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The cost-effectiveness of an indicated blended care intervention in primary care compared to usual care in patients with moderate persistent somatic symptoms

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ABSTRACT

Introduction: Appropriate treatment for people with an increased risk for developing chronic Persistent Somatic Symptoms (PSS) is of great importance at an early stage to improve quality of life and prevent high costs for society.
Objective: To evaluate the cost-effectiveness of an integrated blended care intervention compared to usual care for QALYs, subjective symptom impact and physical and mental health status in patients with moderate PSS.
Methods: This economic evaluation was conducted alongside a 12-month prospective, multicenter cluster randomized controlled trial in Dutch primary care. 80 participants received the intervention and 80 participants received usual care. Seemingly unrelated regression analyzes were performed to estimate cost and effect differences. Missing data were imputed using multiple imputation. Bootstrapping techniques were used to estimate uncertainty.
Results: We found no significant difference in total societal costs. Intervention, primary and secondary healthcare and absenteeism costs were higher for the intervention group. The ICER for QALYs demonstrated the intervention was on average less costly and less effective compared to usual care. For the subjective symptom impact and physical health, the ICER indicated that the intervention group was on average less costly and more effective. For mental health, the intervention was on average more costly and less effective.
Conclusion: We didn't find an integrated blended primary care intervention to be cost-effective compared to usual care. However, when looking on relevant, but specific outcome measures (subjective symptom impact and physical health) for this population, average costs are found to be lower and the effectiveness found to be higher.

1. Introduction

Persistent Somatic Symptoms (PSS) are defined as pain, fatigue, and/or dizziness or a combination of these which last at least several weeks and for which no sufficient explanation can be found after proper medical examination [1–3]. PSS are very common, especially in primary care. Around 25–50% of the complaints that patients present to their general practitioner (GP) can be classified as PSS [4]. Based on severity and disease impact, PSS can be classified as mild, moderate or chronic [5]. In mild symptoms, symptoms recover generally within 3 months [5]. Patients with moderate PSS experience severe unexplained symptoms, with psychological and physical distress, but without a diagnosis

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of a functional somatic syndrome (FSS), or a somatic symptom disorder (SSD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [6,7]. Patients with chronic PSS experience severe physical symptoms and a high level of psychological distress with a major impact on daily functioning and quality of life [8–10].

Early identification of patients with an increased risk of developing chronic PSS is of great importance [7,11]. After identification, these patients can then be offered an intervention with the focus on improving coping strategies and disease perception [12]. This is an example of proactive care where the aim is to prevent chronicity and subsequent long-term care [13]. Support in patients' self-management and integration of technology is an efficient way to provide this type of care [14–16]. For patients with moderate PSS, a 12- week primary care intervention (PARASOL) has recently been introduced with the aim to prevent chronicity. First, patients were identified, after which they received the PARASOL intervention. The intervention was offered in a blended way, meaning that face-to-face sessions with a physical therapist and a mental health nurse were integrated with a web-based program [17]. On short-term, at the end of the intervention, this intervention was found to be effective in improving the subjective symptom impact of patients with moderate PSS compared to usual care. However, no significant short- and long-term differences in quality of life were found [18].

Beyond the effects of the intervention on the quality of life of patients, interventions of this type might also prevent high costs for society by offering early treatment. Literature shows that patients with chronic PSS make extensive use of healthcare services, with is in turn associated with high societal costs [19]. Amongst others, these costs are associated with receiving, often unnecessary, diagnostic procedures and medication [20,21]. The use of inpatient and outpatient care is approximately twice as high in patients with chronic PSS compared to patients without PSS [22]. Societal costs are further increased by the high levels of presenteeism and absenteeism related to PSS [23]. The average total societal cost per patient with PSS in general is estimated at EUR 6815 per year [10].

Prevention of the development of chronic PSS is therefore important especially from a societal cost-perspective. Therefore, this study evaluates the cost-effectiveness of the PARASOL intervention compared to usual care in patients with moderate PSS from a societal perspective.

2. Methods

2.1. Design overview

An economic evaluation is conducted alongside a 12-month prospective, multicenter cluster randomized clinical trial in primary care. The trial protocol and study materials were approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht (MREC document number: NL57931.041.16). The trial was registered in the Dutch trial register with number NL6581. This study is reported according to The Consolidated Health Economic Evaluation Reporting Standards (CHEERS). A total of fifteen Dutch multidisciplinary healthcare centers, with in total 110,000 patients, participated. The healthcare centers were randomized using a web-based random generation of a sequence of numbers. Cluster randomization was performed at the healthcare center level to avoid professionals within one healthcare center offering both the PARASOL intervention and usual care. Eventually, eight healthcare centers were randomized to the PARASOL intervention and seven to usual care. The healthcare centers were informed about their allocation by email. Due to the nature of the intervention, the participating healthcare professionals and patients could not be blinded. The main investigators were also not blinded to group assignment. The physical therapists and mental health nurses of the healthcare centers assigned to the intervention group were trained in how to treat patients with moderate PSS during a two-day training on the content of the PARASOL intervention. The physical therapists and mental health nurses of the seven control healthcare centers were not instructed, but treated patients as usual. Enrollment of 160 eligible patients lasted from March 2017 till April 2018, after which they were followed-up for 12 months.

2.2. Participants

Patients were proactively approached for participation if identified with moderate PSS. Identification of patients was based on the PRESUME screening method, which included the presence of PSS-related symptoms, aged ≥18 years with five or more GP consultations [7]. Patients with an established psychiatric and/or medical diagnosis who were part of a chronic disease management program for chronic obstructive pulmonary disease, hypertension, or diabetes mellitus were excluded. Patients were also excluded when identified with chronic PSS, based on an established chronic PSS diagnosis. Besides the proactive approach, two other recruitment strategies were used to recruit participants. Participating GPs actively approached patients with moderate PSS during consultations, and - if they met PRESUME criteria - matched them to the study group for inclusion. Finally, patients were recruited via flyers and newsletters in the waiting rooms of the participating healthcare centers. Patients with moderate PSS who were interested in participating were accepted if they met PRESUME criteria, had access to the internet and had mastered the Dutch language. All of the patients gave their written informed consent after receiving detailed information about the study's aims and procedures.

