Mindfulness-based cognitive therapy for patients with medically unexplained symptoms: A cost-effectiveness study

Hiske van Ravesteijn [a,b,*], Janneke Grutters [c,d], Tim olde Hartman [a], Peter Lucassen [a], Hans Bor [a], Chris van Weel [a], Gert Jan van der Wilt [c], Anne Speckens [b]

[a] Department of Primary and Community Care, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
[b] Department of Psychiatry, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
[c] Department for Health Evidence, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
[d] Department of Operating Rooms, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

ARTICLE INFO

ABSTRACT

Objective: Our aim was to assess cost-effectiveness of mindfulness-based cognitive therapy (MBCT) compared with enhanced usual care (EUC) in treating patients with persistent medically unexplained symptoms(MUS).
Methods: A full economic evaluation with a one year time horizon was performed from a societal perspective. Costs were assessed by prospective cost diaries. Health-related Quality of Life was measured using SF-6D. Outcomes were costs per Quality-Adjusted Life Year (QALY). Bootstrap simulations were performed to obtain mean costs, QALY scores and incremental cost-effectiveness ratios (ICERs).
Results: MBCT participants (n = 55) had lower hospital costs and higher mental health care costs than patients who received EUC (n = 41). Mean bootstrapped costs for MBCT were €6269, and €5617 for EUC (95% uncertainty interval for difference: −€1576; €2955). QALYs were 0.674 for MBCT and 0.663 for EUC. MBCT was on average more effective and more costly than EUC, resulting in an ICER of €56,637 per QALY gained. At a willingness to pay of €80,000 per QALY, the probability that MBCT is cost-effective is 57%.
Conclusion: Total costs were not statistically significantly different between MBCT and EUC. However, MBCT seemed to cause a shift in the use of health care resources as mental health care costs were higher and hospital care costs lower in the MBCT condition. Due to the higher drop-out in the EUC condition the cost-effectiveness of MBCT might have been underestimated. The shift in health care use might lead to more effective care for patients with persistent MUS. The longer-term impact of MBCT for patients with persistent MUS needs to be further studied.

© 2013 Elsevier Inc. Open access under the Elsevier OA license.

Introduction

Medically unexplained symptoms (MUS) are commonly encountered across all healthcare settings. About one in five patients presenting at the general practitioner (GP)'s office has medically unexplained symptoms [1,2]. Often, these symptoms resolve spontaneously. However, in 10–16% of primary care patients the symptoms persist and result in functional impairment [1,3]. Frequent attendance because of persistent medically unexplained symptoms is seen in 2.5% of primary care patients. This group mainly consists of women with a lower socioeconomic status [4].

Societal costs associated with persistent MUS are substantial [5,6], they mainly consist of health care costs and costs of lost productivity. Health care costs of patients with persistent MUS are high due to high consultation rates in both primary and secondary care [7,8] and due to often unnecessary medical procedures with the potential for iatrogenic harm [5,9,10]. In the United Kingdom the incremental annual health care cost incurred by patients with MUS was estimated at approximately 10% of the total health care expenditure for the working-age population [11]. In the United States 16% of the total medical care costs are attributable to the incremental costs of MUS [7]. In addition, disabilities caused by MUS lead to diminished employment participation: patients with persistent MUS are more on sick leave and have higher rates of unemployment [12].

Clearly, effective interventions for MUS are needed in order to diminish functional impairment and societal costs. Mindfulness-based cognitive therapy (MBCT) is a promising treatment in the field of MUS as it appears to be effective [13] and provides us with a new approach: MBCT stimulates acceptance of symptoms [14]. An economic evaluation of MBCT for patients with somatization disorder has been performed within a recent Danish trial. MBCT was compared to a specialized treatment consisting of a two-hour individual consultation by a psychiatrist [15]. Total health care costs did not differ

* Corresponding author at: Department of Primary and Community Care, internal code 117, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500HB Nijmegen, The Netherlands. Tel.: +31 243614646; fax: +31 243541862.
E-mail address: h.vanravesteijn@psy.umcn.nl (H. van Ravesteijn).

between the conditions, but the percentage of patients on disability pension had decreased significantly more in the MBCT condition.

In a recently randomized controlled trial the effectiveness of MBCT was compared to enhanced usual care (EUC) for frequently attending patients with persistent MUS [13]. Both MBCT and EUC succeeded in improving current health status and mental and physical functioning. However, MBCT led to an earlier improvement of mental functioning, especially with regard to vitality and social functioning. In the context of health care budget constraints, an economic evaluation of this effect can inform decisions which health care services to offer to these patients. Therefore, we performed a cost-effectiveness analysis comparing MBCT versus EUC for patients with persistent MUS.

Methods

Design of RCT

This study was embedded in a randomized controlled trial examining the effects of MBCT on frequently attending patients in primary care with persistent MUS. 125 Patients were randomly allocated to either MBCT (n = 64) or EUC (n = 61) [13]. All patients belonged to the 10% most frequently attending patients of the participating GPs (n = 19), and they fulfilled the DSM-IV criteria of an undifferentiated somatoform disorder, which means that they had at least one physical symptom which was not (fully) explained by a physical disorder or by substance abuse, lasted for at least 6 months, led to functional impairment and could not be put down to another psychiatric disorder. All patients received a psychiatric interview at the pre-randomization assessment which included the Mini-International Neuropsychiatric Interview (MINI) [16] and the section on somatoform disorders of the Structural Clinical Interview for DSM IV axis I disorders (SCID-I) [17].

Primary outcomes were current health status and mental and physical functioning (SF-36 PCS and MCS) [18]. Assessments took place at baseline, end of treatment and 9-month follow-up by filling out postal or online questionnaires. Patients randomized to the EUC condition were requested to refrain from attending mindfulness training during the study period and they had the possibility to participate in the mindfulness training after completion of the study.

Interventions

Participants randomized to MBCT received eight 2.5-hour sessions of MBCT from experienced mindfulness trainers. Both trainers had participated in an intensive two-year teacher training course for mindfulness teachers, had many years of ongoing meditation practice, and both trainers taught more than 30 MBCT or MBSR courses to patients with psychiatric disorders and/or physical conditions. Participants were instructed to practice at home 6 days a week for approximately 45 min a day. To support home practice, patients received a folder with information about the individual sessions, homework assignments and forms to keep a record of their practice, together with CDs with guided meditations and movement exercises. Group size varied between 7 and 14 participants. Our training protocol was based on the MBCT format for patients with recurrent depression [19]. We made minor adaptations to the MBCT training protocol to make it more suitable for patients with physical symptoms. The program consisted of formal meditation exercises such as the body scan, sitting meditation, walking meditation and mindful movement. Participants were encouraged to cultivate awareness of everyday activities, such as eating or taking a shower. In line with the original Mindfulness-Based Stress Reduction format [20], we incorporated a silent day to give participants the opportunity to deepen their mindfulness practice [21].

