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# Cost-effectiveness of cognitive behaviour therapy for patients with chronic fatigue syndrome

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## Summary

**Background:** There is some evidence that cognitive behaviour therapy (CBT) is efficacious in chronic fatigue syndrome (CFS), but little data on its cost-effectiveness.

**Design:** Prospective economic analysis alongside a randomized clinical trial.

**Methods:** CFS patients were randomly assigned to CBT, guided support groups (SG), or the 'natural course' (NC, no protocol-based interventions). Patients were treated for 8 months and followed-up for another 6 months. Costs per patient showing clinically significant improvement, based on the CIS fatigue scale, and costs per quality-adjusted life year, were determined for a time period of 14 months.

**Results:** Data were available for 171 patients at 8 months and for 128 at 14 months. At 8 and 14 months, the percentages of improved patients were 31% and 27% for CBT, 9% and 11% for SG, and 12% and 20% for NC. Mean QALYs gained at

14 months were, for CBT, SG and NC, respectively, 0.0737, -0.0018 and 0.0458. CBT and SG mean treatment costs were €1490 and €424. Other medical costs for CBT, SG, and NC, respectively, were €324, €623 and €412 for the first period, and €232, €561 and €378 for the second period. Non-medical costs for these periods for CBT, SG and NC were €262, €550, €427 and €226, €439, €287, respectively. Productivity costs were considerable, but not significantly different between groups.

**Discussion:** CBT was less costly and more effective than SG. Compared to NC, the baseline incremental cost-effectiveness of CBT was €20 516 per CFS patient showing clinically significant improvement, and €21 375 per QALY. The bootstrap ratios showed considerable uncertainty regarding the results. Future research should focus on productivity costs, and follow patients prospectively over a longer period.

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## Introduction

Because of the tension between budget constraints and the growing possibilities of diagnosing and treating patients, economic evaluations of interventions in health care are increasingly important. After the efficacy of a health care technology has been established in a highly controlled situation for

selected patients, the effectiveness and efficiency (or cost-effectiveness) has to be studied empirically, to assess its usefulness in day-to-day health care.

Economic evaluations generally compare alternative courses of action, either pharmaceutical products, medical devices or treatment procedures.<sup>1</sup>

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Because of this explicit comparison, differences in effectiveness can be related to differences in costs, to determine the relative efficiency of (most often) a newly introduced health care intervention. Comparisons can be made with the regular intervention for the specific patient population, the most effective intervention so far, the cheapest, the intervention of first choice and so on. Of course, the correct choice of comparison is essential if the study is to be useful to decision-makers.<sup>2</sup>

Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least 6 months, resulting in substantial reduction in previous levels of occupational, educational social and personal activities.<sup>3</sup> Other symptoms such as musculoskeletal pain, sleep disturbance, impaired concentration and headaches may also be present.<sup>4</sup> The economic burden related to the disability and health care use resulting from CFS underscores the need for analysis of the costs involved.<sup>5</sup> Cognitive behaviour therapy (CBT) can be considered to be an efficacious treatment for CFS, but in the first randomized controlled trials,<sup>6,7</sup> the therapy was administered by a highly skilled therapist in a specialized centre, and thus the generalizability of the findings was uncertain.<sup>4</sup> Before CBT is used to treat CFS in day-to-day health care practice, some information about effectiveness and cost-effectiveness would be desirable.

For full economic evaluation of an intervention, both effectiveness and costs must be measured. We report the results of a cost-effectiveness analysis as part of the randomized controlled trial mentioned above, evaluating the differences in both costs and effectiveness of CBT for CFS patients compared to first another treatment (guided support groups), and secondly a control group ('natural course').

## Methods

### Study design

The methods of the clinical part of this study have been previously described.<sup>8</sup> The study was designed as a prospective, controlled, randomized multi-centre clinical trial and was approved by the institutional review board.

