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The cost-effectiveness of a care manager collaborative care programme for patients with depression in primary care – economic evaluation of a pragmatic randomised controlled study

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Abstract

Objective To evaluate the cost effectiveness of a care manager programme compared to care as usual (CAU) for treatment of depression at primary care centres (PCCs) in from a health care as well as societal perspective.

Design Cost effectiveness analysis.

Setting 23 PCCs in two Swedish regions.

Participants Patients with depression (n=342).

Main outcome measures A cost effectiveness analysis was applied on a cluster randomised trial at PCC level where depression patients had 3 months of contact with a care manager (CM) (11 intervention PCCs, n=163) or care as usual (CAU) (12 control PCCs, n=179), with follow-up 3 and 6 months. Effectiveness measures were based on the number of depression free days (DFD) calculated from the Montgomery-Åsberg Depression Rating Scale-Self (MADRS-S) and quality-adjusted life years (QALYs). Results were expressed as the incremental cost-effectiveness ratio (ICER): ΔCost/ΔQALY and ΔCost/ΔDFD. Sampling uncertainty was assessed based on non-parametric bootstrapping.

Results Health benefits were higher in intervention group compared to CAU group: QALYs (0.357 vs. 0.333, $p < 0.001$) and DFD reduction of depressive symptom score (79.43 vs. 60.14, $p < 0.001$). The mean costs per patient for the 6-month period were €368 (health care perspective) and €6,217 (societal perspective) for the intervention patients and €246 (health care perspective) and €7,371 (societal perspective) for the control patients (n.s.). The cost per QALY gained was €6 773 (health care perspective) and from a societal perspective the care manager programme was dominant.

Discussion The care manager programme was associated with a gain in QALYs as well as in DFD, while also being cost-saving compared to CAU from a societal perspective. This result is of high relevance for decision makers on a national level, but it must be observed that a care manager programme for depression implies increased costs at the primary care level.

Keywords: Depression, primary care, care manager collaborative care, health economic analysis, cost-effectiveness, intervention

Strengths and limitations of this study

- The study should be relevant both on a national health care level as well as at a clinical level, as mental health problems today constitute a growing part of health care costs at all levels and also affect health insurance costs.
- Both health care costs as well as societal costs were used for analyses, as societal costs widely exceed health care costs in the form of sick leave costs.
- We used robust and accepted methods for health economic analyses and modelling.
- By scrutinising electronic patient records extensive patient, care consumption, and sick leave data could be obtained.
- As in most cost-effectiveness studies of depression treatment, sick leave (absenteeism) was the measure used to estimate loss of productivity, but the cost of loss of productivity during depression is highly likely to be considerably underestimated, as presenteeism was not taken into account.

Background

Depression is a major source of human suffering and a great and growing challenge for societies worldwide.[1] Depression affects 10-15% of the population.[2] From an economic point of view, the disorder puts a high burden on affected individuals and also on society, including health care costs, sick leave, and disability pension.[3] The total annual cost for mood disorders in Europe 2010 was estimated to approximatively 113.4 billion EURO, which corresponds to almost 1% of the Gross Domestic Product (GDP) in the European Union.[4]

The majority of people with depressive symptoms seek care and are treated in primary care.[1 2 5] However, recommendations and guidelines for depression treatment are mainly based on research at the psychiatric, secondary care, level.[2] In order to provide access to the most effective care for depression, new evidence-based treatment methods and organisational forms of care need to be evaluated at the primary care level. International studies conclude that isolated actions such as increased screening for depression, special training of doctors and nurses, or increased psychological expertise in primary care in itself does not result in higher quality of care or better effect than care as usual (CAU).[6 7]

Currently, best evidence internationally for high quality care and effectiveness of treating depression supports collaborative care with a care manager.[8-10] A care manager provides continuous supporting contact with the patients including behavioural activation, follow-up, and feedback regarding the patients' progress to the doctor and the primary health care team. An important function of the care manager is also to facilitate the engagement of the patients in their care through self-management support.[8 10] The Swedish Council on Health Technology Assessment (SBU) has stressed that studies on collaborative care with a care manager organisation in primary care need to be conducted in Sweden to evaluate the effect

of this intervention in a Swedish context, where primary care mostly is organised in group practices also with specialised nurses, physio- and psycho-therapists, and triage systems. Consequently, the randomised controlled trial (RCT) PRIM-CARE was performed in Sweden 2014-2016, which compared collaborative care with a care manager to care as usual (CAU) as treatment for depression in the primary care setting.[11] The results showed that a care manager organisation at the PCC has positive effects on patients with depression regarding depression course, remission frequency, return to work, and quality of life compared to CAU.

A large amount of evidence shows that besides having positive effects on symptom reduction and quality of care, this type of intervention also is cost-effective. [12] However, in a systematic review of enhanced primary care for treating depression, Gilbody et al. concluded that improved outcomes are expected for collaborative care, but at an increased cost that will require investments.[13] At present there are no Swedish studies on cost-effectiveness of a care manager programme for treatment of depression in Swedish primary care context.

Aim

The aim of this study was to evaluate the cost effectiveness of a care manager programme compared to CAU for treatment of mild to moderate depression in the Swedish primary care setting.

Method

Study design

A commonly used form of health economic evaluation is cost-effectiveness analysis (CEA). CEA evaluates the effects/benefits of a health care intervention and one or more alternative

options in relation to their costs. The results serve as guidance for decision makers in order to allocate scarce health care resources most efficiently.[14] In this study, two effectiveness measures were used: depression free days (DFD), which was calculated based on scores from symptoms expressed in changes on the Montgomery-Åsberg Depression Rating Scale-Self assessment (MADRS-S)[15] and quality-adjusted life years (QALYs).[16] The results of a CEA are expressed in the incremental cost-effectiveness ratio (ICER), which is the difference in costs divided by the difference in effectiveness of implementing the care manager programme compared to CAU: ICER= $(Cost_{care\ manager} - Cost_{CAU}) / (Effectiveness_{care\ manager} - Effectiveness_{CAU})$. The following two ICERs were calculated in this study: ΔCost/ΔQALY and ΔCost/Δ DFD. The cost-effectiveness of the intervention was assessed at 6 months follow-up.

PRIM-CARE

The CEA was based on primary data collected from the pragmatic cluster RCT PRIM-CARE using PCCs as the level of randomisation (project clinical trials NCT02378272).[11] It can be seen as a pragmatic (randomised controlled) effectiveness trial, which is generally regarded as the best vehicle for CEA.[17] The study was performed at 23 Swedish PCCs in the Regions Västra Götaland and Dalarna between December 2014 and January 2016 and included 376 patients with newly diagnosed mild to moderate depression (< 1 month, according to MADRS-S < 35). The PCCs were randomised into two groups: intervention (n=11) and control (n=12), where intervention patients (n = 192) received care manager contact during 3 months and control patients (n = 184) received CAU. The main outcomes of PRIM-CARE were patients' depressive symptoms measured by MADRS-S and Beck Depression Inventory II (BDI-II),[18] patients' quality of life (assessed by EuroQoL-5D 3L scale[19] (weighted UK time

trade-off values), sick leave days and return to work, service satisfaction, and antidepressant medication. Patients were assessed at baseline, 3 months, and 6 months.

The intervention

Intervention PCCs each established a nurse as care manager, who used 20-25% of her/his working time to coordinate and manage care and support of patients with depression. Before the trial started, participating staff members were educated according to their tasks within the care manager programme (2 days for general practitioners (GPs), 5 days for nurses/care managers). Programme services for participating patients included an individual care plan (1 hour session per patient with care manager), regular telephone contacts between care manager and patient in order to assess self-rated depressive symptoms (at least 6-8 times during the 12-week intervention period), as well as the opportunity to contact the care manager at any point of unscheduled time if needed. Furthermore, care managers were in constant dialogue with GPs, therapists, and other health care personnel in order to follow up patients' development. Thus, they did not perform any psycho-therapeutic measures beyond behavioural activation and functioned as a supportive link between specialists and patients while improving accessibility and continuity of care, as well as treatment adherence.

In addition, care managers had regular follow-up meetings (every second month) during the study, where difficulties as well as successes were discussed together with the research team and the region's implementation team.

CAU

CAU could consist of visits to a GP, nurse, antidepressants, face-to-face psychotherapy (or being on the waiting list for such psychotherapy), sick listing, or combinations of these.

