receive components of TaU treatment, except for any type of psychotherapy other than ICBT.²³

Health outcomes

The changes in health status were assessed in terms of QALYs and changes in the BDI-II. QALYs is the combination of length of life and health-related quality of life (HRQoL) measured on an index scale from 0 to 1 (with 0 being 'equal to death' and 1 being the best possible health state). One QALY can thus be viewed as living 1 year in the best possible health state. The HRQoL was assessed using the EQ-5D-3L instrument, which assesses health status using five dimensions of health (mobility, self-care,

ability to undertake usual activities, anxiety, depression) with three levels of health state in each dimension. The responses to the EQ-5D-3L instrument were scaled to the 0–1 index scale based on the often-used 'Dolan-tariff'.³¹ Patient scores were available at baseline, and at 3, 6 and 12 months post baseline and QALYs were then calculated by calculating the product of HRQoL and the time spent in each health state. Graphically QALYs can be seen as the area under the curve of HRQoL weights across all measurement points (see online supplementary figure A1 in the appendix for a graphical example).

BDI-II is a self-assessment instrument developed for measuring level of depression.²⁸ The BDI-II contains 21 items, and the patient scores between 0 and 3 on each item. Maximum score is 63. The cut-off level for mild depression is 14, for moderate depression 20 and for severe depression 29. BDI-II scores are available at baseline, and at 3, 6 and 12 months post baseline.

Cost data

Costs were measured in Swedish kronor (SEK) and based on the 2013 price level. One SEK approximately corresponds to the value of €0.105. The resource use items that were identified are described below.

Healthcare utilisation

The number of visits and phone counselling events regarding GPs, nurses and therapists were retrieved at individual patient level from electronic patient records (EPR). Hourly wages for healthcare personnel were calculated using salary data from Statistics Sweden³² and were used to value personnel costs by combining wage costs with the average time per visit.³³

Intervention

The costs of the intervention comprised the ICBT software including technical support and the working hours of the therapist. The cost of the ICBT software was defined as the market price of similar commercially available programmes.

Medication

Drug consumption was retrieved from EPR and patients' questionnaires. Costs of these drugs were estimated based on prices retrieved from the Dental and Pharmaceutical Benefits Agency³⁴ and by using the market price of 26 February 2013.

Productivity loss

The human capital approach was used to measure and value the costs due to productivity loss. The approach values work/productivity at the market price of what someone (ie, employer) is willing to pay per hour of labour, and this is the gross wage plus social fees. Sick leave data were patient-reported. Hourly wages for patients were calculated using individual income data from the Taxpayers' directory 2013 and were multiplied by the total hours of sick leave to value productivity loss.

Patient costs

The patient costs covered the time spent on healthcare treatment including transportation time. Transportation time and transportation expenses were calculated using postal codes of the PCCs and the patients' residential addresses.

We performed the economic evaluation from both a 'payer/healthcare' perspective, including resource use of healthcare, intervention and medication, and from a societal perspective, additionally including resource use consequences due to productivity loss and patient costs. No discounting was applied since all costs (and health outcomes) analysed were within a 1-year period.

Data collection

Collection of data at baseline included socio-demographic and economic variables, for example, age, gender, education, socioeconomic status, employment, sick leave status during past year, use of drugs, marital status, place of residence, alcohol consumption, physical activity and ethnicity.²³ Health outcome measurements (EQ-5D-3L and BDI-II) were conducted at baseline, and thereafter 3, 6 and 12 months post baseline.

Handling of missing data

Cost data were complete for all patients included in the PRIM-NET pragmatic effectiveness trial except for sick leave data. In cases where sick leave data were missing (at baseline: 2 in the TaU group and 2 in the ICBT group, at 3 months follow-up: 10 in the TaU group and 17 in the ICBT group and at 12 months follow-up: 10 in the TaU group and 15 in the ICBT group).

With regards to the health outcome data (BDI-II and EQ-5D-3L), there were some missing responses at both 3 and 12 months follow-up (7 cases in the ICBT group and 11 in the TaU group). If data on 3 or 6 months follow-up were missing, the value between first and last observation was imputed from patients' own data.