Patients in the EUC condition received usual care provided by their GP and other health care professionals. The term 'enhanced usual care' was considered appropriate as all patients received a psychiatric interview. The GP was explicitly informed about the psychiatric diagnoses resulting from the interview [22].

Main results RCT

In the randomized controlled trial, current health status and physical functioning did not significantly differ between groups. However, participants in the MBCT group reported a significantly greater improvement in mental functioning at the end of treatment (adjusted mean difference 3.9, 95%CI 0.24 to 7.6), in particular with regard to vitality and social functioning. Within the MBCT group, almost half of the secondary outcome measures had significantly improved at end of treatment, whereas in the EUC group none had.

Assessments cost-effectiveness study

A face-to-face pre-randomization assessment was performed in which we assessed socio-demographic and clinical characteristics, the current employment status and medication use in the past month. Further assessments were performed with online or postal questionnaires at baseline, 3 months and 12 months after randomization. To assess health care use and employment participation we used a prospective cost diary in which patients were asked to note their health care use and their employment participation per calendar day. Given a societal perspective, the prospective cost diaries covered employment participation and health care use per day. The prospective diaries were mailed to the patients before the start of each month during the whole year of the trial. Patients were requested to send the diary back at the end of each month. If the patient did not send in the diary in time, our research team made a phone call to the patient. We kindly requested patients to keep filling out the diaries. A final follow-up assessment was made by telephone at 12 months after baseline in which we assessed again the current employment status and medication use in the past month. The number of attended MBCT sessions was registered by the mindfulness trainer.

Unit prices

We used Standardized Dutch unit prices [23]. When a standardized unit price was not available, prices were based on tariffs. Medication costs were obtained from the Dutch 'Pharmacotherapeutic Compass' (the most used drug reference in The Netherlands) [24]. Medication costs which were not retrieved from these resources (e.g. vitamin pills), were derived from suppliers on the Internet. If these medication costs varied, we used the lowest price.

Productivity costs (i.e. when patients are unable to perform paid work) were calculated according to the Friction Cost (FC) method [25], implying that the number of hours patients were absent from their job is multiplied with the actual gross wage per hour. The cause for absence is not taken into account. Absence could for example be due to illness, being fired or resigning from a job. In FC, productivity costs are only counted as long as it takes to replace someone. The friction period is defined as the time needed to restore the initial production level. After this friction period, costs to society fall back to zero. For FC, standardized FC tariffs as well as the friction period of 160 days were obtained from the Dutch Manual for Costing studies [23]. The tariffs are calculated based on the average value added per working person. FC was calculated according to the standards, implying that when a patient was continuously absent for more than 160 days, it was assumed that this patients' place in the production process was filled again and productivity returned to its original level. Therefore, after these 160 days had passed, productivity costs were considered zero. Price indices were used to convert costs to the 2010 price level.

Outcome measures

Effectiveness was expressed as Quality Adjusted Life Years (QALY). A QALY is a measure of life expectancy, weighted by the health-related quality of life (HRQoL) represented by utility scores.

HRQoL was measured with the SF-6D [26] which is based on the SF-36 [18]. The SF-6D revised the SF-36 into a six-dimensional health state classifications system. This classification system allows the calculation of a utility score, which is a component of the QALY. It contains 6 dimensions: physical functioning, role participation (combined role-physical and role-emotional), social functioning, pain, mental health and vitality [26]. Each dimension has four to six levels. The specific areas or activities contributing to the SF-6D index include current ability to engage in both moderate and vigorous activities and current ability to bathe and dress oneself. From the SF-36 Health Survey data, individual respondents can be classified on any of four to six levels of functioning or limitations, on each of six domains. These SF-6D health states can be converted into utility scores by assigning preference weights. The preference weights are derived from valuations of a sample of 249 SF-6D health states using the standard gamble in a representative sample of the UK population and range from 0.29 to 1.00 [27], with 1 representing perfect health. From these utility scores, Quality-Adjusted Life Years (QALYs) were derived using the area under the curve method by using the SF-36 measurements at baseline, 3 months and 12 months after baseline [28].

Data analysis

Patients who had filled out six or more prospective diaries and whose data on the SF-6D were available from all three assessments were included in the analysis. Costs were divided by the total number of days filled out in the diaries and multiplied by 365 to reach an estimation of the costs per year. We used the independent sample Mann–Whitney U test to determine whether the costs differed between the two conditions at a significance level of p = 0.05. Since cost data are generally highly skewed, and not distributed normally, bootstrap simulations with 1000 replications were performed [29,30] to estimate uncertainty intervals around the mean costs. For the same reasons, QALY scores were bootstrapped with 1000 replications. The uncertainty interval is represented by the 2.5th and 97.5th percentiles.

Results of Incremental Cost-Effectiveness Ratios (ICER) bootstraps are presented in cost-effectiveness planes. Cost-effectiveness planes show differences in costs on the vertical axis and differences in effect on the horizontal axis. Bootstrapped cost-effectiveness pairs located in the north-west quadrant indicate MBCT to be inferior to EUC (more costly and less effective than EUC). Cost-effectiveness pairs located in the south-east quadrant show MBCT to be dominant over EUC (more effective and less costly than EUC). With respect to the other two quadrants (higher costs for better effectiveness and lower costs for lower effectiveness), the choice of an intervention depends on the threshold value, i.e. what society is prepared to pay for an effectiveness gain, or willing to accept as savings for effectiveness loss. In these cases, an ICER is determined. An ICER is calculated by dividing the difference in costs between the treatments by the difference in effectiveness between the treatments. An ICER represents the extra amount of money that has to be invested or will be saved to gain or lose one extra unit of effect. In our study, the unit of effect was a QALY. Cost-effectiveness acceptability curves (CEACs) [31] were constructed. They represent the probability that, given a certain threshold for the willingness to pay for a QALY, the intervention is cost-effective.

Secondary analyses

Secondary analyses were performed to assess robustness of the results.