Outcome measures

Main outcome measures were depression free days (DFD) calculated based on depressive symptoms expressed as change in MADRS-S and QALYs based on EQ-5D-3L scores (weighted time trade-off values) assessed using the Dolan tariff. The number of DFDs was assessed by estimating the number of days each patient scored equal or below 12 on the MADRS-S. Considering that we have data from each patient at baseline, 3 and 6 months, linear interpolation was carried out between the measurement points to predict a MADRS-S score for each day. Additionally, sensitivity analysis was carried out calculating DFDs based on responses to the BDI-II instrument (depression free assumed at a score equal to or below 9). The same linear interpolation used to calculate DFDs between the measurement points was also carried out for the EQ-5D-3L scores to be able to calculate the QALYs for each patient.

Cost measurements

Costs were estimated both from a health care perspective taking into account the health care costs and from a societal perspective including the health care costs plus the costs due to loss of productivity. The currency of reference was Swedish Krona, corresponding to ~ 0.1 Euro (€). Costs were measured in Swedish kronor (SEK) and based on the 2016 price level, but throughout the manuscript we also present the main results in Euro.

All costs were obtained from primary data collected via electronic patient records (EPR) and patient research interviews in the RCT and then linked to market prices. Health care costs included education costs for PCC personnel (only for the intervention group), contacts with health care professionals (physical and via telephone), and medication (meaning mostly antidepressants). Since Sweden has a publicly administered health care system, where

professionals are employed by the counties, costs per health care contact and for staff education were calculated by means of time spent and gross wages (including social fees) of the respective professional groups. There was no inpatient care cost for this patient group. Consumption of pharmaceuticals was recorded per patient during the follow-up period and was then linked to Swedish market prices, derived from the Swedish Pharmaceutical Industry Association's Service (LIF).[20] Costs for loss of productivity were calculated by means of the human capital approach[14], using registered sick leave days (percentagewise) during the follow-up period and the average gross wage (including social fees) for women in Sweden (since almost two-thirds of the study population were female). Given the short follow-up period, discounting was not applied.

Analysis of cost-effectiveness

The ICER was calculated as the ratio of differences in mean costs per patient and mean QALYs ($\frac{\Delta Costs}{\Delta QALYs}$) or mean DFDs per patient $\left(\frac{\Delta Costs}{\Delta DFD}\right)$, respectively, between the intervention group and the CAU group at 6 months follow-up. Considering that the design was a cluster randomised study, the difference in effectiveness and costs were analysed using a multi-level model where patients were nested within the PCCs. Patients were included (342 of 376) if data was available for baseline and at least one follow-up assessment. Missing values at the 3 or 6 months follow-up were imputed using linear regression analysis using non-missing EQ-5D-3L data together with individual characteristics (age, sex, education level, ethnicity, marital status) as predictors. Nine percent of the randomised patients (34 out of 376) dropped out just after randomisation. Analysing the patients lost after randomisation indicated that the only significant predictor was age (sex, educational level, marital status, number of children, smoking, use of snuff, whether taking any anti-depressant medication, were not at all related

to dropping out of the study); where increasing in age by one year increased probability of missing by 0.4%. Data analysis was carried out in Microsoft Excel and Stata v.15. Statistical significance was accepted at $p < 0.05$.

Sampling uncertainty was assessed using non-parametric bootstrapping focusing on the cost per QALY, which is the primary outcome measure in health economic evaluations and therefore facilitates the widest comparisons. ICERs for both effectiveness measures were estimated based on 5,000 bootstrap resamples and summarised in a cost-effectiveness plane (CE-plane) and in a cost-effectiveness acceptability curve (CEAC). For the cost-effectiveness plane we show confidence ellipses showing the area containing 95%, 75% and 50% of the bootstrapped ICERs, together with the point estimate from the main analysis. In cases where the ICER results in a negative value, it is difficult to tell whether it is located in the north-west quadrant of the CE-plane (less effective and more costly, referred to as a "dominated treatment") or in the preferable south-east quadrant of the CE-plane (more effective and less costly, referred to as a "dominant treatment"). We addressed this potential confusion by estimating the net monetary benefit (NMB) instead of the ICER, which was subsequently used to construct the CEAC. The NMB is calculated using a different assumption of the monetary value of a QALY, i.e. how much the decision-maker is willing to pay for a gain of 1 QALY. The formula to calculate the NMB is: $\Delta QALY \times Value\ per\ QALY - \Delta Cost$. An intervention is considered cost-effective as long as the NMB is positive, since this indicates that the costs to achieve the health benefits are below the respective willingness-to-pay threshold.[14]

Patient and public involvement

No patients were involved in the development of the research question or outcome measures, nor in the recruitment to or conduct of the study. The results will be disseminated to study participants through news media.

Results

Baseline characteristics of the study population are presented in Table 1.

(Place Table 1 around here)

Cost outcome

A detailed overview of identification, valuation, and distribution of costs can be seen in Table 2. From a health care perspective, total cost per patient for the intervention group during the 6 months follow-up period were 3 674 SEK (€367). Adding the costs for loss of productivity resulted in a cost per patient of 62 174 SEK (€6 217). For patients assigned to the control group, the corresponding values were 2 464 SEK (€246) per patient and 73 705 SEK (€7 371) per patient (Table 2). In both groups the greatest share of health care costs was related to contacts with health care professionals (60% in the intervention group and 77% in the control group). Medication (mostly antidepressants) accounted for 15% of total health care costs in the intervention group and 23% in the control group. Education costs of personnel at intervention PCCs represented 25% of total health care costs. When considered from a societal perspective, costs for loss of productivity accounted for 94% of total costs in the intervention group and 96% in the control group. Distribution of health care costs among the two groups was rather similar. The most remarkable differences were observed in visits to and

phone contacts with the nurse (due to the nature of the intervention) and education costs, which were likewise only related to the care manager programme. Difference in mean costs between the two groups was not statistically significant (p = 0.19).

Health outcome

As seen in the mid-part of Table 3, health benefits were higher in the intervention group compared to the CAU group regarding both QALYs (0.357 v. 0.333) and depression free days (79.43 v. 60.14). Both differences showed statistical significance with p<0.001. Sensitivity analyses based on calculating depression free days from the BDI-II instrument produced qualitatively similar results (2% difference compared to the results shown in Table 3).

(Place Table 3 around here)

Cost-effectiveness

From a societal perspective, the care manager programme dominated CAU, i.e. it produced larger health benefits to a lower cost. From a health care perspective the cost per QALY was €6 773 and the cost per depression free day was €7 (Table 3).

(Place Fig. 1 around here)

The bootstrapped ICERs drawn from the study sample are presented in the form of cost-effectiveness ellipses on the cost-effectiveness plane in Figure 1. From a societal perspective, most ICERs are in the south-east quadrant of the cost-effectiveness plane, which indicates that the care manager programme is likely to be more effective and less costly compared to CAU. From a health care perspective, most ICERs are in the north-east quadrant, albeit at a

relatively low increasing cost per QALY, indicating that the care manager programme increases costs at the same time as it improves health.

The CEAC in Figure 2 shows the probability of the care manager programme being cost-effective for several willingness-to-pay thresholds per QALY (in Euros). At a willingness-to-pay threshold of €10 000 per QALY, there was a 93% probability of the care manager programme being cost-effective from a societal perspective and 97% likelihood that it was cost-effective from a health care perspective (higher due to less variability).

(Place Fig. 2 around here)

Discussion

This health economic evaluation showed that health benefits were statistically significantly greater in a PCC care manager organisation for patients with depressive disorder compared to CAU regarding both QALYS and depression free days. Health care costs differed to the advantage of CAU, but the difference in total costs between the two groups was not significantly different. The cost-effectiveness analysis showed that from a societal perspective the care manager programme dominated CAU by leading to higher health benefits and lower costs. From a health care perspective the cost per QALY gained was €6 773 and the cost per depression free day was €7. Already at a willingness to pay per QALY of €10 000, it was 93% (societal) to 97% (health care) likelihood that the care manager programme was cost-effective.

Strengths and limitations of this study

This health economic evaluation of an organisational intervention has several strengths. The study is relevant both on a national health care level as well as a societal level, as mental health problems today constitute a growing part of health care costs, especially at the primary care level, and also affect health and social insurance costs. Among the strengths are the extensive patient, care consumption, and sick leave data obtained by examining electronic patient records in addition to retrieving data from the patients and the PCCs' personnel.