For our main estimate of the cost-effectiveness analysis, we assumed a sick leave of zero if none reported by patients and we excluded patients where two or more measurements of health outcome data were lacking. The base case consisted of the remaining patients where both cost and outcome data were sufficient (40 ICBT vs 33 TaU patients). In both the ICBT and the TaU groups, the excluded cases were relatively healthy patients with low levels of care consumption. However, as a sensitivity analysis, results were also calculated based on multiple imputation techniques for missing data.³⁵

Cost-effectiveness analyses and the net monetary benefit

Standard descriptive methods (eg, frequencies, percentages and means) were used to summarise the demographic and clinical features of the intervention and control group.

We estimated the ICER both for the cost per reduced score on the BDI-II scale and the cost per QALY. The ICER was calculated as

$$\begin{aligned} & (Cost_{ICBT} - Cost_{TaU}) / (Health\ outcome_{ICBT} - Health\ outcome_{TaU}) \\ & = \Delta Cost / \Delta Outcome \end{aligned}$$

with the outcome being BDI-II and QALYs in the two respective analyses. The ICER can be viewed as the 'price tag' to gain one unit increase in the health outcome measure. A lower ICER implies that an intervention is more cost-effective since it means that we have to use less resources (lower costs) to achieve one unit of the health gain. With regards to priority setting between alternative treatment options, recommending treatments with a lower ICER implies that larger patient health gains may be achieved for a given budget.

The ICER (as a ratio) is prone to difficulties in interpretations if results contain both 'dominant' (lower costs and better health outcomes) and 'dominated' (higher costs and worse health outcomes), in which case it is typically recommended to estimate the net monetary benefit (NMB) instead.²⁵ We will therefore also estimate and present results using the NMB metric.

The NMB translates the cost-effectiveness calculation into a linear expression and is calculated as $V \times \Delta Outcome - \Delta Cost$, where V is the assumed value per outcome unit (change in BDI-II score or QALY). If the NMB is positive, the treatment is cost-effective, whereas if the NMB is negative, the treatment is not cost-effective. Considering that the exact 'true' estimate of different decision makers' V is unknown, we present the NMB using a range of different V s.

For example, imagine that the gain with ICBT compared with TaU is on average 0.1 QALYs but with an associated increase in costs by €1000. Also, assume that the decision maker's value per QALY (sometimes referred to as the threshold value) is €30 000. In this situation, the ICER is $\text{€}1000/0.1 = 10\,000$, whereas the NMB is $-\text{€}30\,000 \times 0.1 - \text{€}1000 = \text{€}2000$. The conclusion is identical irrespective of if we look at the ICER or the NMB (the treatment is cost-effective) since the ICER is below the decision maker's value per QALY and the NMB is positive. Conclusions based on the ICER and the NMB will always be identical, but the advantage with the NMB expression is that we do not confuse 'dominant' with 'dominated' outcomes and we can therefore always calculate appropriate CIs.

Assessing uncertainty

To assess uncertainty, deterministic sensitivity analyses were carried out using 'scenario analysis', that is, changing relevant assumptions in different analyses to assess how they affected the cost-effectiveness. To assess sampling uncertainty, CIs of the NMB were constructed using non-parametric bootstrapping (1000 bootstrap resamples) of the observed data.³⁶

RESULTS

Demographic data as well as income data, and use of antidepressants and sedatives at inclusion, are presented in [table 1](#), including test of mean differences between ICB

Table 1 Primary sample description for participants in the PRIM-NET trial

	ICBT (n=52)	TaU (n=38)	P values difference in means/proportions
Women, n (%)	31 (60)	39 (75)	0.16
Age, mean (SD)	39 (13)	38 (10)	0.63
Living alone, n (%)	24 (46)	13 (38)	0.44
University-level education, n (%)	19 (37)	9 (24)	0.19
High socioeconomic status*, n (%)	28 (65)	18 (60)	0.63
Employed, n (%)	38 (73)	29 (78)	0.59
On sick leave during past year, n (%)	24 (46)	15 (39)	0.51
Antidepressants, n (%)	12 (23)	9 (24)	0.91
Sedatives, n (%)	9 (17)	0	0.01
Income years (SEK), mean (SD)	290 885 (93 094)	268 496 (60 508)	0.20

*According to socioeconomic index.