1. An analysis with a healthcare perspective, meaning that only direct healthcare costs, including costs of MBCT and medication use, were considered. For this analysis we excluded the productivity losses from our analysis.
2. A per protocol analysis: analyzing only those patients who adhered to the study protocol. In line with previous MBCT trials, an adequate dose of MBCT (i.e. the treated "per protocol" cases) was defined as participation in at least four MBCT group sessions [19,32]. Data are presented from the societal perspective.
3. An analysis without extreme cost outliers due to physical disease. Data are presented from the societal perspective.

The results of all three secondary analyses are represented in a CEAC.

Results

Patients

Although 125 patients participated in the randomized controlled trial, we obtained data for the cost-effectiveness analysis of only 96 patients, 55 in the MBCT condition and 41 in the EUC condition (Fig. 1). Filling out prospective monthly diaries was experienced as burdensome by many patients, for 15 patients this was the main reason to stop filling out these diaries. Of the 29 patients who were excluded from the cost-effectiveness analysis, twenty-seven patients filled out less than six monthly diaries. Two patients did hand in the monthly diaries, but not the questionnaires. Patients who withdrew or dropped-out (n = 29) seemed more severely impaired in their daily functioning at baseline. They were less often employed (41% v. 52%), had a lower level of education (17% only attended primary education v. 9%) and these patients had a depressive or anxiety disorder (48% v. 28%) more often than those included in the cost-effectiveness analysis. We present the cost-effectiveness data of the 96 patients for whom sufficient data were available. Table 1 shows baseline characteristics of these patients. There were no significant differences in baseline characteristics between patients in the MBCT condition and patients in the EUC condition. Costs, QALY results, and cost per QALY ratios are based on all 96 patients.

Employment status

At baseline 53% in the MBCT condition had a paid job, and 51% in the control condition. At the end of follow-up 44% in the MBCT condition and 51% in the control condition had a paid job. Unemployment rates were 11% in the MBCT condition and 15% in the control condition at baseline. The unemployment rates increased in both conditions to 20%. The percentage of patients on disability pensions was 13% in the MBCT condition and 12% in the EUC condition at baseline. The percentage of patients on disability pensions slightly increased in both conditions: at the end of follow-up disability pensions were provided to 16% in the MBCT condition and to 15% in the control condition.

Costs

Bootstrapped societal costs over 1 year were €6269 for MBCT and €5617 for EUC which is a non-significant difference (Table 2). With respect to health care costs, treatment costs (including costs of the attended MBCT sessions and, if attended, the 6-hour silence retreat) were €450 per person randomized to MBCT. Apart from the costs for the MBCT training, patients in the MBCT condition had lower hospital care related costs than the patients in the EUC condition (€636 versus €861, p = 0.18) and higher mental health care costs (€431 versus €224, p = 0.98). The majority of patients (63%) did not make use of mental health care. Mean costs of participants who did use mental health care were €1185 in the MBCT condition and €574 in the EUC condition (p = 0.29). In both conditions about one in five patients made use of alternative healers. Mean costs for all patients were €100 per patient in this study, which makes the mean costs per patient who used alternative healers approximately €500. Medication costs were higher in the MBCT condition (€673 versus €386, p = 0.27 Mann–Whitney test). This was partially due to a single very high cost outlier in the MBCT condition who used antiretroviral HIV medication and had annual medication costs of €9513. His medication costs accounted for 60% of the difference between MBCT and EUC medication costs.

Effectiveness

Table 3 presents mean societal costs and SF-6D utility scores. Baseline utility scores were 0.632 (SD 0.11) for MBCT and 0.639 (SD 0.10) for EUC, (p = 0.983) (Fig. 2). Utility scores increased in both conditions; from 0.63 to 0.69 in MBCT patients, and from 0.64 to 0.68 in EUC patients, an improvement of 0.06 and 0.04, respectively. As a result, total QALY's over the 1-year period were 0.674 for MBCT and 0.663 for EUC. The bootstrapped difference in QALY's between MBCT and EUC of 0.012 (95% CI −0.019 to 0.041) was not statistically significant.
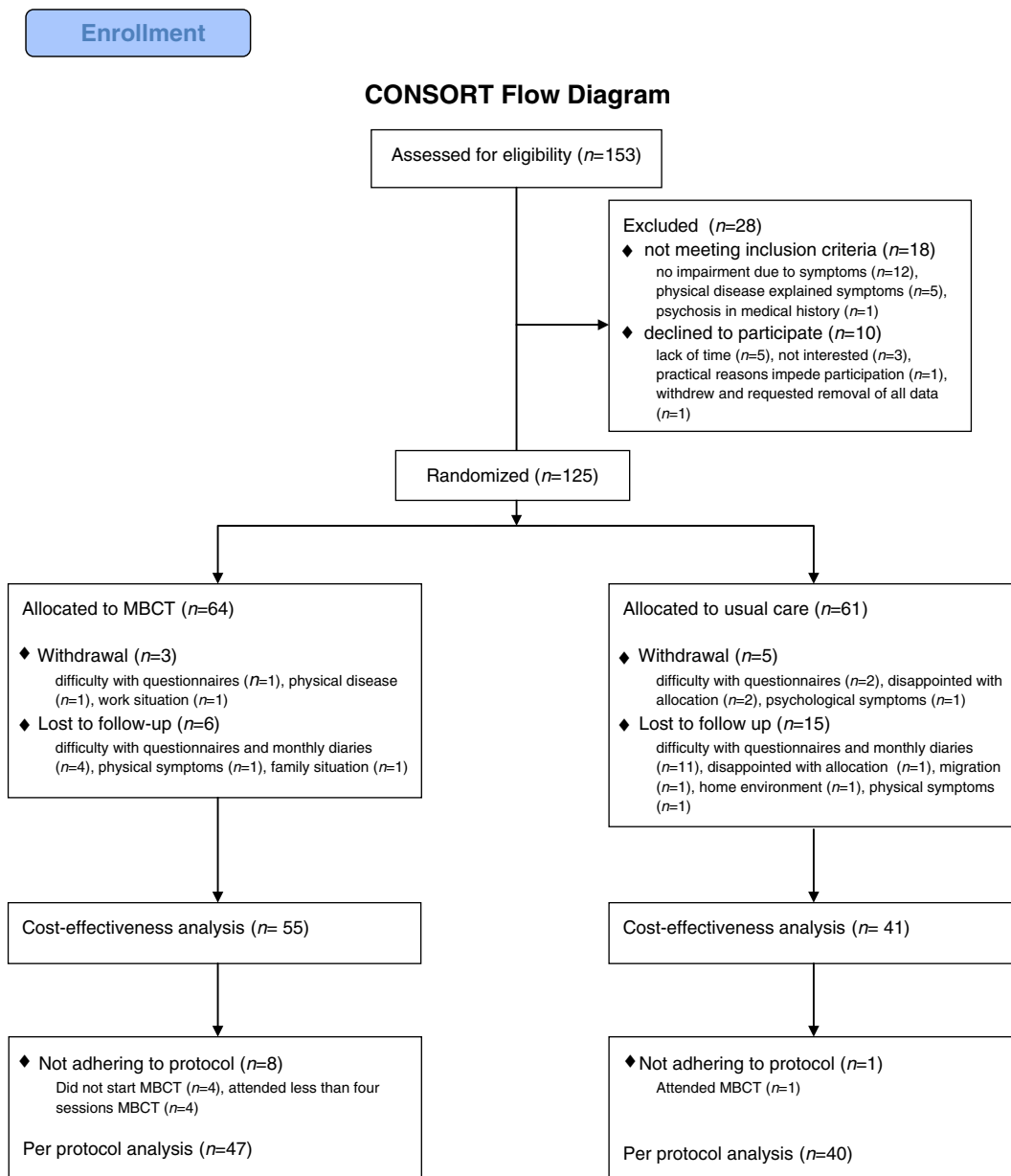
Enrollment