Participating patients were acceptably diversified in age and gender. Both patients and PCCs showed very good participation rates, partly due to support from the study group, which had thorough experience from primary care and accomplishment of primary care clinical trials. We used both health care costs as well as societal costs for our analyses, as societal costs widely exceed health care costs in the form of sick leave costs. We used robust and accepted methods for health economic analyses and modelling. The results may be regarded as generalisable and representative for Swedish primary care.

A limitation was the follow-up time, which was only 6 months. Health economic consequences with regard to health care consumption, health status, and sick leave should preferably be assessed within a longer time perspective. This will be done further on when data from a long term follow-up become available. However, it should be noted that it is likely that the care manager programme would be even more cost-effective with a longer follow-up time, considering that the improved health was maintained also at 6 months.

In this study, as well as in most cost-effectiveness studies of depression treatment, sick leave (absenteeism)[21] was the measure used to estimate loss of productivity, and which also represented the largest societal cost for depression. However, patients with depression are

usually present at work, but their performance can be substantially reduced because of their state (presenteeism).[21] As much as 81 % of the productivity loss cost could be explained by reduced performance while at work during depression.[21] The cost of loss of productivity during depression is highly likely to be considerably greater than currently measured, as presenteeism was not taken into account.

Findings in relation to other studies

Due to differences in health care systems including aspects such as professional roles, resources, access to health care, or organisational levels of care, comparison between cost-effectiveness studies is limited. Moreover, included cost categories and health effects may differ. Nevertheless, the results in the present study are in line with the overall results in the literature. The systematic review of Gilbody et al. showed that the majority of the included economic evaluations from the US found positive health effects as well as increased health care costs associated with the intervention.[13] ICERs varied between $15,463 - $36,467 ($13,138 - $30,984) and were located in the north-east quadrant of the CE plane (i.e. intervention is effective but more costly compared to CAU). This might be due to the fact that none of the studies included societal costs such as loss of productivity. A more recent systematic review showed incremental costs per QALY from dominant (located in the south-east quadrant of the CE-plane, i.e. intervention is more effective and less costly) to $874,562 (€743,059) but only five out of 19 studies had used a societal perspective.[22] Since our study considered costs from a societal perspective, direct comparisons are not possible here. Nonetheless, our results indicated larger health benefits and lower costs, yielding more favourable results in terms of cost-effectiveness. The recent CADET study had an estimated mean cost per QALY of £14,248 (€16,236) but included no costs for loss of productivity.[23]

Gilbody et al. noted that a societal perspective is more meaningful to policy makers and that there is evidence for collaborative care programmes having positive effects on sick leave. [13] The latter study's results correspond to our findings. Furthermore, 70% of the current study population were in the work force, indicating that a societal perspective was of high relevance for this study.

More recent evaluations have accounted for societal costs and are therefore more suitable for comparison. Aragonès et al. found in Spain that the collaborative care programme INDI was cost-effective (ICER = $4,056 per QALY). Nonetheless, due to only small differences in sick leave days between the study groups, total costs in the intervention group were still higher than the ones in the control group.[24] This located the ICER in the north-east quadrant of the cost-effectiveness plane (INDI more effective and more costly than CAU). On the other hand, the results of a German study were similar to ours, meaning that total costs for the control group exceeded total costs for the intervention group, when loss of productivity was included. The ICER for total societal costs was not clearly stated, but the tables suggested an ICER of €66,092 per QALY. Our more favourable result is mainly due to lower costs in nearly all cost categories. Effects regarding QALYs were almost identical to our study.[25] Both of the studies identified the societal costs as the biggest share of total costs, which was also the case in our study.

Significance of the study

The evaluation of interventions that can facilitate the implementation of evidence-based care for patients with depression in primary care is of great importance, as there is an identified knowledge gap in this area.[6] To assess the cost-effectiveness of an intervention is crucial, as the societal as well as the health care resources are limited, and decision-makers need thorough documentation to be able to prioritise between different options. In primary care, the

cornerstones of high quality care are accessibility and continuity, aspects that are promoted by care adjusted to the individual's needs and also support of the individual's capacity to manage the illness during the course of the rehabilitation. A care organisation at the PCC, where the care manager is the hub and facilitates both the patient's contacts with health care and the collaborative care model within the PCC, can be effective in several ways, both for the patient, for the primary care unit, and for society at large. This health economic evaluation confirms beneficial effects on several levels that can be useful for policymakers as well as for clinicians.

Implications for health care

The high incidence of depression makes it important to evaluate and implement new effective forms of care. This study shows that a care management organisation at primary care centres is beneficial for depression patients as well as for the national economic system. However, the major benefits are obtained on a societal level, while the costs (~ 14 % increase) for increasing quality of care and effectiveness are generated on the health care level. As a next step, the Swedish authorities should evaluate whether a nationwide implementation of the care manager programme is feasible. In case of feasibility, the financing of the implementation should include transformation of the societal health insurance (monetary) gain to (primary) health care level. Unlike some other countries, Sweden does not have an "official" threshold to determine whether an intervention should be implemented. However, there is an informal rule which considers any intervention below 500 000 SEK per QALY (€50 000) as cost-effective, substantially higher than the estimate reported in this study.[26]

Conclusions

The results of this study indicate that a collaborative care programme involving a care manager organisation for patients with depression is highly cost-effective in a primary care

setting over a follow-up period of 6 months. From a societal perspective, the programme is dominant for both effectiveness measures – depression free days and QALYs – which means that it generates higher health benefits for the patient at lower costs compared to usual primary care of today. This result is of high relevance for decision makers on a national level. It is further noteworthy that the care manager programme has low implementation costs (education of PCC personnel), which may result in even higher cost-effectiveness in the future.

Declarations

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration: Corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval: Ethical approval was given by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr 903-13; January 2, 2014). After being provided with oral and written information and prior to inclusion of the study, participants signed written informed consent.

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Patient involvement statement: N/A.

Data sharing statement: The datasets generated during and/or analysed during the current study are not publicly available due to Swedish law, but are available from the corresponding author on reasonable request.

Copyright: We attest that we have no copyright protected materials.

Details of contributors: AH, MS, CB, AG, DH, IS, E-L P, JW, MA, CW, LW, CM participated in the design of the study. AH, MS, CB, AG, handled and analyzed data. AH, MS, CB, AG, DH, IS, E-L P, JW, MA, CW, LW, CM drafted and revised the paper. CB was chief investigator and initiated the project, chaired trial management group, and is guarantor. All authors had full access to all of the study data and take responsibility for the integrity and accuracy of the data.

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Table 1. Baseline characteristics for primary care patients in the PRIM-CARE RCT; intervention group (Care manager) and control group (TAU). Figures indicate numbers and percentage (%) of patients.

	Intervention n = 192	**Control n = 184**	**Total n = 376**	**p-value**
Age				
Mean (SD)	40.8 (15.0)	41.6 (15.4)	41.2 (15.2)	0.61
Gender, n (%)				
Women	131 (68.2)	137 (74.5)	268 (71.3)	0.18
Men	61 (31.8)	47 (25.5)	108 (28.7)	
Occupation, n (%)				
Working	137 (72.9)	122 (66.3)	259 (69.6)	
Studying	18 (9.6)	19 (10.3)	37 (9.9)	
In search of work/other	23 (17.6)	43 (23.4)	76 (20.5)	0.52
Working, n (%)				
Full-time	157 (87.7)	149 (87.6)	306 (87.7)	0.98
Other (25%-75%)	22 (12.3)	21 (12.4)	43 (12.3)	
Marital status, n (%)				
Cohabiting	122 (67)	122 (68)	244 (67)	0.82
Single	61 (33)	58 (32)	119 (33)	
Born				
Outside of Nordic country, n (%)	18 (9.4)	21 (11.5)	39 (10.4)	0.63
Educational level, n (%)				
Primary education	17 (8.9)	27 (14.8)	44 (11.8)	
Secondary education	103 (53.9)	90 (49.2)	193 (51.9)	
University	71 (37.2)	66 (36.1)	137 (36.6)	0.21
Sick leave, n (%)				
At baseline	93 (50.5)	94 (55.0)	187 (52.7)	0.40
MADRS-S m (SD)	20.8 (7.2)	21.9 (7.1)	21.4 (7.1)	0.12
BDI-II m (SD)	23.9 (8.7)	25.1 (8.5)	24.5 (8.7)	0.16
EQ-5D m (SD)	0.58 (0.24)	0.56 (0.25)	0.57 (0.24)	0.41

Table 2. Cost items, volumes used, prices per unit, and average cost per patient.