2.3. Intervention: PARASOL

The PARASOL intervention comprised of a 12-week integrated blended primary care program, consisting of four face-to-face consultations with a mental health nurse and five physical therapy sessions, supplemented with an integrated web-based program. The web-based program consisted of (1) information modules and video's on self-management and educative themes, (2) video's and instructions on prescribed home exercises, and (3) assignments to gradually increasing physical activity. The intervention uses a cognitive-behavioral approach and therapeutic neuroscience education, and encourages self-management and an active lifestyle using graded activity. The web-based program was based on expert opinions [24].

2.4. Control: usual care

Usual care was defined as routine care for patients with PSS as provided by the GP, physical therapist, mental health nurse and psychologist, without restrictions. The physical therapists and mental health nurses of the control healthcare centers were not instructed, and treated patients as they would otherwise.

2.5. Outcome measures

This economic evaluation consisted of utility and clinical outcomes. An overview of the corresponding questionnaires and timing of administering them can be found in Table 1.

- The EQ-5D-5L was assessed at baseline, three and 12 months and measures the patients' health state on a 5-point scale of complaints on five health domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Scores generally range from <0 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility. Health states were converted into utility values using the Dutch tariff [25]. Quality Adjusted Life Years (QALYs) were estimated by multiplying the duration a patient spent in a certain health state by the utility value of that health state, using linear interpolation between measurement points.

Table 1
Overview of outcome measures.

Outcome measures	Data collection instrument	Follow-up measurements				
		Baseline	3 months	6 months	9 months	12 months
Baseline characteristics	Questionnaire	√				
Quality of life	36-Item Short Form Health Survey (RAND-36)	√	√			√
Subjective symptom impact	Adequate relief question	√ *Weekly between baseline and 3 months*	√ *Monthly between 6 and 12 months*	√	√	√
General health	EuroQol-5 Dimensions	√	√			√
Cost-effectiveness	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness	√	√	√	√	√

- The subjective symptom impact was assessed with the adequate relief question. This is a validated single question measurement, which is scored on a dichotomous scale on weekly basis ("Over the past week have you had adequate relief of your symptoms?") [26,27]. Adequate short-term relief is defined as a participant who reported adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. If not, a participant is defined as a non-responder [27]. Adequate long-term relief is defined as a participant who reported adequate relief of their symptoms for at least four of the seven months between the 6- and 12-month follow-up.
- Health related quality of life was assessed at baseline, 3 and 12 months with the RAND 36-Item Health Survey (RAND-36) [28]. The RAND-36 consists of eight subscales, which were merged into two summary component scales: "Physical Component Scale" (PCS) and "Mental Component Scale" (MCS). The norm-base score for the PCS and MCS is 50, where a score below 50 mean a less favorable physical and mental health state [29].

2.6. Cost outcome measures

Costs were determined during the 12 months of follow-up using a retrospective 3-monthly cost questionnaire 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (TIC-P) [30].

- The intervention costs were estimated using a bottom-up micro-costing approach. That is, information was gathered about the patients' total number of appointments with the physical therapist and mental health nurse, which were in turn valued using Dutch standard costs [31]. In addition, we estimated the development costs of the PARASOL intervention per patient. For this, we estimated the expected number of patients with PSS that would be eligible for PARASOL during the first 5 years after implementation and assuming an implementation rate of 10% in primary care. With total development costs of 9900 euros, this resulted in a total cost of EUR 0.39 per patient.
- Healthcare utilization was divided into the use of primary and secondary care and medication. Healthcare utilization was valued using Dutch standard costs [31]. If unavailable, prices according to professional organizations were used. Medication use was valued using priced derived from http://www.medicijnkosten.nl.
- Absenteeism was assessed by asking patients to report their total number of work-related sick days. In agreement with the Friction Cost Approach (FCA), sick days were valued using gender-specific price weights [32,33]. The FCA assumes that production losses are confined to the "friction period" (i.e. time needed to replace; 12 weeks or 60 days).
- Presenteeism was defined as being less productive at work, assessed by asking patients about their total number of working days on which patients had complaints and rated using gender-specific price weights.
- Unpaid productivity loss was valued using the Dutch recommended shadow price of 15.15 Euro/h [31] and consist of unpaid work that the patient can no longer do due to their physical or psychological problems.
- All costs were converted to Euros 2020, using consumer price indices provided by Statistics Netherlands.

2.7. Demographics

Patient characteristics, including age, sex, educational level, duration of complaints, work status, marital status and the presence of comorbidities and recruitment strategy were measured at baseline.

2.8. Statistical analyses

Statistical analyses were performed according to the intention-to-treat principle. Descriptive statistics were used to describe and compare general characteristics of patients in the PARASOL intervention and the usual care group. Missing data were multiply imputed (MI) using the MICE procedure [34] with predictive mean matching. Ten complete data sets were created in order for the loss of efficiency to be <5%. The imputation model consisted of confounder variables that have >10% change in the estimate of the effect. These variables were recruitment strategy, marital status, age, and duration of symptoms. In addition, we included all available baseline and follow-up costs variables and variables at baseline and follow-up related to the cost, utility, and clinical outcomes. Imputed datasets were analyzed as outlined below. Pooled estimates were calculated using Rubin's rules.