ICBT, internet-mediated cognitive behavioural therapy; TaU, treatment as usual.

and TaU. The baseline characteristics of the ICBT and TaU groups showed that the groups were closely comparable (no statistically significant differences) with regards to all key variables, except for the use of sedatives. Six patients in the intervention group and five patients in the control group had other chronic somatic disease. Patients lost to follow-up did not differ in baseline characteristics, except that significantly more patients lost to follow-up were living alone.

Costs results

Unit costs and total costs are presented in [table 2](#) for ICBT and TaU, respectively. The mean total cost per patient and year was SEK47 679 (€5027) for ICBT and SEK50 343 (€5308) for TaU. The mean costs of the payer for healthcare consumption, drugs and ICBT

software were SEK4044 (€426) for ICBT and SEK4434 (€468) for TaU. There were no statistically significant differences between the two groups concerning total healthcare costs, total non-healthcare costs or total societal costs per patient.

Health outcomes

Both ICBT and TaU groups showed a significant within-group reduction of depressive symptoms,²³ measured both as a reduction in the BDI-II score and an increase in the EQ-5D-3L score (see [table 3](#)). The TaU group had a larger reduction in BDI-II score by 0.46 points and a larger increase in the EQ-5D score by 0.07 points. However, neither of these differences were statistically significant.

Table 2 Mean healthcare and non-healthcare costs during the first year of follow-up

Cost items (time spent)	Cost/unit (SEK)	ICBT n=40	TaU n=33	P values
GP visits	333	782	1098	0.15
Therapist, ICB support therapist and nurse	Varies	856	2198	0.002
Phone counselling (15 min)	115	1025	699	0.007
Medication (antidepressants+sedatives)	Varies	382	440	0.19
ICBT programme	1000	1000	0	–
Mean healthcare cost per patient (SD)		4044 (1853)	4434 (2651)	0.73
Time cost (treatment+transportation)	Varies	1598	1421	0.39
Sick leave	Varies	41 997	44 321	0.90
Transportation	Varies	39	165	0.001
Mean non-healthcare cost per patient (SD)		43 634 (77 394)	45 909 (85 951)	0.86
Mean total cost per patient (SD)		47 679 (77 641)	50 343 (87 176)	0.85

Costs in SEK (SEK1 = ~€0.105).

GP, general practitioner; ICBT, internet-mediated cognitive behavioural therapy; TaU, treatment as usual.

Table 3 Health outcomes

	BDI-II		EQ-5D-3L score	
	ICBT	TaU	ICBT	TaU
Baseline	24.38 (21.77 to 26.98)	25.66 (21.98 to 29.33)	0.66 (0.59 to 0.73)	0.61 (0.52 to 0.70)
3 months	13.39 (9.75 to 17.02)	12.46 (8.25 to 16.68)	0.72 (0.64 to 0.81)	0.76 (0.69 to 0.83)
6 months	12.68 (9.25 to 16.11)	10.9 (7.50 to 14.30)	0.78 (0.71 to 0.85)	0.81 (0.76 to 0.87)
12 months	10.97 (7.66 to 14.28)	11.83 (8.29 to 15.36)	0.79 (0.72 to 0.87)	0.81 (0.75 to 0.87)
Within-group change	-13.40 (-17.5 to -10.5)	-13.83 (-17.90 to -9.17)	0.13 (0.05 to 0.21)	0.19 (0.12 to 0.28)
Between-group change (ICBT-TaU)	-0.46 (-5.83 to 4.91)		-0.07 (-0.18 to 0.04)	
Total QALYs*	-	-	0.74 (0.75 to 0.84)	0.79 (0.70 to 0.78)

Means and 95% CIs in parentheses.

*Adjusted for baseline difference in the EQ-5D-3L score. No differences comparing ICBT to TaU are statistically significant. The within-group changes are statistically significant for both ICBT and TaU (for both BDI-II change and EQ-5D-3L score change).

BDI-II, Beck Depression Inventory-II; ICBT, internet-mediated cognitive behavioural therapy; TaU, treatment as usual.