Identification	Volume		Price per volume unit (SEK)		Cost per patient (SEK)	
	Care Man	CAU	Care Man	CAU	Care Man	CAU
Education physicians (per physician)	11	-	7747.00	-	443.84	-
Education nurses (per nurse)	11	-	8287.00	-	474.78	-
Nurse contacts (face to face)	384	203	103.59	103.59	207.18	114.28
Physician contacts (face to face)	447	413	363.14	363.14	845.44	815.09
Psychologist contacts (face to face)	370	421	262.97	262.97	506.77	601.69
Physiotherapist contacts (face to face)	29	79	145.23	145.23	21.94	62.36
Nurse contacts (phone)	1513	417	51.79	51.79	408.15	117.38
Physician contacts (phone)	298	284	121.05	121.05	187.87	186.83
Psychologist contacts (phone)	39	41	60.69	60.69	12.33	13.52
Medication[1]	-	-	-	-	566.05	552.62
Sum of health care costs					**3 674**	**2 464**
Sick leave (days)	5756	7076	1823.90	1823.90	58 500	71 241
Sum of total costs					**62 174**	**73 705**

Care Man: Care Manager; CAU: Care as Usual; SEK: Swedish Kronor (approx. 1 SEK = 0.1 Euro). Data for all 376 randomized patients.

[1] Amounts of pharmaceuticals consumed were calculated individually per patient, according to prescription records during the study. Prices were obtained from a national pharmaceutical register (LIF) and then individually assigned to each preparation.

Table 3. Mean health care and societal costs per patient, as well as difference between care manager and care as usual (CAU) group in the PRIM-CARE RCT with 95% CI.

Costs in Swedish kronor / €	**Care Manager**	**CAU**	**Adjusted difference (95% CI)** **
Health care costs	3 674 / €368	2 464 / €246	1 210 / €121 (569 to 1852)
Societal costs	58 500 / €5 850	71 241 / €7 124	- 11 531 / €-1 153 (-37 690 to 14 627)
Total costs	*62 174 / €6 217*	*73 705 / €7 371*	*- 11 945 / €-2 001 (-38 010 to 14 120)*
Patient Outcome Measures			
QALYs	0.357	0.333	0.018* (0.016 to 0.019)
Depression Free Days (DFD)	79.43	60.14	17.16* (3.84 to 30.47)
Incremental Cost-Effectiveness Ratios in Swedish kronor (SEK) / €			
Cost per QALY: Societal perspective	Care Manager is dominant		
Cost per QALY: Health care perspective	67 731 SEK / €6 773		
Cost per DFD: Societal perspective	Care Manager is dominant		
Cost per DFD: Health care perspective	71 SEK / €7		

Note: * p-value for difference in mean <0.001. ** 95% CI is adjusted for the fact that patients are clustered within primary care centres and difference estimates are adjusted for baseline data on health status.

Figure legends

Figure 1. Cost-effectiveness planes with confidence ellipses. The horizontal axis represents the difference in QALYs between the care manager programme and CAU. The vertical axis represents the difference in costs between the two alternatives (left graph: societal perspective, right graph: health care perspective).

Figure 2. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds for one QALY gained based on a health-care and societal perspective.

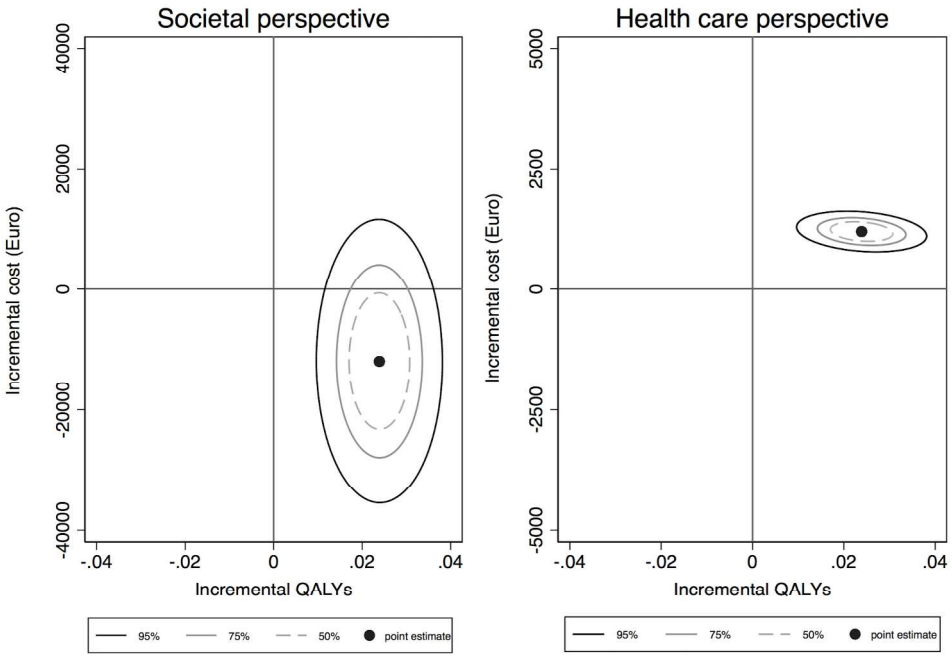

Figure 1. Cost-effectiveness planes with confidence ellipses. The horizontal axis represents the difference in QALYs between the care manager programme and CAU. The vertical axis represents the difference in costs between the two alternatives (left graph: societal perspective, right graph: health care perspective).

366x266mm (300 x 300 DPI)

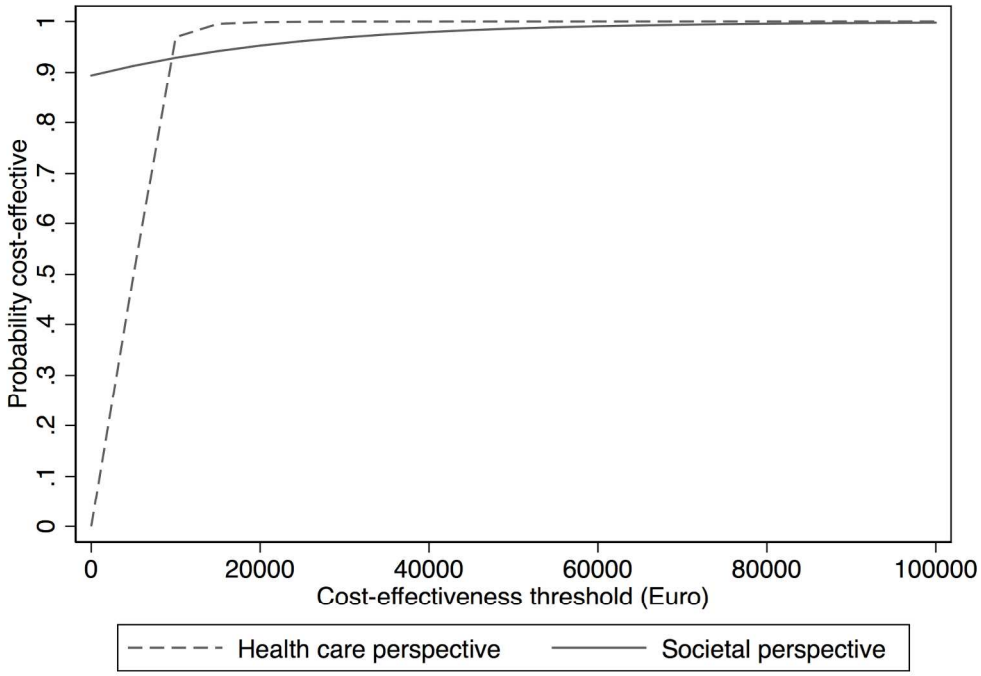

Figure 2. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds for one QALY gained based on a health-care and societal perspective.

366x266mm (300 x 300 DPI)

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	4
		Present the study question and its relevance for health policy or practice decisions.	5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6-7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5-6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	8-9
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8-10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	9-10
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	6, 8

Section/item	Item No	Recommendation	Reported on page No/ line No
preference based outcomes			
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8-9
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	9
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9-10
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 and 3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2; Fig 1

Section/item	Item No	Recommendation	Reported on page No/ line No
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	11-12
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	n.a.
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	19
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	19

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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The cost-effectiveness of a care manager collaborative care programme for patients with depression in primary care – economic evaluation of a pragmatic randomised controlled study

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Secondary Subject Heading:	General practice / Family practice, Mental health, Medical management
Keywords:	depression, PRIMARY CARE, care manager, collaborative care, health economic analysis, intervention

The cost-effectiveness of a care manager collaborative care programme for patients with depression in primary care – economic evaluation of a pragmatic randomised controlled study

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Abstract

Objective To evaluate the cost effectiveness of a care manager programme compared to care as usual (CAU) for treatment of depression at primary care centres (PCCs) in from a health care as well as societal perspective.