Average aggregate and disaggregate cost differences between groups were calculated. Seemingly unrelated regression analyzes (SUR) were performed to estimate cost and effect differences, while adjusting for baseline values, confounders, and their possible correlation [35,36]. The 95%CIs around the cost differences were estimated using bias-corrected and accelerated bootstrap intervals with 5000 replications. Incremental Cost-Effectiveness Ratios (ICERs) were calculated by dividing the differences in total costs between the two groups by the difference in effects. Bootstrapped incremental cost-effect pairs were plotted on cost-effectiveness planes. Cost-effectiveness acceptability curves (CEAC) were estimated, which indicate the probability that the PARASOL intervention is cost-effective compared to usual care at different values of willingness to pay. For the societal perspective, willingness to pay threshold values of EUR 10,000 to EUR 80,000 per QALY are used in the Netherlands [37]. For the other outcomes, willingness to pay threshold values are lacking. The primary analysis was carried out from the societal perspective and a secondary analysis was performed from the healthcare perspective. The societal perspective consists of the total costs related to PSS, regardless of who paid for it. The healthcare perspective only includes costs accruing to the formal Dutch healthcare sector.

As in the majority of trial-based economic evaluations, the power/sample size estimates were not performed for this study because cost

data are right skewed and therefore require larger sample sizes to detect relevant differences. Such large sample sizes, however, may be neither feasible nor ethically acceptable [38]. All analyses were performed using STATA 13.0. For the cost and effect differences, a two-sided significance level of 0.05 was considered statistically significant.

2.9. Sensitivity analysis

Three sensitivity analyses were performed to test the robustness of the results. First, the analysis used data at three months as the final measurement instead of 12 months. A second sensitivity analysis was performed, in which outliers were selected (>3 standard deviations from the mean) and removed. Finally, results were analyzed separately for employed and unemployed patients.

3. Results

Of the 160 included participants, 130 (81%) participants were identified with the PRESUME method, five (3%) were recruited during the GP consultation and 25 (16%) through flyers in the waiting rooms and study information in the newsletters of the participating healthcare centers. On average, five participants per healthcare center were included (range = 2–34). After randomization, 80 patients were allocated to the intervention group and 80 in the control group (usual care). The two patient groups did not considerably differ in demographic characteristics (Table 2).

3.1. Resource use and costs. Difference in costs between the PARASOL intervention and usual care

Total healthcare costs of the PARASOL intervention were found to be significantly higher (MD: 753€; 95% CI: 122 to 1384) compared to usual care. From the societal perspective, however, we found no significant difference in total societal costs when comparing the PARASOL intervention to usual care (MD: −213€; 95% CI: −2072 to 1647). As for the disaggregate cost categories, the cost of the intervention, primary and secondary healthcare costs and absenteeism were higher for the PARASOL intervention group compared to usual care. Lower costs were found for medication, presenteeism and unpaid productivity. Of the disaggregate cost differences, only the difference in unpaid productivity was significantly in favor of PARASOL (MD: −1294€; 95% CI: −2571 to −16). An overview of the costs per group and the differences in costs can be found in Table 3.

3.2. Cost-effectiveness analysis, primary analysis; societal perspective

For QALYs, the ICER was 33,798, demonstrating that a QALY lost in the PARASOL intervention group was on average associated with a societal cost saving of EUR 33,799 compared to usual care (Table 4). However, as shown by the CEAC and CE–plane, the uncertainty surrounding this ICER was large (Figs. 1 and 2). The CEAC also showed that if one is willing to pay EUR 0 per QALY gained, the probability that the PARASOL intervention is cost-effective compared with usual care was 0.6. However, this probability decreases to a minimum of 0.5, at a willingness to pay of EUR 50,000 per QALY.

The ICER for the subjective symptom impact demonstrated that the PARASOL intervention was on average associated with a societal cost saving of EUR 708 compared with usual care per point improvement on subjective symptom impact. Again, however, the uncertainty surrounding the ICER was large. The CEAC showed that at a willingness to pay of EUR 0 on the subjective symptom impact, the probability that PARASOL intervention being cost-effective compared with usual care was 0.5. At the willingness to pay level of EUR 10,000, the probability that PARASOL intervention being cost-effective compared with usual care increased to 0.8.

For the physical and mental scale on the RAND-36 the ICER was EUR −99 and 279, respectively. For the physical scale, the ICER indicated that the PARASOL intervention group dominated usual care (i.e. on average less costly and more effective). The CEAC showed a probability of 0.6 at a willingness to pay of EUR 0 per point improvement. The probability increased to >0.9 at a willingness to pay level of EUR 10.000 per point improvement. The ICER for the mental scale, however, indicated that the PARASOL intervention was on average more costly and less effective than usual care. Here, the CEAC showed that at a

Table 2
Characteristics of participants at baseline [a].

Characteristics	Baseline		
	All participants (n = 160)	PARASOL intervention (n = 80)	Usual care (n = 80)
Gender, female	119 (74.4)	57 (71.3)	62 (77.5)
Age *(yr)*, mean (SD)	48.4 (13.7)	47.1 (12.4)	49.7 (14.9)
Duration of symptoms			
0 mo. – 1 y.	22 (13.7)	8 (10)	14 (17.5)
≥1 y.	138 (86.3)	72 (90)	66 (82.5)
Education level			
Low	41 (25.6)	18 (22.5)	23 (28.8)
Middle	65 (40.6)	38 (47.5)	27 (33.8)
High	54 (33.8)	24 (30)	30 (37.5)
Work status			
Employed	103 (64.4)	53 (66.3)	50 (62.5)
Unemployed	57 (16.9)	27 (33.8)	30 (37.5)
Marital status [b]			
Unmarried	56 (35)	22 (27.5)	34 (42.5)
Married/living with a partner	103 (64.4)	57 (71.3)	46 (57.5)
No. of comorbidities			
0	85 (53.1)	45 (56.2)	40 (50)
1	31 (19.4)	15 (18.8)	16 (20)
≥2	44 (27.5)	20 (25)	24 (30)
Recruitment strategy			
PRESUME screening	130 (81.3)	57 (71.3)	73 (91.3)
GP during consultation	5 (3.1)	5 (6.3)	0 (0)
Open recruitment	25 (15.6)	18 (22.5)	7 (8.8)

[a] Data are reported as number (percentage) of participants unless otherwise indicated.
[b] One participant included in the experimental group refused to answer here marital status.

Table 3
Unadjusted and adjusted between-group differences in the PARASOL intervention group and usual care group during 12 months follow-up.