CONSORT Flow Diagram

Assessed for eligibility (*n*=153)

Excluded (*n*=28)
- ♦ not meeting inclusion criteria (*n*=18)
  no impairment due to symptoms (*n*=12),
  physical disease explained symptoms (*n*=5),
  psychosis in medical history (*n*=1)
- ♦ declined to participate (*n*=10)
  lack of time (*n*=5), not interested (*n*=3),
  practical reasons impede participation (*n*=1),
  withdrew and requested removal of all data
  (*n*=1)

Randomized (*n*=125)

Allocated to MBCT (*n*=64)

- ♦ Withdrawal (*n*=3)
  difficulty with questionnaires (*n*=1), physical disease
  (*n*=1), work situation (*n*=1)
- ♦ Lost to follow-up (*n*=6)
  difficulty with questionnaires and monthly diaries
  (*n*=4), physical symptoms (*n*=1), family situation (*n*=1)

Allocated to usual care (*n*=61)

- ♦ Withdrawal (*n*=5)
  difficulty with questionnaires (*n*=2), disappointed with
  allocation (*n*=2), psychological symptoms (*n*=1)
- ♦ Lost to follow up (*n*=15)
  difficulty with questionnaires and monthly diaries
  (*n*=11), disappointed with allocation (*n*=1), migration
  (*n*=1), home environment (*n*=1), physical symptoms
  (*n*=1)

Cost-effectiveness analysis (*n*= 55)

Cost-effectiveness analysis (*n*= 41)

- ♦ Not adhering to protocol (*n*=8)
  Did not start MBCT (*n*=4), attended less than four
  sessions MBCT (*n*=4)

Per protocol analysis (*n*=47)

- ♦ Not adhering to protocol (*n*=1)
  Attended MBCT (*n*=1)

Per protocol analysis (*n*=40)

Fig. 1. Patient enrollment.

Cost-effectiveness

In comparison to the EUC condition, bootstrapped total societal costs were €652 higher and QALY's were 0.012 higher in the MBCT condition. The ICER based on the QALY shows that for one QALY gained the costs are €56,637, as MBCT was more costly and more effective than EUC (Table 3). The bootstrapped results (Fig. 3) show that 52% of the cost-effectiveness pairs are in the north-east quadrant, where MBCT is more costly and more effective. Twenty percent are located in the north-west quadrant, which is the inferiority quadrant. The south-east quadrant, i.e. the dominance quadrant, contains 25% of the replications. And the final 4% of the cost-effectiveness pairs are in the south-west quadrant, where MBCT is less costly and less effective. The CEAC (Fig. 4) indicates that the probability of MBCT being cost-effective increases with an increasing threshold value. If society's maximum willingness to pay would be €0 for a QALY gain, the probability of MBCT being cost effective is 28%. And at a threshold of €40,000 this is 48%. Assuming that society's maximum willingness to pay is €80,000 for a QALY gain [33] the probability that MBCT is cost-effective is 57%.

Secondary analyses

Health care perspective

Costs per QALY gained when regarded from the health care perspective did not significantly differ from the costs per QALY gained when regarded from the societal perspective (Table 3). In the MBCT condition bootstrapped costs were €756 higher and

QALYs 0.011 higher than in the EUC condition. Leaving out productivity losses led to an ICER of €66,450 per QALY gained. Analysis from the health care perspective resulted in higher costs per gained QALY than analysis from the societal perspective (ICER of €56,637 per QALY gained). Assuming that society's maximum willingness to pay is €80,000 for a QALY gain [33] the probability that MBCT is cost-effective is 55%.

Per protocol analysis

In the MBCT condition 8 patients (of patients included in the cost-effectiveness analysis) did not follow the protocol, they attended less than four sessions of MBCT. In the EUC one patient did not follow the protocol, she attended MBCT during the year of study. Therefore the per protocol analysis consists of 87 patients (MBCT n = 47, EUC n = 40). In the MBCT condition bootstrapped costs were €562 higher and QALYs 0.011 higher than in the EUC condition. With respect to costs per QALY, costs dropped from €56,637 in the main analysis to €53,198 in the per protocol analysis. Assuming that society's maximum willingness to pay is €80,000 for a QALY gain [33] the probability that MBCT is cost-effective is 56%.

Analysis without extreme cost outliers due to physical disease

There was one extreme cost outlier, this was a patient in the MBCT condition. This patient had exceptionally high medication costs due to antiretroviral drugs, which were prescribed for HIV. Medication costs exceeded €9500 per year, whereas all other patients had medication costs between €0 and €2600, with mean €453 and median €230. After exclusion of this patient cost data of 95 patients were analyzed using

Table 1
Baseline characteristics of 96 study participants.

	MBCT (n = 55)	EUC (n = 41)	p-Value[a]
Age in years (SD)	47.0 (11.3)	48.1 (12.3)	0.66[b]
Women	43 (80.3)	31 (67.9)	0.78
Civil class			
Married	27 (49.1)	18 (43.9)	0.18
Single/unmarried	20 (36.4)	12 (29.3)	
Divorced	8 (14.5)	8 (19.5)	
Widowed	0 (0.0)	3 (7.3)	
Education level[c]			
Low	14 (25.5)	17 (41.5)	0.20
Middle	26 (47.3)	13 (31.7)	
High	15 (27.3)	11 (26.8)	
Employment status			
Labor	29 (52.7)	21 (51.2)	0.94
Sick leave	3 (5.5)	3 (7.3)	
Disability pension	7 (12.7)	5 (12.2)	
Unemployment benefit	2 (3.6)	1 (2.4)	
Social welfare	2 (3.6)	4 (9.8)	
Elderly pension	7 (12.7)	5 (12.2)	
Student	3 (5.5)	1 (2.4)	
No income	2 (3.6)	1 (2.4)	

[a] Based on Pearson chi-square test, if no other test is indicated.