Design Cost effectiveness analysis.

Setting 23 PCCs in two Swedish regions.

Participants Patients with depression (n=342).

Main outcome measures A cost effectiveness analysis was applied on a cluster randomised trial at PCC level where depression patients had 3 months of contact with a care manager (CM) (11 intervention PCCs, n=163) or care as usual (CAU) (12 control PCCs, n=179), with follow-up 3 and 6 months. Effectiveness measures were based on the number of depression free days (DFD) calculated from the Montgomery-Åsberg Depression Rating Scale-Self (MADRS-S) and quality-adjusted life years (QALYs). Results were expressed as the incremental cost-effectiveness ratio (ICER): ΔCost/ΔQALY and ΔCost/ΔDFD. Sampling uncertainty was assessed based on non-parametric bootstrapping.

Results Health benefits were higher in intervention group compared to CAU group: QALYs (0.357 vs. 0.333, $p < 0.001$) and DFD reduction of depressive symptom score (79.43 vs. 60.14, $p < 0.001$). The mean costs per patient for the 6-month period were €368 (health care perspective) and €6,217 (societal perspective) for the intervention patients and €246 (health care perspective) and €7,371 (societal perspective) for the control patients (n.s.). The cost per QALY gained was €6 773 (health care perspective) and from a societal perspective the care manager programme was dominant.

Discussion The care manager programme was associated with a gain in QALYs as well as in DFD, while also being cost-saving compared to CAU from a societal perspective. This result is of high relevance for decision makers on a national level, but it must be observed that a care manager programme for depression implies increased costs at the primary care level.

Keywords: Depression, primary care, care manager collaborative care, health economic analysis, cost-effectiveness, intervention

Strengths and limitations of this study

- The study should be relevant both on a national health care level as well as at a clinical level, as mental health problems today constitute a growing part of health care costs at all levels and also affect health insurance costs.
- Both health care costs as well as societal costs were used for analyses, as societal costs widely exceed health care costs in the form of sick leave costs.
- We used robust and accepted methods for health economic analyses and modelling.
- By scrutinising electronic patient records extensive patient, care consumption, and sick leave data could be obtained.
- As in most cost-effectiveness studies of depression treatment, sick leave (absenteeism) was the measure used to estimate loss of productivity, but the cost of loss of productivity during depression is highly likely to be considerably underestimated, as presenteeism was not taken into account.

Background

Depression is a major source of human suffering and a great and growing challenge for societies worldwide.[1] Depression affects 10-15% of the population.[2] From an economic point of view, the disorder puts a high burden on affected individuals and also on society, including health care costs, sick leave, and disability pension.[3] The total annual cost for mood disorders in Europe 2010 was estimated to approximatively 113.4 billion EURO, which corresponds to almost 1% of the Gross Domestic Product (GDP) in the European Union.[4]

The majority of people with depressive symptoms seek care and are treated in primary care.[1 2 5] However, recommendations and guidelines for depression treatment are mainly based on research at the psychiatric, secondary care, level.[2] In order to provide access to the most effective care for depression, new evidence-based treatment methods and organisational forms of care need to be evaluated at the primary care level. International studies conclude that isolated actions such as increased screening for depression, special training of doctors and nurses, or increased psychological expertise in primary care in itself does not result in higher quality of care or better effect than care as usual (CAU).[6 7]

Currently, best evidence internationally for high quality care and effectiveness of treating depression supports collaborative care with a care manager.[8-10] A care manager provides continuous supporting contact with the patients including behavioural activation, follow-up, and feedback regarding the patients' progress to the doctor and the primary health care team. An important function of the care manager is also to facilitate the engagement of the patients in their care through self-management support.[8 10] The Swedish Council on Health Technology Assessment (SBU) has stressed that studies on collaborative care with a care manager organisation in primary care need to be conducted in Sweden to evaluate the effect

of this intervention in a Swedish context, where primary care mostly is organised in group practices also with specialised nurses, physio- and psycho-therapists, and triage systems. Consequently, the randomised controlled trial (RCT) PRIM-CARE was performed in Sweden 2014-2016, which compared collaborative care with a care manager to care as usual (CAU) as treatment for depression in the primary care setting.[11] The results showed that a care manager organisation at the PCC has positive effects on patients with depression regarding depression course, remission frequency, return to work, and quality of life compared to CAU.

A large amount of evidence shows that besides having positive effects on symptom reduction and quality of care, this type of intervention also is cost-effective. [12] However, in a systematic review of enhanced primary care for treating depression, Gilbody et al. concluded that improved outcomes are expected for collaborative care, but at an increased cost that will require investments.[13] At present there are no Swedish studies on cost-effectiveness of a care manager programme for treatment of depression in Swedish primary care context.

Aim

The aim of this study was to evaluate the cost effectiveness of a care manager programme compared to CAU for treatment of mild to moderate depression in the Swedish primary care setting.

Method

Study design

A commonly used form of health economic evaluation is cost-effectiveness analysis (CEA). CEA evaluates the effects/benefits of a health care intervention and one or more alternative

options in relation to their costs. The results serve as guidance for decision makers in order to allocate scarce health care resources most efficiently.[14] In this study, two effectiveness measures were used: depression free days (DFD), which was calculated based on scores from symptoms expressed in changes on the Montgomery-Åsberg Depression Rating Scale-Self assessment (MADRS-S)[15] and quality-adjusted life years (QALYs).[16] The results of a CEA are expressed in the incremental cost-effectiveness ratio (ICER), which is the difference in costs divided by the difference in effectiveness of implementing the care manager programme compared to CAU: ICER= $(Cost_{care\ manager} - Cost_{CAU}) / (Effectiveness_{care\ manager} - Effectiveness_{CAU})$. The following two ICERs were calculated in this study: ΔCost/ΔQALY and ΔCost/Δ DFD. The cost-effectiveness of the intervention was assessed at 6 months follow-up.

PRIM-CARE

The CEA was based on primary data collected from the pragmatic cluster RCT PRIM-CARE using PCCs as the level of randomisation (project clinical trials NCT02378272).[11] It can be seen as a pragmatic (randomised controlled) effectiveness trial, which is generally regarded as the best vehicle for CEA.[17] The study was performed at 23 Swedish PCCs in the Regions Västra Götaland and Dalarna between December 2014 and January 2016 and included 376 patients with newly diagnosed mild to moderate depression (< 1 month, according to MADRS-S < 35). The PCCs were randomised into two groups: intervention (n=11) and control (n=12), where intervention patients (n = 192) received care manager contact during 3 months and control patients (n = 184) received CAU. The main outcomes of PRIM-CARE were patients' depressive symptoms measured by MADRS-S and Beck Depression Inventory II (BDI-II),[18] patients' quality of life (assessed by EuroQoL-5D 3L scale[19] (weighted UK time

trade-off values), sick leave days and return to work, service satisfaction, and antidepressant medication. Patients were assessed at baseline, 3 months, and 6 months.

The intervention

Intervention PCCs each established a nurse as care manager, who used 20-25% of her/his working time to coordinate and manage care and support of patients with depression. Before the trial started, participating staff members were educated according to their tasks within the care manager programme (2 days for general practitioners (GPs), 5 days for nurses/care managers). Programme services for participating patients included an individual care plan (1 hour session per patient with care manager), regular telephone contacts between care manager and patient in order to assess self-rated depressive symptoms (at least 6-8 times during the 12-week intervention period), as well as the opportunity to contact the care manager at any point of unscheduled time if needed. Furthermore, care managers were in constant dialogue with GPs, therapists, and other health care personnel in order to follow up patients' development. Thus, they did not perform any psycho-therapeutic measures beyond behavioural activation and functioned as a supportive link between specialists and patients while improving accessibility and continuity of care, as well as treatment adherence.

In addition, care managers had regular follow-up meetings (every second month) during the study, where difficulties as well as successes were discussed together with the research team and the region's implementation team.

CAU

CAU could consist of visits to a GP, nurse, antidepressants, face-to-face psychotherapy (or being on the waiting list for such psychotherapy), sick listing, or combinations of these.