The estimates of total QALYs for the ICBT and TaU group resulted in an average of 0.74 QALYs in the ICBT group and an average of 0.79 QALYs in the TaU group. These estimates were adjusted for the baseline difference in the EQ-5D-3L score (the ICBT group had a slightly better self-assessed health at baseline) but were not statistically significantly different.

Cost-effectiveness results

The main cost-effectiveness results are shown in [table 4](#). Based on a societal perspective, that is, including all cost items, the cost per QALY with ICBT compared with

Table 4 Cost-effectiveness results

Scenario	Cost per QALY	Cost per BDI-II point
Main estimates (ICBT vs TaU)		
Societal perspective	SEK53874* (€5387)	SEK3896* (€411)
Healthcare perspective	SEK5371* (€537)	SEK388* (€41)
Sensitivity analyses (ICBT vs TaU from a societal perspective)		
With non-commercial ICBT programme (ie, freeware)	SEK38117* (€3812)	SEK2756* (€291)
With multiple imputations for missing data	SEK17245* (€1725)	SEK1247* (€132)
Without adjusting for baseline differences in health	SEK118753* (€11875)	ICBT dominant

Cost per QALY and cost per BDI-II point reduction. Costs in SEK and in euros in parentheses (SEK1 = ~ € 0.105) for ICBT versus TaU.

*Results indicate savings per lost QALY (BDI-II point) since ICBT was less expensive but also with less beneficial health outcomes. 95% CIs not defined since it includes estimates in all four cost-effectiveness plane quadrants (and thus not shown). Main estimates based on QALYs and BDI-II changes adjusted for differences in baseline health status.

BDI-II, Beck Depression Inventory-II; ICBT, internet-mediated cognitive behavioural therapy; QALY, quality-adjusted life-years; TaU, treatment as usual.

TaU was SEK53874 (€5681), and the cost per reduced BDI-II score was SEK3896 (€411).

In the typical cost-effectiveness study, the ratio is interpreted as the increase in costs for an improved health outcome. Considering the fact that the incremental cost was negative (ICBT less expensive) and the incremental health outcome also was negative (ICBT less beneficial), these cost-effectiveness ratios should be interpreted as the cost savings for each lost QALY and increased BDI-II score. Thus, for every lost QALY there was a cost saving equal to SEK53 874, and for every increase in the BDI-II score, there was a cost saving equal to SEK3896.

From a healthcare perspective, that is, excluding patient costs and productivity losses, the results are relatively similar at a savings per lost QALY of SEK5371 and a savings per increased BDI-II score at SEK388 (€41).

[Table 4](#) also shows the results from a number of deterministic sensitivity analyses ('scenario analyses') without any substantial impact on the results, that is, they are all in the same domain with savings per lost health (measured as lost QALYs or increased BDI-II score). The exception is the scenario where we do not adjust for baseline differences in health, and the analyses using BDI-II as a health outcome indicate that ICBT is a dominant alternative, that is, both less expensive and better health outcomes. However, this scenario does not merit any further interpretation since the results are not very precise given the large variation.

Assessing uncertainty

The 95% CI for the cost-effectiveness ratios are not defined in a meaningful way since the range included estimates in both 'dominant' (cost savings and health improvements) and 'dominated' outcomes (increasing costs and worse health outcomes). We initially assessed the uncertainty by graphing the cost-effectiveness plane for the cost per QALY based on 1000 bootstrap replications.

The ICERs ([figure 1](#)) were scattered throughout all four quadrants of the cost-effectiveness plane. To be