[b] Based on independent samples *t*-test.

[c] Education level was classified as low (primary and lower secondary education), middle (upper secondary education) and high (higher vocational training and university).

the societal perspective (MBCT n = 54, EUC n = 41). In the MBCT condition bootstrapped costs were €647 higher and QALY's 0.016 higher than in the EUC condition. With respect to costs per QALY, costs dropped to €41,167. Assuming that society's maximum willingness to pay is €80,000 for a QALY gain [33] the probability that MBCT is cost-effective is 62%.

Discussion

General results

Total societal costs did not significantly differ between treatments, costs per patient were approximately €650 higher for MBCT than for

EUC in the 1-year follow-up. The costs of lost productivity did not significantly differ between groups. There were notable differences in the distribution of health care resources. Patients in the MBCT condition used less hospital care and more mental health care than those in the EUC condition. Mean medication costs were higher (p = 0.27) in the MBCT condition, however this was mainly caused by one extreme cost-outlier. In addition, we had less patients in the EUC condition (n = 41) than in the MBCT condition (n = 55), this was due to higher drop-out in the EUC condition. Patients who dropped out seemed more severely impaired, therefore our results might underestimate the costs of the EUC condition.

Utility scores increased from 0.63 to 0.69 in MBCT patients, and from 0.64 to 0.68 in EUC patients, an improvement of 0.06 and 0.04, respectively. The minimally important difference for SF-6D utility scores is considered to be 0.04 points [34]. So, in both conditions there was a clinically relevant effect on HRQoL. QALY's based on the 1-year period were slightly higher for MBCT, resulting in an ICER indicating a costing €56,637 for a QALY gain. In the per protocol analysis the societal costs for a QALY gain were €53,198. There was one extreme cost outlier due to the use of antiretroviral drugs for HIV in the MBCT condition, leaving out the extreme outlier led to an ICER of €41,167 per QALY gained.

To date, there is no consensus about a reasonable threshold value for cost-effectiveness. Most studies with the explicit goal to determine a threshold resulted in values ranging from €10,000 to €27,000 [35–37]. However, in practice, thresholds used for appraisal of new interventions may be higher, around €40,000 [38] for the UK and €80,000 for The Netherlands [33]. The CEACs (Fig. 4) show a range of thresholds, varying from €0 to €150,000. In the present study, when applying a €80,000 per QALY threshold, the chance that MBCT was cost-effective within the year of study lies between 56% and 62%.

Comparison to literature

Another intervention for MUS, cognitive behavioral therapy (CBT), has been economically evaluated [39]. CBT was combined with drug

Table 2
Total mean costs per cost item and bootstrapped mean costs for subtotals per patient for MBCT (n = 55) and EUC (n = 41).

Cost Category	% of patients in EUC condition	Mean EUC costs per person (n = 55)	% of patients in MBCT condition	Mean MBCT costs per person (n = 41)	p-Value, difference in costs[A]	Incremental	CI 2.5–97.5
Health care costs							
MBCT	[B]2%	16	[C]93%	450	0.00		
Primary care[D]	91%	252	93%[b]	286	0.94		
Hospital care[E]	79%	861	66%	636	0.18		
Paramedical care[F]	57%	497	55%	504	0.77		
Mental health care[G]	38%	224	36%	431	0.98		
Occupational health care[H]	14%	26	14%	26	0.80		
Alternative healers[I]	19%	101	18%	100	0.91		
Medication[J]	95%	386	95%	673	0.27		
Subtotal		2363		3106	0.07		
Bootstrapped subtotal		2351		3107		+755	+73 to +1418
Costs of lost production							
Absent from paid work	49%	3283	45%	3354	0.49		
Bootstrapped subtotal		3251		3350		+99	−1905 to +2045
Total costs		5646		6460	0.38		
Bootstrapped total costs		5617		6269		+652	−1576 to +2955

[A] Mann–Whitney test.

[B] One patient in the EUC condition deviated from the study protocol and received MBCT.

[C] Four patients in the MBCT condition did not start MBCT.

[D] Costs consist of contact with general practitioner (GP), home visit by GP, telephone or e-mail contact with GP, consultation with GP in after hours clinic, contact with practice nurse.

[E] Costs consist of outpatient contact with medical specialist, day treatment, inpatient treatment, emergency treatment, ambulance ride.

[F] Costs consist of physiotherapy, movement therapy, speech-therapy, occupational therapy, diet advice, home care.

[G] Costs consist of contact with psychologist, psychiatrist, psychotherapist, social psychiatric nurse, social service.

[H] Costs consist of contact with occupational health physician, company physician.

[I] Costs consist of contact with homeopath, orthomanual therapist, acupuncturist, haptonomist (a.o.).

[J] Costs consist of prescribed medication and over the counter medication.

Table 3
Results of main and secondary analysis (mean bootstrapped costs and QALY's in Euros).

	MBCT		EUC		Differences		ICER
	Costs per year	QALY's	Costs per year	QALY's	Incremental costs	Incremental QALY's	Costs per QALY (n=96)
Societal perspective (n=96)	6269	0.674	5617	0.663	+652	0.012	56,637
Health care perspective (n=96)	3107	0.674	2351	0.663	+756	0.011	66,450
Per protocol analysis (n=87)	6249	0.670	5686	0.660	+562	0.011	53,198
Analysis without extreme cost outliers (n=95)	6263	0.679	5617	0.663	+647	0.016	41,167

management and compared to usual care. The cost-minimization study showed non-significant differences in total costs. Costs due to lost productivity were slightly lower in the intervention group, but this difference was not significant. Although the study reports an increase in mental health outcomes on the SF-36, no cost-effectiveness analysis was reported. Therefore we cannot compare our cost effectiveness analysis to their study.