Outcome measures

Main outcome measures were depression free days (DFD) calculated based on depressive symptoms expressed as change in MADRS-S and QALYs based on EQ-5D-3L scores (weighted time trade-off values) assessed using the Dolan tariff. The number of DFDs was assessed by estimating the number of days each patient scored equal or below 12 on the MADRS-S. Considering that we have data from each patient at baseline, 3 and 6 months, linear interpolation was carried out between the measurement points to predict a MADRS-S score for each day. Additionally, sensitivity analysis was carried out calculating DFDs based on responses to the BDI-II instrument (depression free assumed at a score equal to or below 9). The same linear interpolation used to calculate DFDs between the measurement points was also carried out for the EQ-5D-3L scores to be able to calculate the QALYs for each patient.

Cost measurements

Costs were estimated both from a health care perspective taking into account the health care costs and from a societal perspective including the health care costs plus the costs due to loss of productivity. The currency of reference was Swedish Krona, corresponding to ~ 0.1 Euro (€). Costs were measured in Swedish kronor (SEK) and based on the 2016 price level, but throughout the manuscript we also present the main results in Euro.

All costs were obtained from primary data collected via electronic patient records (EPR) and patient research interviews in the RCT and then linked to market prices. Health care costs included education costs for PCC personnel (only for the intervention group), contacts with health care professionals (physical and via telephone), and medication (meaning mostly antidepressants). Since Sweden has a publicly administered health care system, where

professionals are employed by the counties, costs per health care contact and for staff education were calculated by means of time spent and gross wages (including social fees) of the respective professional groups. There was no inpatient care cost for this patient group. Consumption of pharmaceuticals was recorded per patient during the follow-up period and was then linked to Swedish market prices, derived from the Swedish Pharmaceutical Industry Association's Service (LIF).[20] Costs for loss of productivity were calculated by means of the human capital approach[14], using registered sick leave days (percentagewise) during the follow-up period and the average gross wage (including social fees) for women in Sweden (since almost two-thirds of the study population were female). Given the short follow-up period, discounting was not applied.

Analysis of cost-effectiveness

The ICER was calculated as the ratio of differences in mean costs per patient and mean QALYs ($\frac{\Delta Costs}{\Delta QALYs}$) or mean DFDs per patient $\left(\frac{\Delta Costs}{\Delta DFD}\right)$, respectively, between the intervention group and the CAU group at 6 months follow-up. Considering that the design was a cluster randomised study, the difference in effectiveness and costs were analysed using a multi-level model where patients were nested within the PCCs. Patients were included (342 of 376) if data was available for baseline and at least one follow-up assessment. Missing values at the 3 or 6 months follow-up were imputed using linear regression analysis using non-missing EQ-5D-3L data together with individual characteristics (age, sex, education level, ethnicity, marital status) as predictors. Nine percent of the randomised patients (34 out of 376) dropped out just after randomisation. Analysing the patients lost after randomisation indicated that the only significant predictor was age (sex, educational level, marital status, number of children, smoking, use of snuff, whether taking any anti-depressant medication, were not at all related

to dropping out of the study); where increasing in age by one year increased probability of missing by 0.4%. Data analysis was carried out in Microsoft Excel and Stata v.15. Statistical significance was accepted at $p < 0.05$.

Sampling uncertainty was assessed using non-parametric bootstrapping focusing on the cost per QALY, which is the primary outcome measure in health economic evaluations and therefore facilitates the widest comparisons. ICERs for both effectiveness measures were estimated based on 5,000 bootstrap resamples and summarised in a cost-effectiveness plane (CE-plane) and in a cost-effectiveness acceptability curve (CEAC). For the cost-effectiveness plane we show confidence ellipses showing the area containing 95%, 75% and 50% of the bootstrapped ICERs, together with the point estimate from the main analysis. In cases where the ICER results in a negative value, it is difficult to tell whether it is located in the north-west quadrant of the CE-plane (less effective and more costly, referred to as a "dominated treatment") or in the preferable south-east quadrant of the CE-plane (more effective and less costly, referred to as a "dominant treatment"). We addressed this potential confusion by estimating the net monetary benefit (NMB) instead of the ICER, which was subsequently used to construct the CEAC. The NMB is calculated using a different assumption of the monetary value of a QALY, i.e. how much the decision-maker is willing to pay for a gain of 1 QALY. The formula to calculate the NMB is: $\Delta QALY \times Value\ per\ QALY - \Delta Cost$. An intervention is considered cost-effective as long as the NMB is positive, since this indicates that the costs to achieve the health benefits are below the respective willingness-to-pay threshold.[14]

Patient and public involvement

No patients were involved in the development of the research question or outcome measures, nor in the recruitment to or conduct of the study. The results will be disseminated to study participants through news media.

Results

Baseline characteristics of the study population are presented in Table 1.

(Place Table 1 around here)

Cost outcome

A detailed overview of identification, valuation, and distribution of costs can be seen in Table 2. From a health care perspective, total cost per patient for the intervention group during the 6 months follow-up period were 3 674 SEK (€367). Adding the costs for loss of productivity resulted in a cost per patient of 62 174 SEK (€6 217). For patients assigned to the control group, the corresponding values were 2 464 SEK (€246) per patient and 73 705 SEK (€7 371) per patient (Table 2). In both groups the greatest share of health care costs was related to contacts with health care professionals (60% in the intervention group and 77% in the control group). Medication (mostly antidepressants) accounted for 15% of total health care costs in the intervention group and 23% in the control group. Education costs of personnel at intervention PCCs represented 25% of total health care costs. When considered from a societal perspective, costs for loss of productivity accounted for 94% of total costs in the intervention group and 96% in the control group. Distribution of health care costs among the two groups was rather similar. The most remarkable differences were observed in visits to and

phone contacts with the nurse (due to the nature of the intervention) and education costs, which were likewise only related to the care manager programme. Difference in mean costs between the two groups was not statistically significant (p = 0.19).

Health outcome

As seen in the mid-part of Table 3, health benefits were higher in the intervention group compared to the CAU group regarding both QALYs (0.357 v. 0.333) and depression free days (79.43 v. 60.14). Both differences showed statistical significance with p<0.001. Sensitivity analyses based on calculating depression free days from the BDI-II instrument produced qualitatively similar results (2% difference compared to the results shown in Table 3).

(Place Table 3 around here)

Cost-effectiveness

From a societal perspective, the care manager programme dominated CAU, i.e. it produced larger health benefits to a lower cost. From a health care perspective the cost per QALY was €6 773 and the cost per depression free day was €7 (Table 3).

(Place Fig. 1 around here)

The bootstrapped ICERs drawn from the study sample are presented in the form of cost-effectiveness ellipses on the cost-effectiveness plane in Figure 1. From a societal perspective, most ICERs are in the south-east quadrant of the cost-effectiveness plane, which indicates that the care manager programme is likely to be more effective and less costly compared to CAU. From a health care perspective, most ICERs are in the north-east quadrant, albeit at a

relatively low increasing cost per QALY, indicating that the care manager programme increases costs at the same time as it improves health.

The CEAC in Figure 2 shows the probability of the care manager programme being cost-effective for several willingness-to-pay thresholds per QALY (in Euros). At a willingness-to-pay threshold of €10 000 per QALY, there was a 93% probability of the care manager programme being cost-effective from a societal perspective and 97% likelihood that it was cost-effective from a health care perspective (higher due to less variability).

(Place Fig. 2 around here)

Discussion

This health economic evaluation showed that health benefits were statistically significantly greater in a PCC care manager organisation for patients with depressive disorder compared to CAU regarding both QALYS and depression free days. Health care costs differed to the advantage of CAU, but the difference in total costs between the two groups was not significantly different. The cost-effectiveness analysis showed that from a societal perspective the care manager programme dominated CAU by leading to higher health benefits and lower costs. From a health care perspective the cost per QALY gained was €6 773 and the cost per depression free day was €7. Already at a willingness to pay per QALY of €10 000, it was 93% (societal) to 97% (health care) likelihood that the care manager programme was cost-effective.

Strengths and limitations of this study

This health economic evaluation of an organisational intervention has several strengths. The study is relevant both on a national health care level as well as a societal level, as mental health problems today constitute a growing part of health care costs, especially at the primary care level, and also affect health and social insurance costs. Among the strengths are the extensive patient, care consumption, and sick leave data obtained by examining electronic patient records in addition to retrieving data from the patients and the PCCs' personnel.