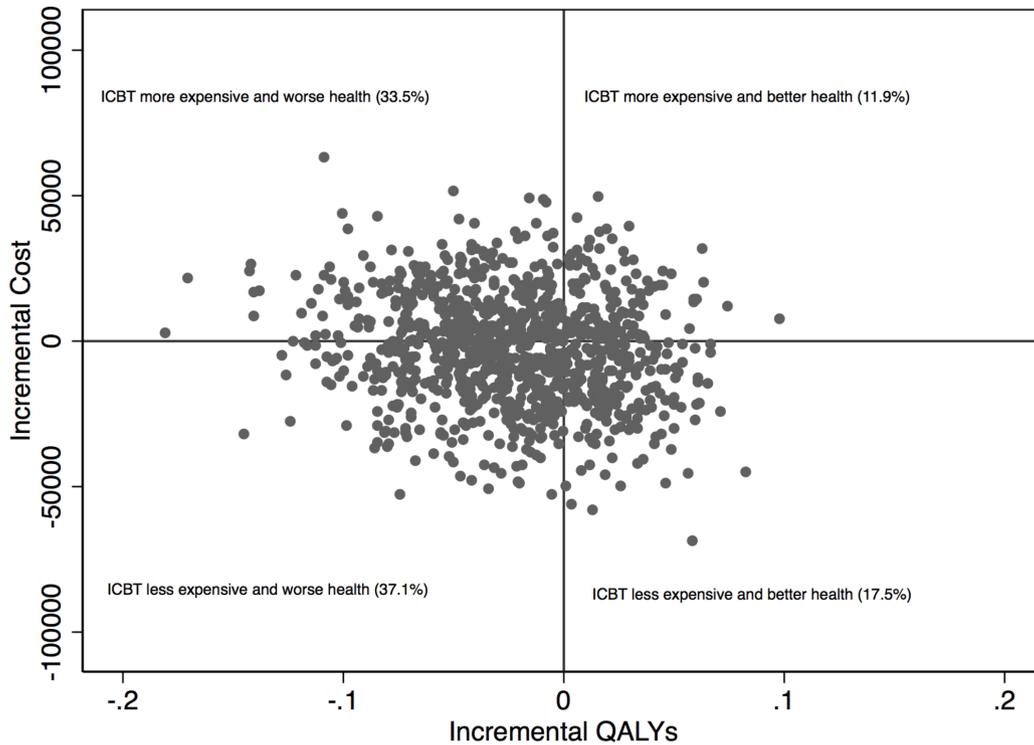


Figure 1 The cost-effectiveness plane based on 1000 bootstrap replications. The percentage number in each quadrant identifies the proportion of replications obtained in the respective quadrant. ICBT, internet-mediated cognitive behavioural therapy; QALY, quality-adjusted life-years.

specific, 33.5% of the ICERs were in the northwest quadrant (ie, ICBT was dominated, both more expensive and worse health outcomes), whereas 17.5% of the ICERs were in the southeast quadrant (ie, ICBT was dominant, both less expensive and better health outcomes), whereas 12% and 37% of the ICERs were in the northeast and southwest quadrant, respectively. Considering that both dominant and dominated ICERs were negative, the distribution of ICERs is difficult to interpret, that is, an ICER of SEK−100,000 could correspond to a very beneficial (‘dominant’) scenario as well as a very poor (‘dominated’) scenario.

Figure 2 therefore shows the NMB result (see section ‘Cost-effectiveness analyses and the net monetary benefit’ for details) for a range of assumed values per QALY together with a 95% CI (‘threshold value per QALY or willingness to pay per QALY’) based on the 1000 bootstrap replications of the primary sample. The mean NMB can be interpreted as the total monetary value of the health benefits (per patient) minus the total monetary costs per patient (for ICBT vs TaU).

As clearly shown, the 95% CI, irrespective of the value per QALY, included both positive and negative NMB estimates. In sum, the results showed that we cannot reject the (null) hypothesis that ICBT is as cost-effective as TaU.

DISCUSSION

We have used 12 months follow-up data from the PRIM-NET pragmatic effectiveness trial²³ to perform an economic evaluation of ICBT versus TaU as a treatment for

mild to moderate depression in the primary care setting, as seen from a healthcare and a societal perspective.

The incremental total cost for ICBT was negative, that is, the total costs for ICBT were modestly lower than for TaU. By far the biggest cost was productivity loss related to sick leave. The mean cost per patient did not differ significantly between ICBT and TaU. The mean QALY was lower but the reduction in BDI-II score was modestly larger in the ICBT group versus the TaU group (unadjusted). However, none of the differences in costs or