	PARASOL intervention	Usual Care	Unadjusted mean cost difference in € (95% CI)	Adjusted[b] mean cost difference in € (95% CI)	Adjusted[b] mean cost difference in € (95% CI) Employed	Adjusted[b] mean cost difference in € (95% CI) Unemployed
	(n = 80)	(n = 80)	(n = 160)	(n = 160)	(n = 110)	(n = 50)
Cost category	Mean Costs in € (SEM)	Mean Costs in € (SEM)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Intervention	408	–	–	–	–	–
Primary Healthcare	974 (153)	825 (118)	149 (−221 to 518)	79 (−208 to 367)	160 (−98 to 418)	−155 (−1065 to 755)
Secondary Healthcare	821 (252)	530 (144)	292 (−305 to 889)	267 (−279 to 812)	279 (−250 to 807)	634 (−976 to 2244)
Medication	36 (4)	38 (4)	−1 (−13 to 10)	−1 (−13 to 10)	0 (−13 to 13)	−4 (−32 to 24)
Absenteeism	1779 (372)	915 (249)	864 (20 to 1707)[a]	364 (−395 to 1124)	798 (−189 to 1784)	0
Presenteeism	268 (45)	234 (37)	34 (−70 to 137)	−36 (−137 to 65)	9.6 (−116 to 135)	0
Unpaid productivity	1091 (409)	1988 (468)	−897 (−2171 to 376)	−1294 (−2571 to −16)[a]	−910 (−2611 to 790)	−1589 (−3713 to 535)
Healthcare costs[c] total	**2240 (323)**	**1393 (218)**	**847 (54 to 1640)[a]**	**753 (122 to 1384)[a]**	**847 (176 to 1517)**	**882 (−887 to 2653)**
Social costs[d] total	**5376 (831)**	**4539 (672)**	**847 (−1303 to 2997)**	**−213 (−2072 to 1647)**	**744 (−1731 to 3219)**	**−775 (−3827 to 2278)**

Costs are expressed in 2020 Euros.
[a] Significant difference between the PARASOL intervention and usual care ($p \leq 0.05$).
[b] Adjusted for age, recruitment, marital status, duration of complaints, HC at baseline, SC at baseline, health related quality of life score at baseline and utility score at baseline.
[c] Healthcare costs are the sum of intervention, primary and secondary healthcare costs and medication.
[d] Societal costs are the sum of the healthcare, absenteeism, presentism and unpaid productivity costs.

Table 4
Differences in pooled mean costs and effects (95% CI), incremental cost-effectiveness ratios, and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness planes.

	n		Outcome	ΔC (95% CI)	ΔE (95% CI)	ICER	Distribution CE-plane (%)			
Analysis	PARASOL	Usual care		€	Points	€/point	NE [a]	SE [b]	SW [c]	NW [d]
Main analysis (imputed dataset)										
Societal perspective	80	80	QALY (0–1)	−333 (−1816 to 1066)	−0.01 (−0.07 to 0.05)	33,799	10.9	27.2	37.8	24.1
	80	80	Subjective Symptom impact (y/n)	−108 (−2159 to 1914)	0.15 (−0.01 to 0.31)	−708	43	53.8	1.7	1.5
	80	80	Physical scale RAND-36 (0−100)	−328 (−1828 to 1116)	3.31 (−0.21 to 6.82)	−99	33.4	63.6	1.4	1.6
	80	80	Mental scale RAND-36 (0–100)	−259 (−1687 to 1215)	−0.93 (−5.07 to 3.21)	279	8.3	24.3	38.6	28.8
Healthcare perspective	80	80	QALY (0–1)	848 (443 to 1612)	−0.01 (−0.07 to 0.05)	−86,180	37.8	0	0	62.2
	80	80	Subjective Symptom impact (y/n)	897 (180 to 2616)	0.15 (−0.01 to 0.31)	5863	95	1.7	0.4	3
	80	80	Physical scale RAND-36 (0–100)	803 (399 to 1497)	3.31 (−0.21 to 6.82)	243	96.9	0	0	3.1
	80	80	Mental scale RAND-36 (0–100)	800 (405 to 1505)	−0.93 (−5.07 to 3.21)	−860	32.6	0	0	67.4

Costs are expressed in 2020 Euros.
ICER = incremental cost-effectiveness ratio.
CE = cost-effectiveness.
C = Costs.
E = Effects.
QALY = Quality-Adjusted Life Years.
[a] Refers to the northeast quadrant of the CE-plane, indicating PARASOL intervention is more effective and more costly than usual care.
[b] Refers to the southeast quadrant of the CE-plane, indicating PARASOL intervention is more effective and less costly than usual care.
[c] Refers to the southwest quadrant of the CE-plane, indicating PARASOL intervention is less effective and less costly than usual care.
[d] Refers to the northwest quadrant of the CE-plane, indicating PARASOL intervention is less effective and more costly than usual care.

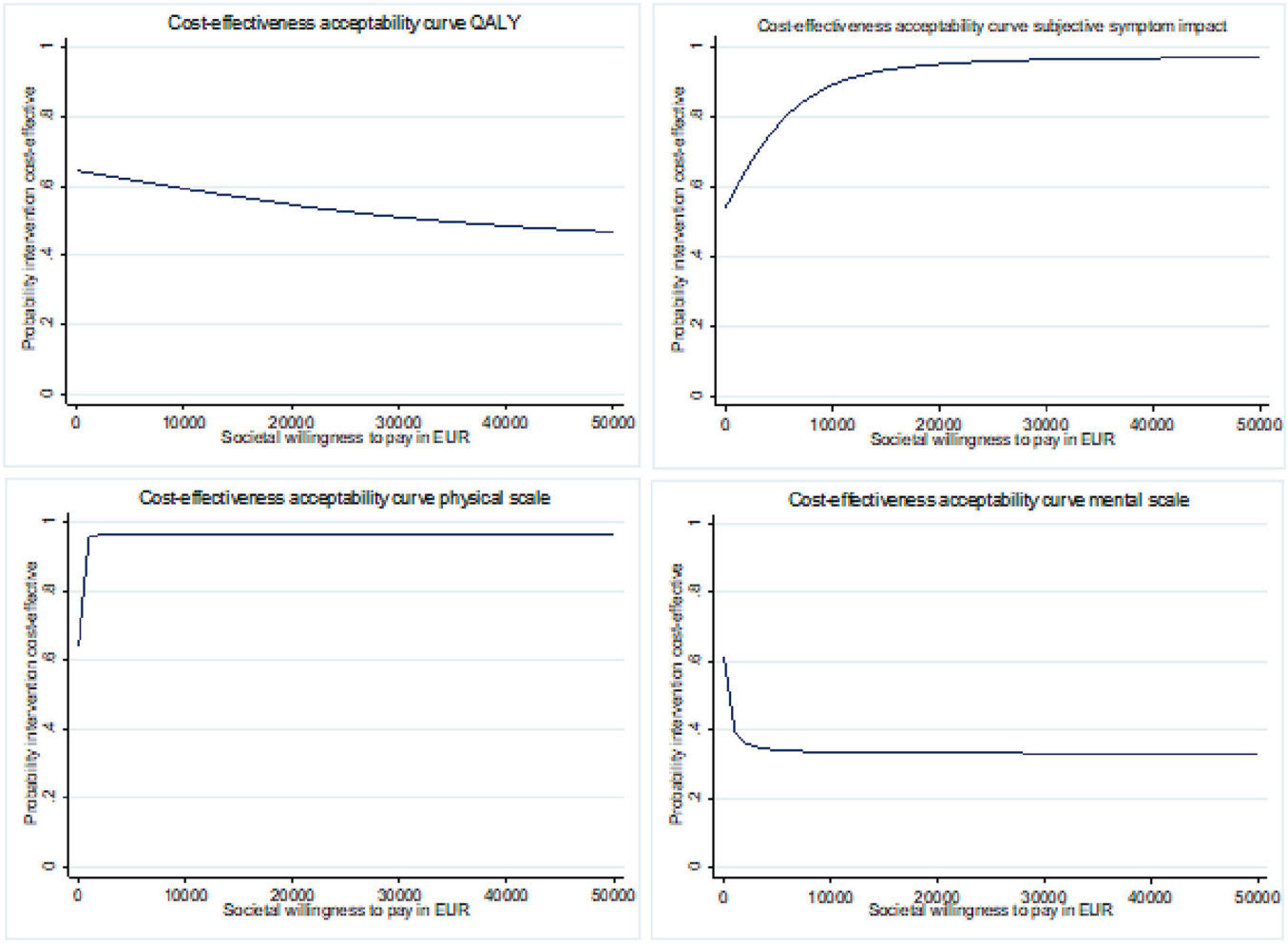


Fig. 1. Cost-effectiveness acceptability curve indicating the probability of cost-effectiveness for different values (€) from a societal perspective.

willingness to pay of EUR 0 per point improvement, the probability of PARASOL to be cost-effective compared to usual care was 0.6. At increasing levels of willing to pay, this probability decreased.

3.3. Cost-effectiveness analyses, secondary analysis; healthcare perspective

The ICER for QALY from the healthcare perspective was −86,180 suggesting an increase of QALY is associated with a healthcare cost of EUR 86,180 for PARASOL intervention compared to usual care (Table 4). The majority of the cost-effect pairs were located in the Northwest quadrant (62.2%), suggesting that the PARASOL intervention was on average more costly and less effective than usual care. The CEAC showed at a willingness to pay of EUR 50,000, the probability of the intervention being more cost-effective than usual care increased to a maximum of 0.2 per point improvement (Appendix A and B).

For the subjective symptom impact the ICER was 5863. The cost-effect pairs were mostly located in the northeast quadrant (95%), indicating that the PARASOL intervention was on average more costly, yet more effective than usual care. At a willingness to pay of EUR 0 the probability of the intervention being more cost-effective than usual care was 0.1 and increased to 0.8 at a willingness to pay of EUR 10,000 per point improvement. The same results were found on the physical scale, with an ICER of 243 and 96.9% of all points in the northeast quadrant. With a willingness to pay of EUR 10,000, the probability of PARASOL being more cost-effectiveness than usual care was >90%. The ICER on the mental scale was found to be −860, where the CEAC showed that the PARASOL intervention was on average less effective with higher costs. The probability that the PARASOL intervention was more cost-effective compared to usual care was 0.3 at a willingness to pay of EUR 10,000 (Appendix A and B).

3.4. Sensitivity analysis

The sensitivity analysis showed similar results when including employment as an additional confounder. Furthermore, when running the analysis for employed (N = 110) and for unemployed (N = 50) participants only, no significant differences between both groups were found (Table 3), demonstrating that the results were not influenced byemployment. As for on the other sensitivity analyses (firstly using three months as final measurement and secondly removing outliers), no significant differences were found between the results of the primary