Participating patients were acceptably diversified in age and gender. Both patients and PCCs showed very good participation rates, partly due to support from the study group, which had thorough experience from primary care and accomplishment of primary care clinical trials. We used both health care costs as well as societal costs for our analyses, as societal costs widely exceed health care costs in the form of sick leave costs. We used robust and accepted methods for health economic analyses and modelling. The results may be regarded as generalisable and representative for Swedish primary care.

A limitation was the follow-up time, which was only 6 months. Health economic consequences with regard to health care consumption, health status, and sick leave should preferably be assessed within a longer time perspective. This will be done further on when data from a long term follow-up become available. However, it should be noted that it is likely that the care manager programme would be even more cost-effective with a longer follow-up time, considering that the improved health was maintained also at 6 months.

In this study, as well as in most cost-effectiveness studies of depression treatment, sick leave (absenteeism)[21] was the measure used to estimate loss of productivity, and which also represented the largest societal cost for depression. However, patients with depression are

usually present at work, but their performance can be substantially reduced because of their state (presenteeism).[21] As much as 81 % of the productivity loss cost could be explained by reduced performance while at work during depression.[21] The cost of loss of productivity during depression is highly likely to be considerably greater than currently measured, as presenteeism was not taken into account.

Findings in relation to other studies

Due to differences in health care systems including aspects such as professional roles, resources, access to health care, or organisational levels of care, comparison between cost-effectiveness studies is limited. Moreover, included cost categories and health effects may differ. Nevertheless, the results in the present study are in line with the overall results in the literature. The systematic review of Gilbody et al. showed that the majority of the included economic evaluations from the US found positive health effects as well as increased health care costs associated with the intervention.[13] ICERs varied between $15,463 - $36,467 ($13,138 - $30,984) and were located in the north-east quadrant of the CE plane (i.e. intervention is effective but more costly compared to CAU). This might be due to the fact that none of the studies included societal costs such as loss of productivity. A more recent systematic review showed incremental costs per QALY from dominant (located in the south-east quadrant of the CE-plane, i.e. intervention is more effective and less costly) to $874,562 (€743,059) but only five out of 19 studies had used a societal perspective.[22] Since our study considered costs from a societal perspective, direct comparisons are not possible here. Nonetheless, our results indicated larger health benefits and lower costs, yielding more favourable results in terms of cost-effectiveness. The recent CADET study had an estimated mean cost per QALY of £14,248 (€16,236) but included no costs for loss of productivity.[23]

Gilbody et al. noted that a societal perspective is more meaningful to policy makers and that there is evidence for collaborative care programmes having positive effects on sick leave. [13] The latter study's results correspond to our findings. Furthermore, 70% of the current study population were in the work force, indicating that a societal perspective was of high relevance for this study.

More recent evaluations have accounted for societal costs and are therefore more suitable for comparison. Aragonès et al. found in Spain that the collaborative care programme INDI was cost-effective (ICER = $4,056 per QALY). Nonetheless, due to only small differences in sick leave days between the study groups, total costs in the intervention group were still higher than the ones in the control group.[24] This located the ICER in the north-east quadrant of the cost-effectiveness plane (INDI more effective and more costly than CAU). On the other hand, the results of a German study were similar to ours, meaning that total costs for the control group exceeded total costs for the intervention group, when loss of productivity was included. The ICER for total societal costs was not clearly stated, but the tables suggested an ICER of €66,092 per QALY. Our more favourable result is mainly due to lower costs in nearly all cost categories. Effects regarding QALYs were almost identical to our study.[25] Both of the studies identified the societal costs as the biggest share of total costs, which was also the case in our study.

Significance of the study

The evaluation of interventions that can facilitate the implementation of evidence-based care for patients with depression in primary care is of great importance, as there is an identified knowledge gap in this area.[6] To assess the cost-effectiveness of an intervention is crucial, as the societal as well as the health care resources are limited, and decision-makers need thorough documentation to be able to prioritise between different options. In primary care, the

cornerstones of high quality care are accessibility and continuity, aspects that are promoted by care adjusted to the individual's needs and also support of the individual's capacity to manage the illness during the course of the rehabilitation. A care organisation at the PCC, where the care manager is the hub and facilitates both the patient's contacts with health care and the collaborative care model within the PCC, can be effective in several ways, both for the patient, for the primary care unit, and for society at large. This health economic evaluation confirms beneficial effects on several levels that can be useful for policymakers as well as for clinicians.

Implications for health care

The high incidence of depression makes it important to evaluate and implement new effective forms of care. This study shows that a care management organisation at primary care centres is beneficial for depression patients as well as for the national economic system. However, the major benefits are obtained on a societal level, while the costs (~ 14 % increase) for increasing quality of care and effectiveness are generated on the health care level. As a next step, the Swedish authorities should evaluate whether a nationwide implementation of the care manager programme is feasible. In case of feasibility, the financing of the implementation should include transformation of the societal health insurance (monetary) gain to (primary) health care level. Unlike some other countries, Sweden does not have an "official" threshold to determine whether an intervention should be implemented. However, there is an informal rule which considers any intervention below 500 000 SEK per QALY (€50 000) as cost-effective, substantially higher than the estimate reported in this study.[26]

Conclusions

The results of this study indicate that a collaborative care programme involving a care manager organisation for patients with depression is highly cost-effective in a primary care

setting over a follow-up period of 6 months. From a societal perspective, the programme is dominant for both effectiveness measures – depression free days and QALYs – which means that it generates higher health benefits for the patient at lower costs compared to usual primary care of today. This result is of high relevance for decision makers on a national level. It is further noteworthy that the care manager programme has low implementation costs (education of PCC personnel), which may result in even higher cost-effectiveness in the future.

Declarations

Corresponding author: Cecilia Björkelund, Cecilia.bjorkelund@allmed.gu.se

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration: Corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval: Ethical approval was given by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr 903-13; January 2, 2014). After being provided with oral and written information and prior to inclusion of the study, participants signed written informed consent.

Funding: This work was supported by grants from Region Västra Götaland, Sweden.

Patient involvement statement: N/A.

Data sharing statement: The datasets generated during and/or analysed during the current study are not publicly available due to Swedish law, but are available from the corresponding author on reasonable request.

Copyright: We attest that we have no copyright protected materials.

Details of contributors: AH, MS, CB, AG, DH, IS, E-L P, JW, MA, CW, LW, CM participated in the design of the study. AH, MS, CB, AG, handled and analyzed data. AH, MS, CB, AG, DH, IS, E-L P, JW, MA, CW, LW, CM drafted and revised the paper. CB was chief investigator and initiated the project, chaired trial management group, and is guarantor. All authors had full access to all of the study data and take responsibility for the integrity and accuracy of the data. All authors have read and approved the final version of the paper.

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Table 1. Baseline characteristics for primary care patients in the PRIM-CARE RCT; intervention group (Care manager) and control group (TAU). Figures indicate numbers and percentage (%) of patients.

	Intervention n = 192	**Control n = 184**	**Total n = 376**	**p-value**
Age				
Mean (SD)	40.8 (15.0)	41.6 (15.4)	41.2 (15.2)	0.61
Gender, n (%)				
Women	131 (68.2)	137 (74.5)	268 (71.3)	0.18
Men	61 (31.8)	47 (25.5)	108 (28.7)	
Occupation, n (%)				
Working	137 (72.9)	122 (66.3)	259 (69.6)	
Studying	18 (9.6)	19 (10.3)	37 (9.9)	
In search of work/other	23 (17.6)	43 (23.4)	76 (20.5)	0.52
Working, n (%)				
Full-time	157 (87.7)	149 (87.6)	306 (87.7)	0.98
Other (25%-75%)	22 (12.3)	21 (12.4)	43 (12.3)	
Marital status, n (%)				
Cohabiting	122 (67)	122 (68)	244 (67)	0.82
Single	61 (33)	58 (32)	119 (33)	
Born				
Outside of Nordic country, n (%)	18 (9.4)	21 (11.5)	39 (10.4)	0.63
Educational level, n (%)				
Primary education	17 (8.9)	27 (14.8)	44 (11.8)	
Secondary education	103 (53.9)	90 (49.2)	193 (51.9)	
University	71 (37.2)	66 (36.1)	137 (36.6)	0.21
Sick leave, n (%)				
At baseline	93 (50.5)	94 (55.0)	187 (52.7)	0.40
MADRS-S m (SD)	20.8 (7.2)	21.9 (7.1)	21.4 (7.1)	0.12
BDI-II m (SD)	23.9 (8.7)	25.1 (8.5)	24.5 (8.7)	0.16
EQ-5D m (SD)	0.58 (0.24)	0.56 (0.25)	0.57 (0.24)	0.41

Table 2. Cost items, volumes used, prices per unit, and average cost per patient.