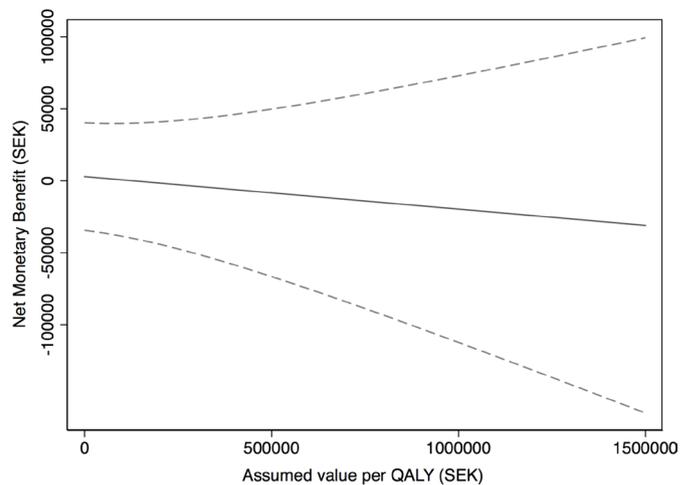


Figure 2 Net monetary benefit (NMB) of internet-mediated cognitive behavioural therapy versus treatment as usual with 95% CIs. The NMB is shown for a range of assumed values for the willingness to pay per quality-adjusted life-year (QALY) (0–1.5 million Swedish kronor).

health outcomes were statistically significantly different. In assessing uncertainty, the bootstrapped ICERs were scattered throughout all four quadrants in the cost-effectiveness plane, indicating that no firm conclusion could be drawn as to whether ICBT treatment compared with TaU was the most cost-effective use of resources. ICBT was thus regarded to be as cost-effective as TaU.

STRENGTHS AND WEAKNESSES

We have studied the cost-effectiveness of ICBT as a treatment for depression 'in the real world',³⁷ which in Sweden most often is primary care. A key strength of this study thus was that the patients were exclusively primary care patients. Somatic comorbidity was not an exclusion criterion, indicating that the study population represented typical primary care patients, who often suffer from both mental and physical health problems.

Included patients were acceptably diversified in age and gender, and a strength was the higher proportion of men in the study population than in previous studies. The thorough scrutinising of EPRs for care consumption surveillance throughout the entire 12-month follow-up period provides healthcare cost outcomes legitimacy.

There are limitations concerning the PRIM-NET trial. Although 90 patients initially were included in the trial, which is a relatively high number of patients for this kind of intervention trial in the primary care setting, this was not sufficient for the sample size calculation. The difficulty to meet estimated inclusion rates in primary care research has been discussed previously.³⁸ Our inability to achieve a higher inclusion rate highlights the uncertainty of the results, as well as our inclusion of another eight patients in the intervention arm to reach a higher number of ICBT-treated patients for the 12-month pragmatic effectiveness study.

Missing data with regard to sick leave for some patients is a weakness as productivity loss from absenteeism constitutes the largest part of the societal costs. However, missing sick leave data occurred in both ICBT and TaU populations. The difference in mean sick leave costs between the two groups was small and may be random.

Another weakness was the significant difference in use of sedatives at baseline between ICBT and TaU. No patients in the TaU group used sedatives compared with 17% in the ICBT group. There were no other significant differences between ICBT and TaU at baseline.

Findings in relation to other studies

Several studies have suggested that ICBT is a cost-effective treatment option for depression.¹⁶⁻¹⁹ However, in the REEACT trial, Littlewood *et al* presented a cost-effectiveness analysis suggesting that none of the ICBT programmes studied were cost-effective compared with usual GP care alone.²² Comparisons between the different studies including the present should be made with caution as there are differences in terms of study design, follow-up and methodology used.

In the cost-effectiveness studies of ICBT as treatment for depression, sick leave (absenteeism) is the most common outcome measure to estimate productivity loss, and productivity loss represents the largest societal cost for depression. However, workers with depression are usually present at work. Their performance can be substantially reduced because of their state (presenteeism).³⁹ According to a study by Stewart *et al*, 81% of the productivity loss costs are explained by reduced performance while at work under during depression.³⁹ The costs of productivity loss during depression might thus be far higher than what has been measured since most studies do not take into account presenteeism. Small improvements in depressive symptoms can therefore have a greater bearing on cost than previously estimated. In future studies of the cost-effectiveness of treatments of depression, presenteeism would be an important factor to take into account.