### Patients and treatment

The inclusion criteria for participation in the trial were as follows. Besides informed consent, the patients, aged 18–60 years, had to have a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength (criteria for CFS or idiopathic chronic fatigue according to Fukuda

*et al.*<sup>3</sup>), and a score of 800 or more on the Sickness Impact Profile. Exclusion criteria were previous or current engagement in CFS research, pregnancy or engaged in pregnancy-stimulating techniques, or living more than 1.5 h travelling time from one of the three centres. Between October 1996 and December 1998, consecutive patients with a major complaint of fatigue, referred to the out-patient departments of internal medicine of the University Medical Centre Nijmegen and the University Hospital Maastricht were enrolled in the study.

After inclusion in the study and baseline measurements, patients were randomized to cognitive behavioural therapy (CBT), guided support groups (SG) or natural course (NC). CBT lasted 8 months and consisted of 16 1-h sessions by trained therapists. Patients in this group had to meet the requirements of no further medical examinations or additional treatments for CFS during the study. The SG group (11 1.5-h meetings over 8 months) was introduced to compare the effect of CBT with that of simple therapist attention. The NC group (no specific intervention) was established to make comparison possible between the CBT intervention and the medical-care-seeking behaviour of CFS patients as is current practice. CBT and SG were performed in three treatment centres (Dept of Medical Psychology, University Medical Centre Nijmegen; Dept of Psychiatry, Leiden University Medical Centre; Dept of Psychotherapy, Maastricht Mental Health Institute). Thirteen therapists were available for CBT, and one social worker for SG.

Before randomization, at 8 months follow-up (shortly after finalizing CBT or SG), and at 14 months follow-up (6 months after finalizing CBT or SG) patient assessments were performed. Because fatigue is the main symptom of CFS patients, for the cost-effectiveness analysis we used the subscale CIS fatigue (Checklist Individual Strength) as a disease-specific outcome measure to determine the fatigue severity during the last two weeks.<sup>9,10</sup> Besides this, because health-related quality of life was considered to be an important outcome, the EuroQol was used as a preference-based measure.<sup>11</sup> Using the patients' answers on the EuroQol-questions indicating their health state of the past two weeks, a single utility value was calculated as an indicator for the quality of life.<sup>12</sup> Utility values can be used to calculate quality-adjusted life years (QALY) either for the duration of a patients life or any shorter time period.

### Cost-effectiveness analysis

We used two perspectives: firstly, a health-care perspective, indicating that only medical costs were

relevant (either paid for by an insurance company or the patients themselves); and secondly, a societal perspective, implying that non-medical costs such as travelling expenses, and productivity costs (related to absence from work due to illness) were also considered to be relevant. Both perspectives implied that the cost analysis was performed on the basis of real costs instead of using charges paid for treatment (for instance, neither patients nor insurance companies had to pay for the experimental CBT and SG treatment, although these costs are a relevant part of our analysis). Costs initiated in the context of the study, but not related to day-to-day patient treatment, the so-called protocol-driven costs were left out of the cost analysis.<sup>1</sup> The time period used for the analyses was equal to the follow-up of patients, thus 14 months after inclusion in the study. Given this short period, the principle of discounting was not applied.

Cost analysis consisted of two main components: first, the resources used by each patient and second, the financial valuation (cost price) of the resources used. The volumes of care and other cost items that were not related to the CBT and SG treatments were measured by means of a monthly diary. Patients indicated on the monthly diary cards the number of CFS-related visits to their GP, medical specialists, physical therapists, and practitioners for alternative medicine, number of hours of formal and informal home care support, hospital admission and number of days in hospital, and use of prescribed medication. Out-of-pocket costs, for instance OTC medication, were based on actual expenses. The number of days not being able to perform paid or unpaid work was also recorded. For the cost price analyses, we followed the Dutch guidelines for costs analyses in health care.<sup>13</sup> Cost prices based on the 1998 price level and converted into Euros were used to value the registered volumes (Table 1). For CBT and SG, integral prices were determined, thus costs were based on actual therapist time, use of medical materials and overhead costs such as costs for therapist training and facilities. The cost prices for GP visits, medical specialist visits, physical therapists, and travelling were based on the guidelines. Visits to psychotherapists, home care, and use of alternative treatment were based on reported expenses or recommended prices from the professional associations. Market prices were used for valuing medication.

To prevent coincidental differences in productivity costs between the trial groups, the days of lost work were valued using the Dutch general wage rate rather than the actual wages of individuals. The diagnostic protocol was identical for all participating patients. However, in daily practice,

**Table 1** Cost prices used to value the different volumes measured in the cost-effectiveness analyses (in Euro, €).

Volume parameter	Cost price (€)
General practitioner (per visit)	14.98
Medical specialist (per visit)	59.90
Physical therapist (per visit)	16.34
Company doctor (per visit)	83.05
Non-physician alternative medicine practitioner (per visit)	44.47
Prescribed medication (average costs per day)	2.27
Unprescribed medication (average cost per day)	2.41
Home care (per hour)	14.48
Informal home care support (per hour)	6.13

only patients who are eligible for CBT will be diagnosed extensively, thus these costs were only relevant for the CBT patients and were left out of the cost analysis for the other groups. For SG, the costs for an intake visit were calculated, as is current practice.

For each patient, the volumes measured were multiplied by the specific cost price, leading to the cost of CFS. A distinction was made between the costs of CFS diagnosis and treatment, other medical costs being reimbursed by the insurance company, patients' expenses, and costs of lost productivity. Besides this, the phases of the therapy period (intake to 8 months) and the follow-up (9–14 months) were recorded.<sup>1</sup>

## Analyses

Analyses were performed on the basis of intention to treat. The patients who were included in our analyses had to have complete data regarding the effectiveness measures, and at least 75% of the cost diaries had to be available. Missing cost data due to missing diaries were constructed by using the patient-year approach, thus extrapolating the available cost data to the end of follow-up.<sup>14</sup> The CIS fatigue score was used to determine the percentage of patients for each randomization group that was clinically significantly improved. As a criterion for improvement, we used both a significant change index and a cut-off score of 36 or lower on the CIS fatigue score.<sup>8</sup> The EuroQol utility score was used to calculate the quality-adjusted life years (QALY) for the period of follow-up. In the QALY concept, the quality of life is expressed as a utility figure between 0 (health state equal to death) and 1 (perfect health) and multiplying the time spent in this health state by this figure. Extrapolation of the utility value at

14 months of follow-up to life expectancy was considered invalid, due to our lack of understanding between CFS and health state valuation.

Costs were expected to be skewed, and therefore the non-parametric Mann Whitney U test was used to detect differences in costs between the groups. For effectiveness regarding the percentage of patients that improved, the incremental cost-effectiveness ratio (ICER) was based on the total treatment costs for each specific patient group. The ICER regarding quality of life was calculated based on the difference in mean costs and difference in mean effectiveness between groups. These ratios indicate the financial investment that is needed to gain the additional effectiveness. To test the robustness of the findings of the cost-effectiveness analysis regarding deterministic variables such as cost prices, one-way sensitivity analyses were done by varying the values of these parameters.<sup>15</sup> For this analysis, we used the most important cost prices in these analyses: the costs of the CBT therapist and the overhead costs for training. The uncertainty of an ICER was estimated by using non-parametric bootstrapping, a method based on random sampling with replacement of a number of the patients in the trial, using the original data.<sup>16</sup> For each of the 1000 bootstrap replicates, a bootstrap ICER was calculated. This information can then be translated and readily presented to decision-makers, using the cost-effectiveness acceptability curve, which plots the probability that a particular intervention is optimal, over a range of cost-effectiveness values.<sup>17</sup> For the bootstrap analyses, we used the costs and effectiveness data regarding the 14 months follow-up.

## Results

Overall, 270 patients were included (92 CBT, 90 SG, 88 NC). The effectiveness and costs data were complete for 171 patients at 8 months (52 CBT, 55 SG, 64 NC) and for 128 patients at 14 months (37 CBT, 36 SG, 55 NC). Missing data were related to 10 patients in CBT and 8 patients in SG, who did not start therapy. Losses to follow-up for the clinical assessments for CBT, SG, and NC were 28%, 21%, and 10%, respectively, during the first 8 months, and 7%, 6%, and 11%, respectively for the 8–14 month period. Missing cost diaries were the reason for the additional loss to follow-up of 7 of the 59 remaining CBT patients, 10/65 SG, and 15/79 NC at 8 months follow-up and 18/55 CBT, 25/61 SG, and 15/70 NC at 14 months. Extensive analysis of differences between patients who completed the study and patients who were lost to follow-up for the cost-effectiveness analysis showed no differences at

**Table 2** Mean utility scores at intake and at 8 and 14 months of follow-up

	Intake	8 months	$\Delta 0$ vs. 8 months	14 months	$\Delta 8$ vs. 14 months
CBT	0.4859	0.5817	+0.0958	0.6014	+0.0197
SG	0.5036	0.4930	-0.0106	0.5035	+0.0105
NC	0.5257	0.5779	+0.0522	0.5999	+0.0220

CBT, cognitive behaviour therapy; SG, guided support groups; NC, natural course.

baseline measurement regarding age, sex, duration of CFS complaints, treatment centre, CIS fatigue score and the clinical assessment measures.

From the clinical results of the study it was concluded that there were no centre effects on the main outcome variables. CBT was statistically significant more effective as in improving CIS fatigue and by other measures such as Karnofsky performance status and Sickness Impact, as described in detail elsewhere.<sup>8</sup> Regarding the criterion of clinically significant improvement, as defined by a CIS fatigue score of 36 or lower, at 8 and 14 months, the percentages of improved patients in the cost-effectiveness study were 31% and 27% for CBT, 9% and 11% for SG, and 12% and 20% for NC. Utility scores at intake, and at 8 and 14 months of follow-up, are shown in Table 2. Based on these utility scores, the mean QALYs gained from intake to 14 months follow-up were: CBT 0.0737; SG -0.0018; and NC 0.0458.

## Cost results

The analysis of the cost involved in diagnosis and both protocol-based treatment strategies, (CBT and SG) resulted in costs of €1490 and €424, respectively. In detail, for the SG, the diagnostic activities were considered to be limited to one intake session by a social worker, costing €34. The cost for the more extensive diagnostic protocol before CBT treatment was €411, consisting of €265 for personnel, €48 for the use of medical equipment and materials, and €65 overhead costs. €34 was recorded as travelling costs by patients. In both cases, main component of the diagnosis and treatment costs were costs for personnel €830 (of which €192 was related to the training of CBT therapists) and €194 (for SG).

Table 3 shows the amounts of non-protocol-based care consumed. These were the basis for calculating the mean medical cost per patient (the above mentioned treatment costs excluded): for CBT, SG and NC for the period from 0 to 8 months (€324,

**Table 3** Care resources used

Group...	CBT			SG			NC		
	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR
<i>0–8 months</i>									
General practitioner	1.3	1	0–2	2.2	1	1–4	2.2	1	0–3
Medical specialist	0.4	0	0–0	0.9	0	0–1	0.7	0	0–0
Physiotherapist	1.4	0	0–0	5.1	0	0–7	3.7	0	0–6
Psychologist	0.5	0	0–0	2.1	0	0–3	1.3	0	0–0
Alternative caregiver	0.3	0	0–0	4.9	0	0–9	3.4	1	0–5
<i>9–14 months</i>									
General practitioner	1.0	0	0–1	1.8	1	0–2	1.4	1	0–2
Medical specialist	0.2	0	0–0	0.8	0	0–2	0.6	0	0–0
Physiotherapist	1.9	0	0–0	3.2	0	0–3	2.9	0	0–4
Psychologist	0.0	0	0–0	1.3	0	0–1	1.5	0	0–0
Alternative caregiver	1.3	0	0–0	4.2	0	0–7	1.4	0	0–2

CBT, cognitive behaviour therapy; SG, guided support groups; NC, natural course.

€623 and €412, respectively) and for the period from 9–14 months (€232, €561 and €378). The non-medical costs for these periods for CBT, SG and NC were, respectively: €262, €550, €427 and €226, €439, €287. Table 4 shows a more detailed break-down of these figures. Thus the 8 months average total costs (productivity costs excluded) for the three groups were (CBT, SG and NC) €2487, €1631 and €839, and for the whole 14 months period, €2534, €2597 and €1504.

In the three groups, the percentage of patients having a paid job at the start of the study were 36.8%, 23.5% and 39.7%, and the mean numbers of working hours were 28.0, 31.7 and 24.7. Based on the absence from paid work (mean number of hours absence from paid work over 4 weeks for CBT, SG and NC were 33.4 and 23.1, 23.1 and 20.1, and 37.0 and 25.3 for the two periods, respectively), the productivity costs from intake to 8 month follow-up and for the 9–14 months period were calculated, but due to the large, overlapping ranges, no significant difference were found (Table 5).

### Incremental ratios

It is already clear from these results that SG is both more expensive and less effective than CBT, regarding both percentages of improved patients and QALYs. Therefore the incremental cost-effectiveness of CBT was only calculated versus NC.

Regarding the percentage of patients that showed clinically significant improvement, incremental cost-effectiveness showed that an investments of €9024 and €20516 were needed to have one

CFS patient improve at 8 months and 14 months, respectively. Table 6 explains the underlying calculation in detail. The cost per QALY using the 14-month follow-up related to (i) treatment costs, (ii) treatment costs, other medical costs and patients costs, and (iii) these costs including productivity costs were, respectively, €60 108, €51 642, and €21 375.

Varying the costs of the CBT therapist and costs for training in a sensitivity analysis showed that this did influence the cost-effectiveness estimates. If training costs are set at zero, the additional treatment cost per extra patient improved changes from €9024 to €7971 at 8 months, and from €20516 to €17778 at 14 months. The cost per QALY, based on total costs (productivity costs included), changed to €14482

The bootstrap simulations based on the costs and effectiveness data regarding the 14 months follow-up showed that the uncertainty surrounding the incremental cost-effectiveness ratios is considerable (Table 7). From the cost-effectiveness acceptability curve, it can be seen that comparing CBT to NC, uncertainty remains over a wide range of cost-effectiveness thresholds (Figure 1).

### Discussion

To our knowledge, the cost-effectiveness of CBT in CFS patients has not been studied prospectively before. An extensive literature review did not reveal any prospective randomized study reporting the cost-effectiveness of CBT in CFS patients (our search strategy is available on request). Especially since

**Table 4** Mean and median cost (€) per patient (with interquartile range) for the 'treatment' period of 8 months and 6 months follow-up

Group...	CBT			SG			NC		
	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR
<b>0–8 months</b>									
<i>Medical costs</i>									
General practitioner	20	15	0–30	34	15	15–60	34	15	0–45
Specialist	22	0	0–0	55	0	0–60	39	0	0–0
Physiotherapist	24	0	0–0	83	0	0–114	62	0	0–98
Company doctor	38	0	0–0	177	0	0–249	105	0	0–0
Prescribed medicine	35	0	0–3	80	22	0–85	70	10	0–93
Home care	173	0	0–0	182	0	0–0	94	0	0–0
<i>Non-medical costs</i>									
Alternative practitioner*	17	0	0–0	128	0	0–152	137	11	0–189
Unprescribed medicine	32	0	0–11	70	8	0–90	62	12	0–90
Informal home care	97	0	0–25	155	0	0–230	104	0	0–57
Other costs	79	0	0–0	166	0	0–45	71	0	0–18
Travelling costs	51	0	0–50	44	9	0–48	61	0	0–70
Total medical costs	324	51	0–373	623	349	75–883	412	176	34–554
Total non-medical costs	262	34	1–422	550	342	851–3728	427	243	5–771
Total 0–8 months	586			1173			839		
<b>9–14 months</b>									
<i>Medical costs</i>									
General practitioner	15	0	0–15	26	15	0–30	20	15	0–30
Specialist	13	0	0–0	45	0	0–90	35	0	0–0
Physiotherapist	31	0	0–0	52	0	0–41	48	0	0–65
Company doctor	2	0	0–0	104	0	0–42	121	0	0–0
Prescribed medicine	29	0	0–9	75	16	0–94	93	5	0–44
Home care	132	0	0–0	250	0	0–0	101	0	0–0
<i>Non-medical costs</i>									
Alternative practitioner*	33	0	0–0	94	0	0–179	55	0	0–68
Unprescribed medicine	19	0	0–2	55	1	0–14	23	0	0–14
Informal home care	82	0	0–0	146	0	0–208	75	0	0–0
Other costs	69	0	0–0	115	0	0–0	89	0	0–0
Travelling costs	31	0	0–5	40	9	0–48	44	12	0–70
Total medical costs	232			561			378		
Total non-medical costs	226			439			287		
Total 9–14 months	458			1000			665		
0–14 months (sums of means)									
Medical costs	556			1184			790		
Non-medical costs	488			989			714		
Total	1044			2173			1504		

CBT, cognitive behaviour therapy; SG, guided support groups; NC, natural course.

\*Non-physician alternative medicine practitioner.

CBT is the only therapy for CFS with evidence-based efficacy, cost-effectiveness information is relevant.<sup>18</sup> Our data suggest that CBT leads to a higher clinical efficacy and that total costs to society are lower than the natural course, but the statistical uncertainty of this finding is considerable.

Compared to the results of the clinical study reported by Prins *et al.*,<sup>8</sup> our results are based on a

smaller number of patients, due to the cost diaries lost to follow-up in a larger number of participants, in the treatment period as well as the whole study period. Although this is a known phenomenon when using cost diaries, this method to collect cost-effectiveness data is considered to be feasible and valid.<sup>19</sup> An extensive comparison between participants in the cost-effectiveness analyse ( $n=171$ ) and

**Table 5** Productivity costs in Euros

	Intake to 8 months			9–14 months			0–14 months
	Mean	Median	IQR	Mean	Median	IQR	Sums of means
CBT	13 248	4030	0–26 838	7242	1072	0–12 325	20 490
SG	8728	0	0–10 896	6437	0	0–13 168	15 165
NC	14 564	3684	0–28 177	7788	2322	0–10 717	22 353

CBT, cognitive behaviour therapy; SG, guided support groups; NC, natural course.

**Table 6** Incremental cost-effectiveness of CBT vs. NC, based on the number of CFS patients showing clinically significant improvement, and costs (treatment and other medical costs) at 8 months and 14 months follow-up

	Costs CBT group	Derivation*	Costs NC group	Derivation*	Cost difference	Effectiveness**	Cost per CFS patient improved
8 months	€159 168	64 × €2,487	€53 696	64 × €839	€105 472	11.69	€9024
14 months	€161 975	55 × €2,945	€82 720	55 × €1504	€79 255	3.86	€20 532

CBT, cognitive behaviour therapy; NC, natural course.

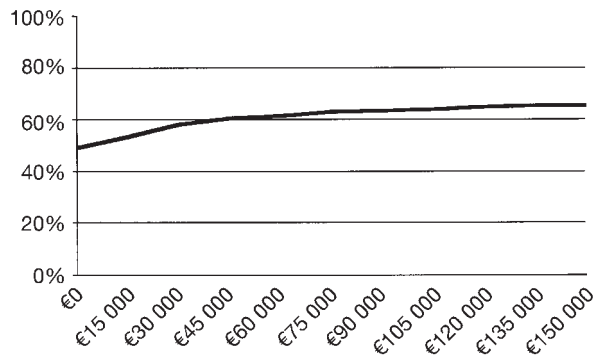
\*To compensate for the coincidental difference in the number of patients in each group, the number of patients in the CBT group was adjusted, results for the original group (*n* = 52) being recalculated for a theoretical size of 64 patients. \*\*In terms of patients who showed significant clinical improvement.

**Table 7** Distribution of the bootstrapped incremental cost-effectiveness ratios over the four quadrants of the cost-effectiveness plane

Quadrant*	NE	NW	SW	SE
Medical and patient costs per CFS patient improved	78%	22%	0%	0%
Medical, patient and productivity costs per CFS patient improved	37%	10%	13%	40%
Medical and patient costs per QALY	64%	36%	0%	0%
Medical, patient and productivity costs per QALY	31%	15%	20%	34%

CBT, cognitive behaviour therapy; NC, natural course.

\*NE, north east quadrant: CBT more effective but more costly than NC; NW, north west quadrant: CBT less effective and more costly than NC; SW, south west quadrant: CBT less effective but less costly than NC; SE, south east quadrant: CBT more effective and less costly than NC.



**Figure 1.** Acceptability curve, showing the probability that CBT is cost-effective over a range of cost-effectiveness thresholds, using medical, patient, and productivity costs per QALY.

the remaining clinical study participants (*n* = 99) did not reveal any statistically significant differences regarding age, duration of CFS complaints, and scores for Sickness Impact Profile, Karnofsky score, physical activity, a self-efficacy scale, a causal attribution list, and functional impairment. Selection bias due to missing data is not expected, and we regard the cost estimates to be a valid reflection of the medical costs of CFS patients.

We found that CBT resulted in a better outcome and a lower use of medical care facilities than the control treatment (SG) and the natural course (NC). The phenomenon that patients receiving active treatment for disorders make less use of other medical services is sometimes referred to as the

medical offset. This is explained by, first, the situation that patients with untreated mental disorders frequently present with physical symptoms and persistent complaints that resolve with appropriate mental health treatment and, second, the idea that physical disorders may contribute to emotional distress, which in turn may exacerbate patients' symptoms or delay recovery. In the literature, a medical offset was reported for patients who were treated for depression and had CFS complaints, thus bringing about less reimbursed costs compared to the period before they were actively treated.<sup>20</sup> Health care visits to either GP and specialists or non-physician practitioners were higher in the SG group than in the CBT and NC groups. During CBT, as part of the therapy, patients were discouraged from using other treatments, in order to facilitate attribution of improvement to themselves instead of to other treatments. Some CBT patients clearly disregarded this advice, as the range of medical costs (CBT costs excluded) was zero to €4122 (mean €324) during the first 8 months. However, given a similar period of follow-up, the number of visits to GP and specialist in our control group was considerably less than found in the literature.<sup>5,21</sup> This might be explained by the Dutch yearly subscription payment system, which discourages physician-induced follow-up visits. The number of non-physician alternative medicine practitioner visits, characterized by a fee for service payment, was comparable. In our study, no patient reported CFS-related hospital admission. Lloyd *et al.*<sup>21</sup> found a mean CFS-related hospital stay of 0.7 days, after making a correction for three exceptional situations. The costs we report probably underestimate the total costs involved in current CFS treatment, as we were not able to examine other services besides visits to care providers and use of drugs, or non-drugs costs such as special diets. However, it can be argued that including these costs would enlarge the cost difference between successfully and unsuccessfully treated patients. Further, an important contribution to the reduction in costs was generated by the ability of successfully treated patients to return to their work. This finding was in accordance with previous studies, because resuming work was clearly related to improvement of CFS symptoms. The best predictors to explain resuming work were changes in the number of physical signs, and psychiatric diagnosis.<sup>22</sup> Regarding our limited follow-up, we expect the cost-effectiveness to improve over a longer time period. Besides this, on an experimental basis CBT is offered as a group therapy which reduces costs, and if effectiveness persists, this might lead to a more favourable cost-effectiveness.

The statistical uncertainty of the cost-effectiveness estimates we found is considerable, as the bootstrap simulations demonstrate. This might be because the clinical trial on which this economic evaluation is based, was powered to show an effect on physical activity, not ideal for a cost-effectiveness analysis because its focus may be too narrow.<sup>1</sup> Using a societal perspective, including productivity costs, has a large impact on the cost-effectiveness estimates. Although not statistically significant, the differences in productivity costs between the groups were considerable, as a small number of patients that were employed were absent from work during a longer period. Therefore, the results have to be interpreted with caution, and we intend to investigate further the longer-term working situation of our patients. The societal perspective is of importance, since in the trial of 270 CFS patients, 76% had been employed before the onset of CFS, whereas only 33% had a job at the start of the study.<sup>8</sup>

In the mean time, the conclusions of this work should be based on the health care perspective as expressed in the medical and patient costs per CFS patient clinically significantly improved, at €20 516. The difference in utility between the experimental treatment and the current situation is small. Given this fact and the short time horizon, the cost per QALY seems high. However, extrapolating the utility values and the cost figures another four years indicates that the cost per QALY will become more acceptable and even indicates profit if the productivity costs are included. This finding has to be interpreted with caution, because in our study the productivity costs were based on a small number of patients. Thus, to be able to estimate the cost-effectiveness of treatment of CFS patients more accurately, future research should give more focus on productivity costs and use a longer period of prospectively following patients.

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