Fjorback et al. performed an economic evaluation of MBCT for patients with a somatization disorder [15]. The study showed a stronger decrease in hospital costs after MBCT. Mental health care costs were significantly higher in the MBCT condition, this was attributable to the extra costs incurred by the intervention. This partially corresponds with our results. We found a difference in the distribution of health care use between patients who attended MBCT and those who did not. During the year of study, there was a trend for patients in the MBCT condition to have lower costs for hospital care and higher costs for mental health care compared with patients in the control condition. In our study, the higher mental health care costs were not caused by the MBCT training itself, because these costs were reported separately. It can be speculated that somatizing patients who attend MBCT become more willing to seek help for psychological problems. They might have reached a deeper understanding of the nature of their problems, or at least a different view upon which health care services could be helpful to them. It would be interesting to examine whether the different distribution of health care use persists over the following years. One could expect that mental health care workers are better equipped to deal with patients with MUS than the more physically oriented specialists in the hospital.

The cost-effectiveness of MBCT has also been studied for patients with recurrent depressions, Kuyken et al. compared MBCT to treatment with antidepressant medication [32]. Similar to our study, the total costs of the MBCT were slightly higher than the costs in the control condition. Exploration of costs over time revealed that MBCT was consistently more expensive than treatment with antidepressant

medication over the first 12 months. MBCT for patients with recurrent depression seems to be cost-effective. Given the assumption that society's willingness to pay for MBCT is zero, the probability of MBCT being more cost-effective than the control treatment, was 42% in the study by Kuyken et al. The results are not fully comparable to our study, because in the study by Kuyken et al. the outcome was prevention of relapse, whereas our outcome was more comprehensive: the increase of a full QALY. In our study the probability of MBCT being more cost-effective than the control treatment, would be 28% (societal perspective) at society's willingness to pay of zero. It is important to realize that society is probably willing to pay for a gain in quality of life.

Strengths

This study has several strengths. We examined a group of patients causing relevant excess costs for society [6]. For the measurement of costs we used a broad perspective: we included in- and outpatient care, medication costs and productivity losses due to sickness absence. In addition, we did not solely focus on costs, but also on the effectiveness of the intervention. Although several economic evaluations of interventions have been performed (cost minimization studies), studies examining the cost-effectiveness of interventions for medically unexplained symptoms are scarce[6]. This is the first full economic evaluation presenting the cost-effectiveness ratios of MBCT for patients with persistent MUS.

Limitations

A number of limitations should be addressed. Firstly, data upon health care use and employment participation combined with effectiveness data were available for only 96 patients out of 125 patients who were randomized for the trial [13]. Filling out prospective monthly diaries was experienced as very burdensome by many patients. During reminder telephone calls, the reason for not wanting
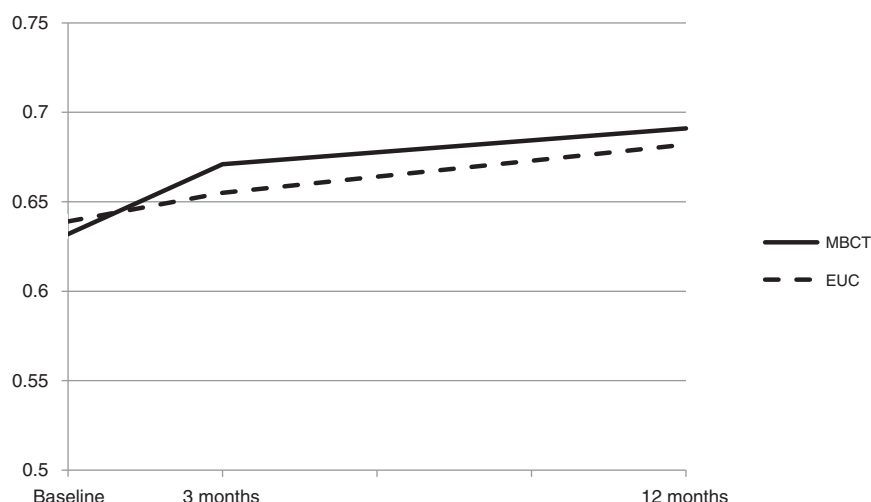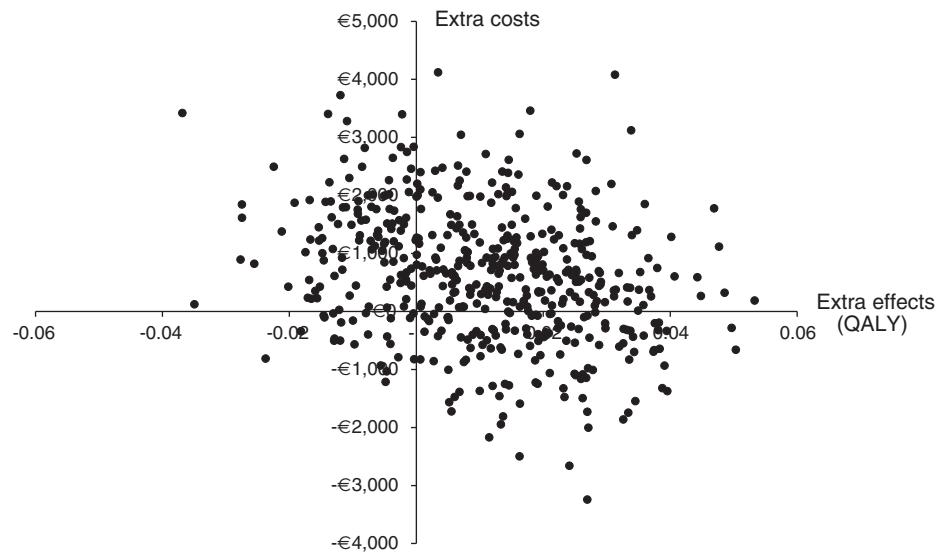
Fig. 2. Utility scores on the SF-6D.

Fig. 3. Bootstrapped costs and effects for cost per QALY, showing 1000 bootstrap replications for incremental cost-effectiveness of MBCT compared to EUC from a societal perspective. Costs are on the y-axis, and effects on the x-axis, so a replication in the north-east quadrant means that MBCT is more effective but also more costly than EUC for that replication.

to fill out the diary was often severe physical or mental illness. Patients who decided to stop filling out the monthly diaries were less often employed and had higher rates of depressive or anxiety disorders at baseline than those who continued. In the EUC condition more participants (n = 19) decided to stop filling out the monthly diaries than in the MBCT condition (n = 8). These patients might have been disappointed because they had to wait a year before they could receive mindfulness training. Another possible reason for lower drop-out in the MBCT condition is that 'a mindful attitude' reduced the aversion towards filling in the monthly diary. The higher drop-out in the EUC condition might have led to an underestimation of health care costs, underestimation of productivity loss and overestimation of HRQoL. Multiple imputation could be used to increase the number of patients included in the analysis [40]. However, the high number of missing values would probably lead to the estimates resulting from the multiple imputation tending towards extreme (and even impossible) values. We therefore decided not to use multiple imputation results in this paper. Due to the higher drop-out in the EUC condition the total costs in the EUC condition might be an underestimation of the true costs and the HRQol might be overestimated in the EUC condition. This underestimates the

cost-effectiveness of MBCT and is therefore conservative toward the strategy under evaluation, which is the recommended approach in cost-effectiveness research.

Second, the time horizon of the analysis was 1 year. This was probably too short to capture the long-term effects of MBCT and EUC on societal costs. Within the health care use we see a shift in the MBCT condition from hospital care towards mental health care. It remains unknown whether the health care use distribution continues to be different between patients with persistent MUS who participated in MBCT and those who received EUC. The follow-up of 1 year might have been too short to measure the total effects of on HRQoL. A qualitative longitudinal interview study was performed alongside the randomized controlled trial [41]. This study described how MBCT stimulated patients to change their behavioral patterns. A year after participation in MBCT these changes were ongoing in about half of the interviewed patients. One might speculate that MBCT may show further cost savings and HRQoL improvements after this time point. Also, the societal costs in the year before participation in the trial would have provided us further information about the cost-effectiveness of our intervention, unfortunately this was not part of the study design. In future trials more long-term information should be collected to confirm or refute the results now presented.
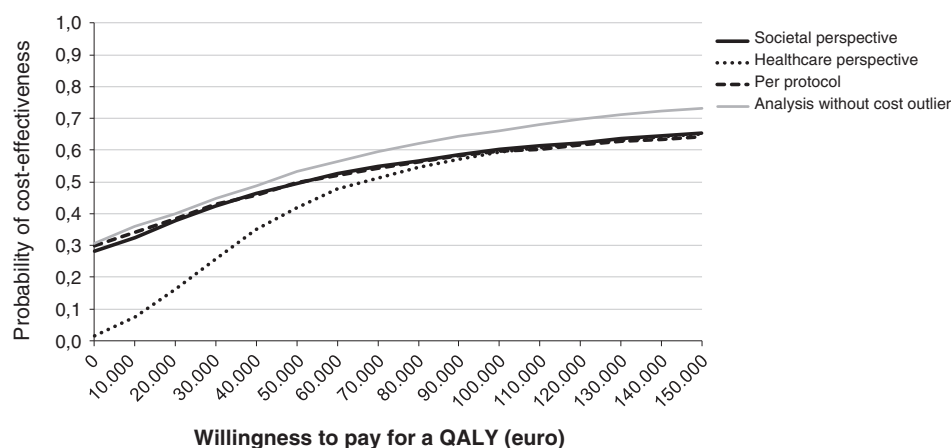

Fig. 4. Cost-effectiveness acceptability curves for costs per QALY. The curves indicate the probability (y-axis) of MBCT being cost-effective compared with EUC, given the threshold value (x-axis) for a QALY.

Third, because the FC method was used to calculate productivity losses, we took into account only the productivity losses of patients who had a paid job during the year of study and who were absent from work. This may have underestimated the actual productivity losses [42]. The reason for absence is not taken into account in this method. It can be expected that the time to replace an employee is shorter if the employee loses his or her job, than when he/she is absent due to illness. In this study we have not examined the reason why participants lost their job, however, in the MBCT condition we had more participants losing their job, this may have overestimated the productivity losses in the MBCT condition. Next to the FC method, the Human Capital (HC) approach can be used to estimate productivity losses. This approach estimates the value of all potentially lost production, whereas the FC method attempts to quantify actual production losses. The FC is therefore considered to be more realistic, and recommended in the Dutch guideline for costing research [23]. Generally, compared to the FC method, the HC method results in higher productivity losses [43]. As the productivity losses were very similar between the groups in the present study, it is not expected that the use of the HC method would have significantly changed our results. Also, we did not incorporate losses due to diminished efficiency at work (presenteeism) and losses of unpaid work and domestic tasks. For these costs it is to date unclear how they should be measured and valued [23,42,44]. We also left out direct costs for the patients such as travel expenses. For the societal perspective this has probably led to an underestimation of costs in both conditions.

At last, the economic evaluation is limited to the comparison of only two possible alternatives. Other alternatives, such as cognitive behavioral therapy have not been considered. The use of a single RCT as a vehicle for economic evaluation is often a non-sufficient basis for decision making, because decision-makers need to be informed about costs and effects for the full range of alternative interventions [45]. In that respect, the present study has contributed evidence to the broader case of cost-effectiveness of treatment for MUS.

Implications

MBCT is a relatively cheap intervention for MUS because it is a group intervention. Individual therapies are generally more expensive due to therapist costs. Although total costs were higher in the MBCT condition in the year of follow-up, the provided health care might have been more efficient in the MBCT condition as these patients had less hospital related costs and higher mental health care costs. Patients might have learned that hospital care is probably not the most effective care for their problems in the long term.

We have several recommendations for future studies. Careful attention should be given to the methods of measuring costs. We lost many patients due to the difficulties which they experienced with filling out the prospective cost-diaries. One could consider providing patients with a reimbursement per returned diary. As this is the first cost-effectiveness study of MBCT for patients with persistent MUS, the cost-effectiveness should be re-examined in studies that follow patients for a longer period of time. MBCT can lead to behavioral change in the long term, studies with only a short term scope might lead to low levels of implementation of MBCT due to the relatively small short term effects. Therefore it is of great importance to examine the costs and effects of MBCT over several years. Also, the cost-effectiveness of MBCT should be compared with the cost-effectiveness of other interventions for MUS, such as cognitive behavioral therapy.

Conclusions and recommendations

Our study shows that MBCT had a clinically relevant effect on HRQoL of patients with persistent MUS. Although it still remains uncertain whether MBCT is cost-effective, it is encouraging that MBCT was acceptable and effective for these patients with persistent MUS. Due to the higher drop-out in the EUC condition the cost-effectiveness of MBCT might have been underestimated. MBCT seemed to cause a shift in the use of health care resources as mental health care use was higher and hospital care lower in the MBCT condition. The shift in health care use might lead to more effective care for patients with persistent MUS. In future research different comparators such as cognitive behavioral therapy should be added, and studies should measure costs and effects with a longer follow-up.

The trial is registered at Trialregister.nl, number NTR2222.

The study obtained ethics approval from the CMO Arnhem–Nijmegen, CMO dossier number 2009/164, ABR number NL27551.091.09. Participants gave informed consent before taking part in the study.

Conflict of interest

The authors declare that there's no conflict of interest.

Acknowledgments

References

[1] de Waal MW, Arnold IA, Eekhof JA, van Hemert AM. Somatoform disorders in general practice: prevalence, functional impairment and comorbidity with anxiety and depressive disorders. Br J Psychiatry 2004;184:470–6.

[2] Barsky AJ, Borus JF. Somatization and medicalization in the era of managed care. JAMA 1995;274:1931–4.

[3] Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV, Hahn SR, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 Study. JAMA 1994;272:1749–56.

[4] Verhaak PF, Meijer SA, Visser AP, Wolters G. Persistent presentation of medically unexplained symptoms in general practice. Fam Pract 2006;23:414–20.

[5] Ring A, Dowrick CF, Humphris GM, Davies J, Salmon P. The somatising effect of clinical consultation: what patients and doctors say and do not say when patients present medically unexplained physical symptoms. Soc Sci Med 2005;61: 1505–15.

[6] Konnopka A, Schaefert R, Heinrich S, Kaufmann C, Luppa M, Herzog W, et al. Economics of medically unexplained symptoms: a systematic review of the literature. Psychother Psychosom 2012;81:265–75.

[7] Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. Arch Gen Psychiatry 2005;62:903–10.

[8] Barsky AJ, Ettner SL, Horsky J, Bates DW. Resource utilization of patients with hypochondriacal health anxiety and somatization. Med Care 2001;39:705–15.

[9] Reid S, Wessely S, Crayford T, Hotopf M. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care. Br J Psychiatry 2002;180:248–53.

[10] Page LA, Wessely S. Medically unexplained symptoms: exacerbating factors in the doctor–patient encounter. J R Soc Med 2003;96:223–7.

[11] Bermingham SL, Cohen A, Hague J, Parsonage M. The cost of somatisation among the working-age population in England for the year 2008–2009. Ment Health Fam Med 2010;7:71–84.

[12] Edwards TM, Stern A, Clarke DD, Ivbijaro G, Kasney LM. The treatment of patients with medically unexplained symptoms in primary care: a review of the literature. Ment Health Fam Med 2010;7:209–21.

[13] van Ravesteijn HJ, Lucassen PLBJ, Bor H, van Weel C, Speckens AE. Mindfulness-based cognitive therapy (MBCT) for patients with medically unexplained symptoms: a randomized controlled trial. submitted for publication.

[14] Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. Clin Psychol Rev 2007;27:781–97.

[15] Fjorback LO. Mindfulness and bodily distress. Aarhus: Aarhus University; 2012.

[16] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22–33 [quiz 4–57].

[17] First Michael B, Spitzer Robert L, Miriam Gibbon, Williams JanetBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version. Washington, D.C.: American Psychiatric Press, Inc.; 1996

[18] Ware JE. SF-36 health survey update. Spine (Phila Pa 1976) 2000;25:3130–9.
[19] Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. J Consult Clin Psychol 2000;68:615–23.
[20] Kabat-Zinn J. Full catastrophe living, how to cope with stress, pain and illness using mindfulness meditation. Bantam Doubleday Dell Publishing; 1990.
[21] Huijbers MJ, Spijker J, Donders AR, van Schaik DJ, van Oppen P, Ruhe HG, et al. Preventing relapse in recurrent depression using mindfulness-based cognitive therapy, antidepressant medication or the combination: trial design and protocol of the MOMENT study. BMC Psychiatry 2012;12:125.
[22] Freedland KE, Mohr DC, Davidson KW, Schwartz JE. Usual and unusual care: existing practice control groups in randomized controlled trials of behavioral interventions. Psychosom Med 2011;73:323–35.
[23] Hakkaart- van Roijen L, Tan SS, Bouwmans CAM. Institute for Medical Technology Assessment, Erasmus University Rotterdam. Handleiding voor kostenonderzoek. Methoden en standaard kostprijzen voor economisch evaluaties in de gezondheidszorg. (Manual for cost research. Methods and unit-prices for economic evaluations in health care)Handleiding: Erasmus University Rotterdam; 2010 [[in Dutch] actualized version].
[24] Cv Zorgverzekeringen. Insurances BoDHC. http://www.fk.cvz.nl/2012. [cited 2012].
[25] Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14:171–89.
[26] Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. J Clin Epidemiol 1998;51:1115–28.
[27] Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271–92.
[28] Drummond MF, MJ Sculpher, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.
[29] Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997;6:327–40.
[30] Efron B, Tibshirani R. An introduction to the bootstrap. Chapmann & Hall; 1993.
[31] van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994;3:309–19.

[32] Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. J Consult Clin Psychol 2008;76:966–78.
[33] Care CfPHaH. Sensible and sustainable care (in Dutch). Zoetermeer: Council for Public Health and Health Care; 2006.
[34] Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005;14:1523–32.
[35] Gyrd-Hansen D. Willingness to pay for a QALY. Health Econ 2003;12:1049–60.
[36] Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146:473–81.
[37] King JT, Tsevat J, Lave JR, Roberts MS. Willingness to pay for a quality-adjusted life year: implications for societal health care resource allocation. Med Decis Making 2005;25:667–77.
[38] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ 2004;13:437–52.
[39] Luo Z, Goddeeris J, Gardiner JC, Smith RC. Costs of an intervention for primary care patients with medically unexplained symptoms: a randomized controlled trial. Psychiatr Serv 2007;58:1079–86.
[40] Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. Appl Health Econ Health Policy 2005;4: 65–75.
[41] van Ravesteijn HJ, Suijkerbuijk YB, Langbroek JA, Muskens E, Lucassen PLBJ, van Weel C, et al. Mindfulness-based cognitive therapy (MBCT) for patients with medically unexplained symptoms: a longitudinal qualitative study. submitted for publication.
[42] van Asselt AD, Dirksen CD, Arntz A, Severens JL. Difficulties in calculating productivity costs: work disability associated with borderline personality disorder. Value Health 2008;11:637–44.
[43] Brouwer WB, Koopmanschap MA. The friction-cost method: replacement for nothing and leisure for free? Pharmacoeconomics 2005;23:105–11.
[44] Zhang W, Bansback N, Anis AH. Measuring and valuing productivity loss due to poor health: a critical review. Soc Sci Med 2011;72:185–92.
[45] Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ 2006;15:677–87.