A study by Bendelin *et al* of personality traits of patients recruited to an ICBT versus TaU study via advertisement showed that ICBT was perceived in different ways depending on personality traits; persons with a practical 'hands-on' approach were more positive about ICBT than those with more of an uncertain and doubtful personality.⁴⁰ Further cost-effectiveness studies of ICBT for depression could benefit from analysing potential differences in costs for different personality profiles or other differences that may exist between different groups of individuals.

A primary prerequisite for inclusion in the PRIM-NET trial was that the patient was positive to ICBT as a treatment option. Despite this, we had some dropouts. This must be kept in mind when introducing ICBT as a widely used therapy alternative. Although there are positive effects for society, the patient's preference must be ascertained during the patient-centred consultation. For the patient, advantages such as accessibility both concerning time and place and the possibility to recapitulate and to reach the supporting therapist rather promptly might also be strong incentives.⁴¹

The results of the PRIM-NET trial suggest that ICBT is as acceptable as TaU in terms of cost-effectiveness, clinical effectiveness and patient's experience.^{24 41} This is in line with the idea of general practice where one of the cornerstones is person-centredness, that is, the treatment of choice very much depends on the individual's needs and preferences, and a plethora of good treatment options to choose between is a strength for achieving the best results.

Conclusions and policy implications

ICBT was regarded to be as cost-effective as TaU as costs, health outcomes and cost-effectiveness were similar for ICBT and TaU, both from a healthcare and societal perspective. Hence, there is no evidence in favour of one over the other as a treatment choice for patients with mild to moderate depression in Swedish primary care. These results, however, need to be confirmed by further more powered primary care studies.

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REFERENCES

- Pelone F, Kringos DS, Spreeuwenberg P, *et al.* How to achieve optimal organization of primary care service delivery at system level: lessons from Europe. *Int J Qual Health Care* 2013;25:381–93.
- Olesen J, Gustavsson A, Svensson M, *et al.* The economic cost of brain disorders in Europe. *Eur J Neurol* 2012;19:155–62.
- depressionssjukdomar. *En systematisk litteraturoversikt. [Treatment of depression. A systematic review]*. Stockholm: Swedish Council on Technology Assessment in Health Care, 2004.
- Bower P, Rowland N, Hardy R. The clinical effectiveness of counselling in primary care: a systematic review and meta-analysis. *Psychol Med* 2003;33:203–15.
- Bodlund O, Andersson SO, Mallon L. Effects of consulting psychiatrist in primary care. 1-year follow-up of diagnosing and treating anxiety and depression. *Scand J Prim Health Care* 1999;17:153–7.
- Leitzén N, Sundquist J, Sundquist K, *et al.* Depression and anxiety in Swedish primary health care: prevalence, incidence, and risk factors. *Eur Arch Psychiatry Clin Neurosci* 2014;264:235–45.
- Nationell utvärdering 2013-vård och insatser vid depression, ångest och schizofreni. *Rekommendationer, bedömningar och sammanfattning [National evaluation, 2013-care and interventions for depression, anxiety and schizophrenia. Recommendations, estimates and summary]*. Stockholm: Swedish National Board of Health and Welfare, 2013.
- Treatment of depression: a systematic review-summary and conclusions*. Stockholm: The Swedish Council of Technology Assessment in Health Care (SBU), 2004.
- de Graaf LE, Gerhards SA, Evers SM, *et al.* Clinical and cost-effectiveness of computerised cognitive behavioural therapy for depression in primary care: design of a randomised trial. *BMC Public Health* 2008;8:224.
- Andersson G. Using the Internet to provide cognitive behaviour therapy. *Behav Res Ther* 2009;47:175–80.
- Proudfoot J, Ryden C, Everitt B, *et al.* Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry* 2004;185:46–54.
- Kessler D, Lewis G, Kaur S, *et al.* Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet* 2009;374:628–34.
- Andersson G, Hesser H, Hummerdal D, *et al.* A 3.5-year follow-up of Internet-delivered cognitive behavior therapy for major depression. *J Ment Health* 2013;22:155–64.
- Cuijpers P, Donker T, van Straten A, *et al.* Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychol Med* 2010;40:1943–57.
- Nationella riktlinjer för vård vid depression och ångestsyndrom 2010 - stöd för styrning och ledning [National guidelines for treatment of depression and anxiety 2010 - Support for governance and management]. Stockholm: Swedish National Board of Health and Welfare, 2010.
- McCrone P, Knapp M, Proudfoot J, *et al.* Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry* 2004;185:55–62.
- Warmerdam L, Smit F, van Straten A, *et al.* Cost-utility and cost-effectiveness of internet-based treatment for adults with depressive symptoms: randomized trial. *J Med Internet Res* 2010;12:e53.
- Titov N, Dear BF, Ali S, *et al.* Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. *Behav Ther* 2015;46:193–205.
- Geraedts AS, van Dongen JM, Kleiboer AM, *et al.* Economic evaluation of a web-based guided self-help intervention for employees with depressive symptoms: results of a randomized controlled trial. *J Occup Environ Med* 2015;57:666–75.
- Weinstein MC, Torrance G, McGuire A. QALYs: the basics. *Value Health* 2009;12(Suppl 1):S5–S9.
- Gilbody S, Littlewood E, Hewitt C, *et al.* Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. *BMJ* 2015;351:h5627.
- Littlewood E, Duarte A, Hewitt C, *et al.* A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the randomised evaluation of the effectiveness and acceptability of computerised therapy (REEACT) trial. *Health Technol Assess* 2015;19:1–174.
- Eriksson MCM, Kivi M, Hange D, *et al.* Long-term effects of Internet-delivered cognitive behavioral therapy for depression in primary care - the PRIM-NET controlled trial. *Scand J Prim Health Care* 2017;35:126–36.
- Kivi M, Eriksson MC, Hange D, *et al.* Internet-based therapy for mild to moderate depression in Swedish primary care: short term results from the PRIM-NET randomized controlled trial. *Cogn Behav Ther* 2014;43:289–98.
- Drummond M, Sculpher MJ, Torrance GW, *et al.* *Methods for the economic evaluation of health care programmes*. 4th edn. New York, United States: Oxford university press, 2015.
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
- Sheehan DV, Lecrubier Y, Sheehan KH, *et al.* 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* 1998;59 Suppl 20(Suppl 20):22–33.
- Arnau RC, Meagher MW, Norris MP, *et al.* Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychol* 2001;20:112–9.
- Beck A, Steer R. *Beck anxiety inventory manual*. San Antonio, TX: The psychological corporation: Harcourt Brace & Company, 1993.
- EuroQol Group. User guide: basic information on how to use EQ-5D. 2009 https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-3L_UserGuide_2015.pdf
- Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095–108.
- SCB. Statistikdatabasen: Lönestatistik (Salary statistics) 2013/2017. 2017 http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__AM__AM0110__AM0110A/
- Läkärförbundet. Lön. 2013 <http://www.slf.se/Forbundet/2013>



34. TLV. äkemedel.: Tandvårds- och läkemedelsförmånsverket (TLV). 2013 <http://www.tlv.se/beslut/sok/lakemedel/2013>
35. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002;7:147–77.
36. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *Br J Psychiatry* 2005;187:106–8.
37. Roy-Byrne PP, Sherbourne CD, Craske MG, *et al.* Moving treatment research from clinical trials to the real world. *Psychiatr Serv* 2003;54:327–32.
38. Newby JM, Mackenzie A, Williams AD, *et al.* Internet cognitive behavioural therapy for mixed anxiety and depression: a randomized controlled trial and evidence of effectiveness in primary care. *Psychol Med* 2013;43:2635–48.
39. Stewart WF, Ricci JA, Chee E, *et al.* Cost of lost productive work time among US workers with depression. *JAMA* 2003;289:3135–44.
40. Bendelin N, Hesser H, Dahl J, *et al.* Experiences of guided Internet-based cognitive-behavioural treatment for depression: a qualitative study. *BMC Psychiatry* 2011;11:107.
41. Holst A, Nejati S, Björkelund C, *et al.* Patients' experiences of a computerised self-help program for treating depression - a qualitative study of Internet mediated cognitive behavioural therapy in primary care. *Scand J Prim Health Care* 2017;35:46–53.