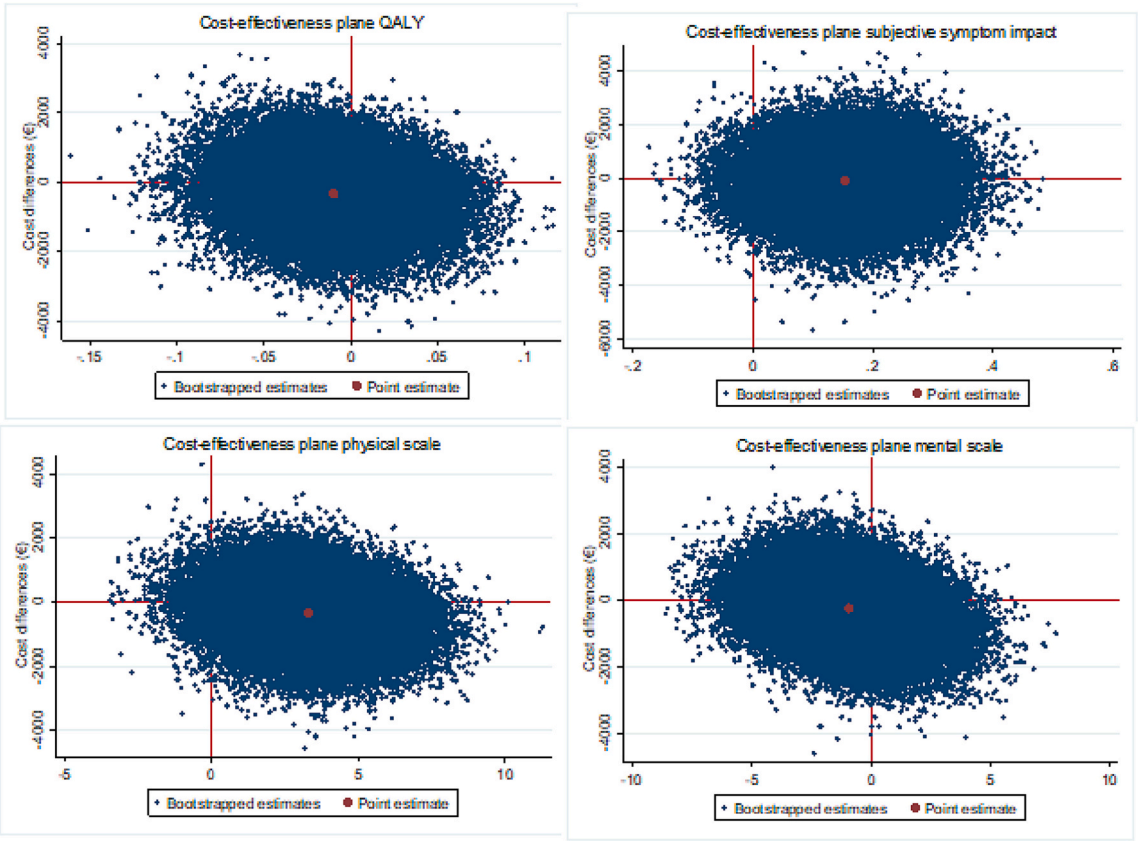


Fig. 2. Cost-effectiveness plane indicating the uncertainty around the incremental cost-effectiveness ratio from a societal perspective.

analysis and the sensitivity analysis. Furthermore, we found no significant differences over time in the average societal costs between the intervention and control group. This also holds when comparing total healthcare costs (Appendix C). By removing outliers, it became clear that the societal cost-differences between the PARASOL intervention group and usual care was driven by outliers on cost items 'secondary care costs' and 'absenteeism'.

4. Discussion

4.1. Main findings

In this study, we could not demonstrate that the PARASOL intervention was cost-effective as compared to usual care. The total healthcare costs of the PARASOL intervention appear to be significantly higher, with the total societal costs not being significantly different compared to usual care. The results of the cost-effectiveness analysis from a social perspective, using QALY as an outcome measure, found the intervention to be less effective, yet less costly compared to usual care. For the outcome measures subjective symptom impact and the physical scale of the RAND-36average costs are found to be lower and effectiveness is found to be higher in the PARASOL intervention group compared to usual care. However, the differences are small and not significant. For the mental scale of the RAND-36, we couldn't demonstrate the cost-effectiveness of the intervention compared to usual care.

One of the explanations for the lack of cost-effectiveness of the PARASOL intervention maybe the duration of the follow-up. The follow-up in this study was 12 months, yet as the intervention was offered proactive to prevent chronic PSS in patients, cost differences may only appear after a longer period. Over time, severity of complaints may increase, increasing their impact on daily life and utility. Hence, the 12-month follow-up period might have been too short for the additional costs incurred by proactively offering this preventive intervention (EUR 408) to be made up in lower overall societal costs. However, these additional costs probably explains the significant difference in total healthcare costs. Literature supports this finding that a 12-month follow-up period may not be sufficient to demonstrate cost-effectiveness [39].

A second explanation for the lack of cost-effectiveness of the PARASOL could lie in the included population. That is, the PARASOL intervention only includes patients with moderate PSS. These patients suffer from less severe complaints in daily life compared to chronic PSS patients [40], and hence may have had lower costs to begin with. Cost differences between usual care and the intervention are hence likely to be smaller and therefore differences are harder to demonstrate. This reasoning is underscored by literature. That is, the mean total societal costs in our study were EUR 5376 for the PARASOL intervention and EUR 4539 for usual care Per Patient Per Year (PPPY). Literature on chronic PSS finds higher average societal costs due to PSS of EUR 6816 PPPY [10]. The same holds for total healthcare costs. We found an average of EUR 2240 in the intervention group and an average of EUR 1393 in the usual care group PPPY. Literature on chronic PSS patients founds an average of EUR 3123 PPPY [10].

Although not statistically significant, a difference was found in the subjective symptom impact and the PCS in favor of the PARASOL intervention This outcome is consistent with literature on a primary care intervention for patients with chronic PSS. The authors suggest that the improvement in PCS was reflected by an improvement in the ability to carry out daily tasks [41]. This may be explained by the fact that patients with PSS often experience physical limitations due to their symptoms, and are therefore not able to carry out daily tasks on their own [42]. At a

willingness to pay of EUR 10,000, the probability of cost-effectiveness of PARASOL on PCS is >0.8 compared to usual care. There is, however, no data on what one is willing to pay for this outcome measure. The amount that has to be invested for an improvement seems high when comparing what an insurance company is willing to pay for a lifestyle intervention. Insurance companies reimburse at maximum EUR 2500 for lifestyle interventions [43].

4.2. Strengths and limitations

This study was the first trial to investigate the cost-effectiveness of an integrated blended primary care intervention in patients with moderate PSS. Therefore, this study provides relevant results regarding cost-effectiveness of a multidisciplinary, blended care intervention to prevent chronic PSS. A strength of this economic evaluation is that we analyzed the data both from the societal perspective as well as the healthcare perspective. In addition, to the different perspectives, various sensitivity analyses were performed to assess the robustness of the study results.

A limiting factor of this study is that little is known about the willingness to pay for the three clinical outcome measures, i.e. subjective symptom impact, PCS and MCS. This makes it impossible to make strong statements about the cost-effectiveness of the PARASOL intervention for these outcomes. In addition, the sample size is too small for analyses of cost-effectiveness in subsets of the sample, requiring the inclusion of more patients. The last limiting factor is the follow up period of 12 months which may not show an effect on costs.

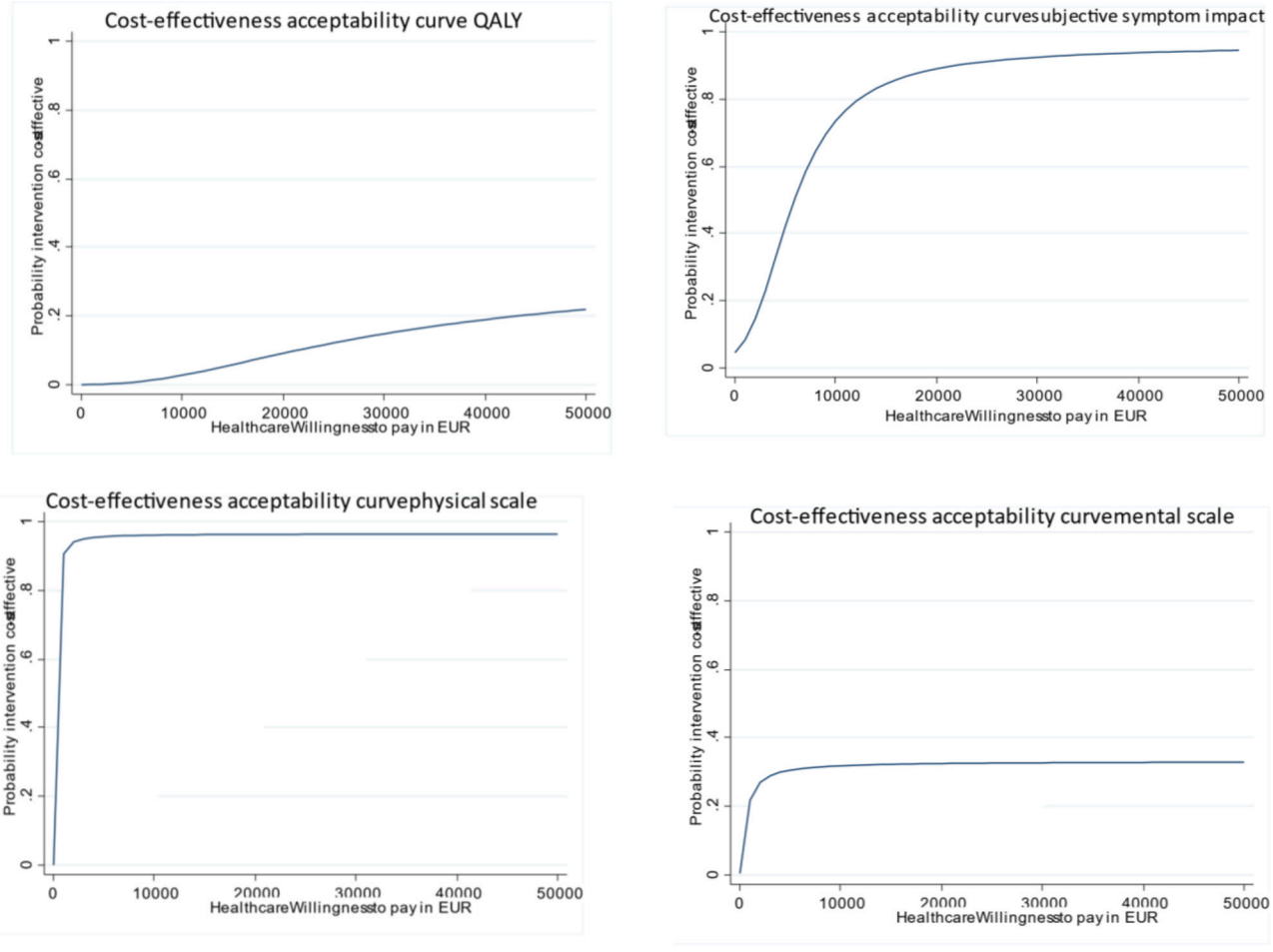
5. Conclusion

Overall, we didn't find an integrated blended primary care intervention to be cost-effective compared to usual care, both from a societal and healthcare perspective. However, when looking on relevant, but specific outcome measures (subjective symptom impact and physical health) for this population, average costs are found to be lower and the effectiveness of the integrated blended primary care intervention is found to be higher compared to usual care.

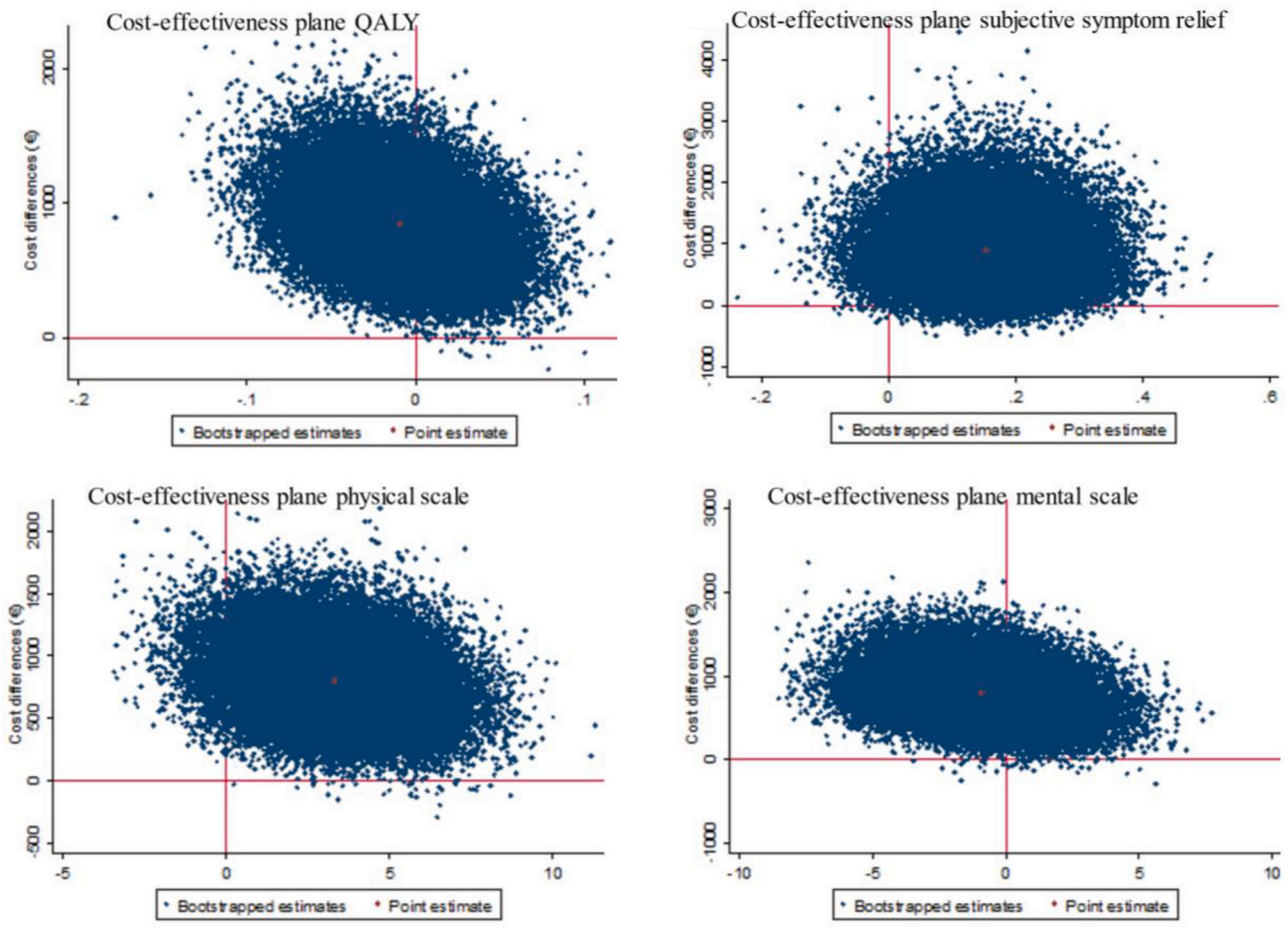
Declaration of Competing Interest

None.

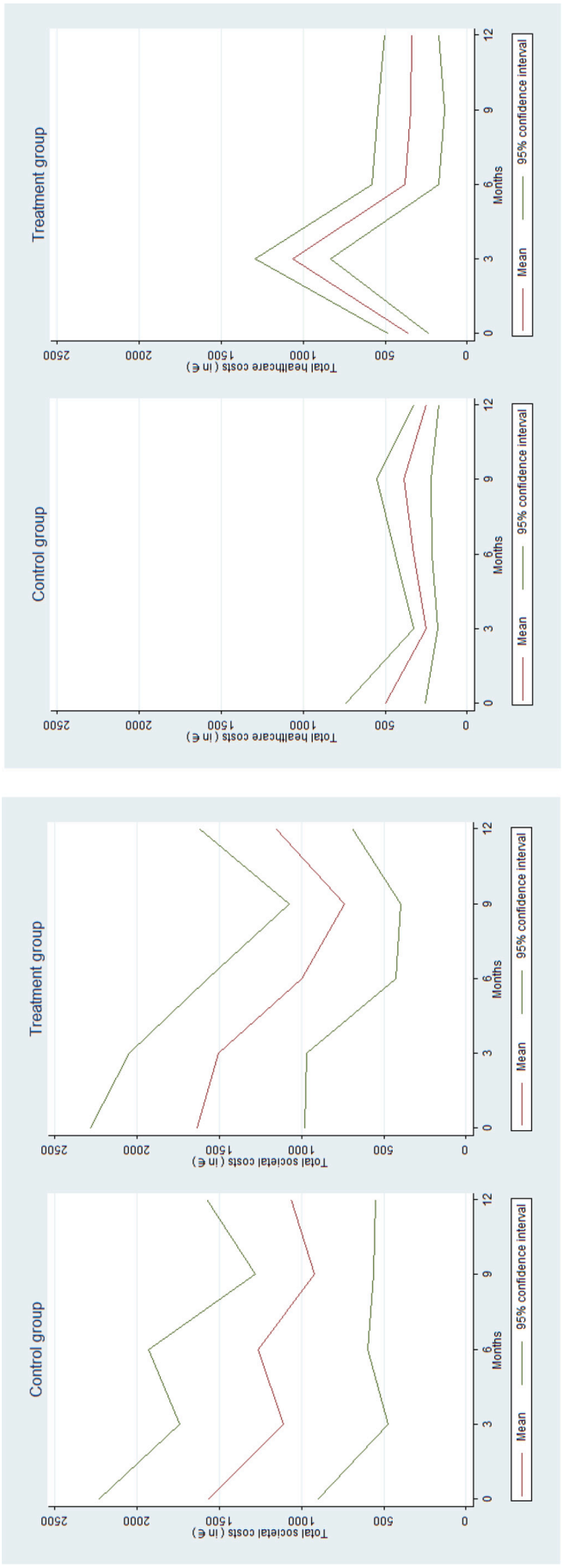
Appendix



Appendix A. Cost-effectiveness acceptability curve indicating the probability of cost-effectiveness for different values (€) from a healthcare perspective.



Appendix B. Cost-effectiveness plane indicating the uncertainty around the incremental cost-effectiveness ratio from a healthcare perspective.



Appendix C. Total cost over time, from the societal (figures on the left) and a healthcare perspective (figures on the right).

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