Identification	Volume		Price per volume unit (SEK)		Cost per patient (SEK)	
	Care Man	CAU	Care Man	CAU	Care Man	CAU
Education physicians (per physician)	11	-	7747.00	-	443.84	-
Education nurses (per nurse)	11	-	8287.00	-	474.78	-
Nurse contacts (face to face)	384	203	103.59	103.59	207.18	114.28
Physician contacts (face to face)	447	413	363.14	363.14	845.44	815.09
Psychologist contacts (face to face)	370	421	262.97	262.97	506.77	601.69
Physiotherapist contacts (face to face)	29	79	145.23	145.23	21.94	62.36
Nurse contacts (phone)	1513	417	51.79	51.79	408.15	117.38
Physician contacts (phone)	298	284	121.05	121.05	187.87	186.83
Psychologist contacts (phone)	39	41	60.69	60.69	12.33	13.52
Medication[1]	-	-	-	-	566.05	552.62
Sum of health care costs					**3 674**	**2 464**
Sick leave (days)	5756	7076	1823.90	1823.90	58 500	71 241
Sum of total costs					**62 174**	**73 705**

Care Man: Care Manager; CAU: Care as Usual; SEK: Swedish Kronor (approx. 1 SEK = 0.1 Euro). Data for all 376 randomized patients.

[1] Amounts of pharmaceuticals consumed were calculated individually per patient, according to prescription records during the study. Prices were obtained from a national pharmaceutical register (LIF) and then individually assigned to each preparation.

Table 3. Mean health care and societal costs per patient, as well as difference between care manager and care as usual (CAU) group in the PRIM-CARE RCT with 95% CI.

Costs in Swedish kronor / €	**Care Manager**	**CAU**	**Adjusted difference (95% CI)** **
Health care costs	3 674 / €368	2 464 / €246	1 210 / €121 (569 to 1852)
Societal costs	58 500 / €5 850	71 241 / €7 124	- 11 531 / €-1 153 (-37 690 to 14 627)
Total costs	*62 174 / €6 217*	*73 705 / €7 371*	*- 11 945 / €-2 001 (-38 010 to 14 120)*
Patient Outcome Measures			
QALYs	0.357	0.333	0.018* (0.016 to 0.019)
Depression Free Days (DFD)	79.43	60.14	17.16* (3.84 to 30.47)
Incremental Cost-Effectiveness Ratios in Swedish kronor (SEK) / €			
Cost per QALY: Societal perspective	Care Manager is dominant		
Cost per QALY: Health care perspective	67 731 SEK / €6 773		
Cost per DFD: Societal perspective	Care Manager is dominant		
Cost per DFD: Health care perspective	71 SEK / €7		

Note: * p-value for difference in mean <0.001. ** 95% CI is adjusted for the fact that patients are clustered within primary care centres and difference estimates are adjusted for baseline data on health status.

Figure legends

Figure 1. Cost-effectiveness planes with confidence ellipses. The horizontal axis represents the difference in QALYs between the care manager programme and CAU. The vertical axis represents the difference in costs between the two alternatives (left graph: societal perspective, right graph: health care perspective).

Figure 2. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds for one QALY gained based on a health-care and societal perspective.

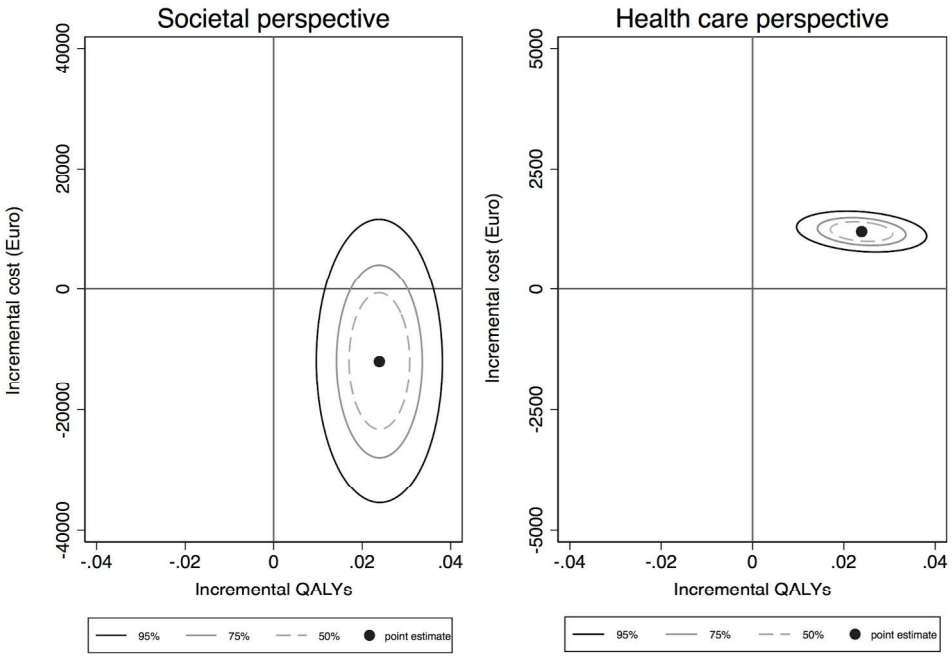

Figure 1. Cost-effectiveness planes with confidence ellipses. The horizontal axis represents the difference in QALYs between the care manager programme and CAU. The vertical axis represents the difference in costs between the two alternatives (left graph: societal perspective, right graph: health care perspective).

366x266mm (300 x 300 DPI)

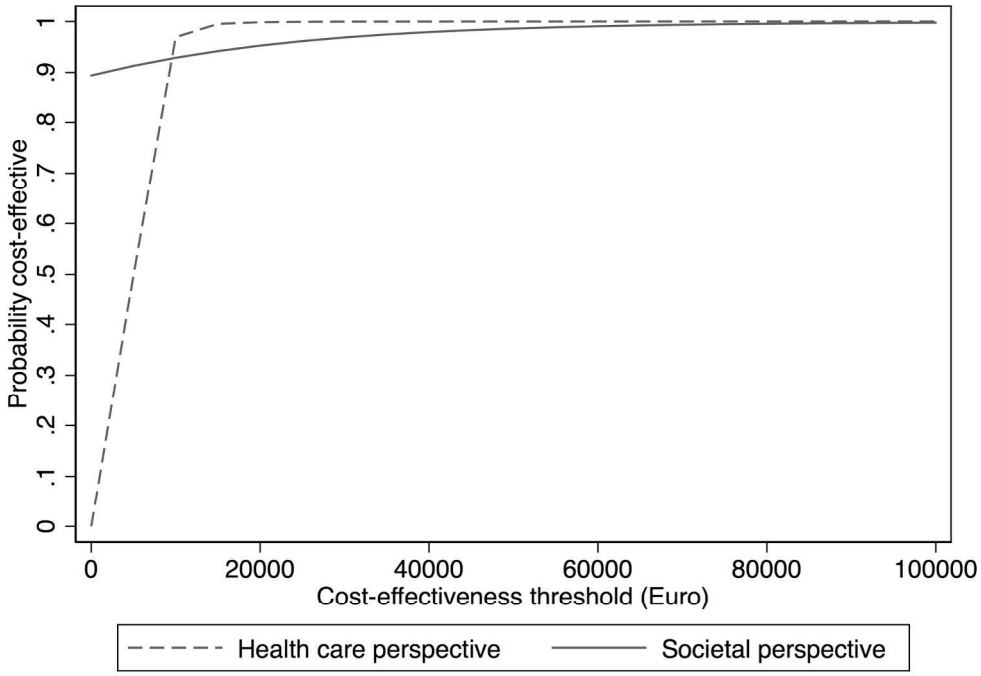

Figure 2. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds for one QALY gained based on a health-care and societal perspective.

366x266mm (300 x 300 DPI)

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	4
		Present the study question and its relevance for health policy or practice decisions.	5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6-7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5-6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	8-9
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8-10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	9-10
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	6, 8

Section/item	Item No	Recommendation	Reported on page No/ line No
preference based outcomes			
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8-9
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	9
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9-10
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 and 3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2; Fig 1

Section/item	Item No	Recommendation	Reported on page No/ line No
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	11-12
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	n.a.
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	19
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	19

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist