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Economic evaluation of four follow-up strategies after curative treatment for breast cancer: Results of an RCT

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ABSTRACT

Background: An economic evaluation was performed alongside a randomised controlled trial (ISRCTN 74071417) investigating the cost-effectiveness of nurse-led telephone follow-up instead of hospital visits, and of a short educational group programme (EGP) in the first year after breast cancer treatment.

Method: This economic evaluation ($n = 299$) compared the one-year costs and the effects of four follow-up strategies: (1) hospital follow-up; (2) nurse-led telephone follow-up; (3) hospital follow-up plus EGP; and (4) nurse-led telephone follow-up plus EGP. Costs were measured using cost diaries and hospital registrations. Quality-adjusted life years (QALYs) were measured using the EQ-5D. Outcomes were expressed in incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves.

Results: Hospital follow-up plus EGP yielded most QALYs (0.776), but also incurred the highest mean annual costs (€4914). The ICER of this strategy versus the next best alternative, nurse-led telephone follow-up plus EGP (0.772 QALYs and €3971), amounted to €235.750/QALY. Hospital and telephone follow-up without EGP both incurred higher costs and less

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QALYs than telephone follow-up plus EGP and were judged inferior. Hospital follow-up plus EGP was not considered cost-effective, therefore, telephone follow-up plus EGP was the preferred strategy. The probability of telephone follow-up plus EGP being cost-effective ranged from 49% to 62% for different QALY threshold values. Secondary and sensitivity analyses showed that results were robust.

Conclusion: Nurse-led telephone follow-up plus EGP seems an appropriate and cost-effective alternative to hospital follow-up for breast cancer patients during their first year after treatment.

1. Introduction

In The Netherlands, one out of eight women will be diagnosed with breast cancer at some moment in her life.[1] After treatment, these women attend frequent follow-up visits in the hospital to be examined for local disease recurrence or second primary breast cancer, and for information and psychosocial support. However, the need for frequent follow-up of breast cancer patients remains controversial despite almost two decades of research. There has been much debate regarding the effectiveness of routine follow-up of these patients,[2,3] while at the same time it is associated with a significant cost burden.[4] Less specialised follow-up strategies have been proposed,[5–7] demonstrating equal patient satisfaction and health-related quality of life (HRQoL) compared to traditional hospital visits. To date, these alternative strategies, however, have not been structurally implemented in clinical practice. Several authors have urged to evaluate the costs in relation to the benefits of current and alternative follow-up strategies.[3,4,8] Therefore, we performed a randomised controlled trial (RCT) investigating the effectiveness of both a nurse-led telephone follow-up instead of hospital visits and a short educational group programme (EGP) during the first year after breast cancer treatment. An economic evaluation was included to determine the most cost-effective follow-up strategy.[9] Effectiveness results of the RCT are reported in a separate paper and showed no differences between the intervention groups and their respective control groups in HRQoL, feelings of anxiety and other psychological outcome measures at 1 year after treatment (paper submitted)[10]. The current paper describes the economic evaluation of the four follow-up strategies of the trial and aims to assist resource allocation decisions.

2. Methods

2.1. Design, sample and interventions

Details of the trial design and protocol execution have been reported previously (ISRCTN 74071417).[9] In sum, between 2005 and 2008, 320 females who had recently completed breast cancer treatment (i.e. less than 6 weeks) were randomly assigned to one of four follow-up strategies (study arms) for the first 18 months following treatment; i.e. (1) hospital follow-up as usual: five outpatient clinic visits in the first 18 months (at 3, 6, 9, 12 and 18 months), including a mammography at 12 months; (2) nurse-led telephone follow-up: a mammography at 12 months combined with an outpatient clinic visit, and telephone interviews at the same time points as for usual follow-up; (3) arm 1 plus EGP; and (4) arm 2 plus EGP.

Telephone follow-up was performed by a trained breast care nurse (BCN) and consisted of a semi-structured questionnaire including a screening for physical and psychological symptoms, treatment side-effects, compliance with hormonal therapy and an open discussion of these issues. The EGP consisted of two interactive group sessions of 2.5 h each: a BCN provided information on possible treatment side-effects and topics such as prostheses, fatigue, and signs and symptoms of a possible recurrence. A health care psychologist addressed psychological and social consequences of breast cancer and discussed psychological coping strategies.

The economic evaluation compared costs and effects of these four follow-up strategies from a societal perspective, with a time horizon of 1 year. During the RCT 21 patients (6.5%) dropped out for various reasons, as reported in a previous paper.[11] Hence, data for the economic evaluation were available for 299 patients (Table 1).

2.2. Measure of effect

The quality-adjusted life year (QALY) was chosen to represent health gain.[12] The QALY is a measure of life expectancy weighted by health-related quality of life (HRQoL), the latter is represented by a utility score. In the present study, HRQoL was measured with the EQ-5D, a questionnaire responsive to changes in health in breast cancer patients after conclusion of treatment.[13] The EQ-5D comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated at three levels: no problems (1), some problems (2) and major problems (3). Based on preferences elicited from a general UK population, EQ-5D health states (e.g. 1-1-2-1-3) may be converted into utility scores (index scores).[14] In the present study, utility scores were measured at baseline, 3, 6 and 12 months after treatment and were subsequently used to calculate QALYs according to the following formula: {[(utility score at baseline + utility score at 3 months)/2] * 3/12 + [(utility score at 3 months + utility score at 6 months)/2] * 3/12 + [(utility score at 6 months + utility score at 12 months)/2] * 6/12}.

2.3. Measure of costs

Cost analysis was performed from the societal perspective, which includes health care and non-health care related costs

Table 1 – Baseline characteristics of participants of the RCT (*n* = 299). Values are percentages (numbers) unless stated otherwise. EGP, educational group programme.

Baseline characteristics	Hospital f-up (*n* = 74)	Telephone f-up (*n* = 76)	Hospital f-up + EGP (*n* = 75)	Telephone f-up + EGP (*n* = 74)	All participants
Age (years)					
Mean (SD)	57.2 (9.8)	55.5 (9.0)	55.3 (11.5)	55.4 (9.2)	55.8 (9.9)
Range	34–78	38–75	23–76	34–75	23–78
Level of education					
Low	29.7 (22)	38.2 (29)	30.7 (23)	37.8 (28)	34.1 (102)
Middle	41.9 (31)	35.5 (27)	41.3 (31)	39.2 (29)	39.5 (118)
High	28.4 (21)	26.3 (20)	28.0 (21)	23.0 (17)	26.4 (79)
Main daily activity					
Paid employment	39.2 (29)	36.8 (28)	42.7 (32)	35.1 (26)	30.4 (91)
Average hours of paid employment per week (SD)	8.4 (12.6)	9.1 (15.0)	10.3 (14.7)	7.4 (12.2)	8.9 (13.6)
Tumour stage					
Stage I	64.9 (48)	63.2 (48)	57.3 (43)	56.8 (42)	60.5 (181)
Stage IIa	21.6 (16)	22.4 (17)	25.3 (19)	23.0 (17)	23.1 (69)
Stage IIb	4.1 (3)	6.6 (5)	6.7 (5)	10.8 (8)	7.0 (21)
Stage III	8.1 (6)	7.9 (6)	9.3 (7)	6.8 (5)	8.0 (24)
Unknown	1.4 (1)	–	1.3 (1)	2.7 (2)	1.3 (4)
Treatment modality					
Surgery	10.8 (8)	10.5 (8)	9.3 (7)	8.1 (6)	9.7 (29)
Surgery & radiotherapy (RT)	58.1 (43)	57.9 (44)	61.3 (46)	60.8 (45)	59.5 (178)
Surgery & chemotherapy (CH)	4.1 (3)	5.3 (4)	5.3 (4)	5.4 (4)	5.0 (15)
Surgery & RT & CH	27.0 (20)	26.3 (20)	24.0 (18)	25.7 (19)	25.8 (77)
Hormonal therapy (yes)	31.1 (23)	30.3 (23)	34.7 (26)	29.7 (22)	31.4 (94)
Health scores					
Utility (mean (SD))	0.74 (0.23)	0.73 (0.21)	0.80 (0.18)	0.73 (0.23)	0.75 (0.22)

(e.g. productivity loss, informal care) as a result of breast cancer.[12,15] Complete individual level hospital resource use data (e.g. diagnostic procedures, outpatient clinic visits, telephone interviews) were retrieved from hospital information systems. We used a set of rules, determined by a team of medical specialists, to decide whether resource use was related to breast cancer. For example, a first rule was whether the resource use was recorded in the patient's medical files from the oncology departments. Also, procedures or diagnostic tests requested by a breast cancer specialist were considered to be breast cancer related. Additionally, some typical breast cancer related procedures (e.g. mammography, breast ultrasound, bone scan) were always included. Resource use outside the hospital (e.g. general practitioner visits, physical rehabilitation and quantities of lost paid work) was determined by means of cost diaries as kept by participants.[16] These were completed prospectively at 3, 6 and 12 months, for 4 week periods each. Cost diaries consisted of pre-defined categories and patients were asked to complete all categories, regardless of whether or not applicable in that specific week. For example, a patient was asked whether she was unable to perform paid work that week; yes or no. If yes, the number of hours for that week needed to be specified. To determine whether resource use was breast cancer related we simply asked the patient to report whether she believed the costs were related to her breast cancer diagnosis and treatment (yes/no). Finally, resource use was interpolated to the study period under the assumption that data obtained from these cost diaries would be representative of the in between periods.[16]

Cost prices for resource use were primarily obtained from the Dutch governmental manual for health care cost analysis.[15] All cost prices were converted to 2008 Euros by means of price index numbers.[17] Cost prices per unit of resource use for the main cost drivers are presented in Table 2. Costs for hospital visits were based on cost prices for academic hospitals. Productivity costs were calculated using the human capital approach (HCA)[18] instead of the anticipated friction cost method.[9,19] In order to use the friction cost method, it was necessary to have information on the number of periods of sick leave, i.e. friction periods. However, we were uncertain as to whether a patient had returned to work and had become sick in between the cost diaries.

Costs for the EGP included the hourly wages of the health care psychologist and BCN, the use of facilities and the information booklet, as well as travel costs of patients. The cost price for telephone follow-up consisted of the average duration of the follow-up (18 min) multiplied by the hourly wage of a specialised nurse, adding 45% for hospital overhead costs and the average costs of a telephone call.

2.4. *Statistical analysis*

The base case analysis of the economic evaluation (*n* = 299) was performed based on intention to treat. Multiple imputations were used to replace the missing values (i.e. missing EQ-5D data or cost categories) with plausible estimates, and generated five data sets.[20] Results were provided as pooled estimates of these sets. Bootstrap simulations with 1000 replications

Table 2 – Unit prices. All unit prices are expressed in Euros at 2008 values. EGP, educational group programme, MS, medical specialist, BCN, breast care nurse.

Cost category	Unit price in Euro (2008)[a,b]
Direct health care costs	
General practitioner	21.88/visit[b1]
Physiotherapist	24.64/visit[b1]
Rehabilitation programme[c]	1500[b2]
Educational group programme (EGP)[d]	135[b3]
Other health care professionals[e]	24.64/visit[b1]
Home care domestic	23.50/h[b1]
Home care nursing	43.75/h[b1]
Medication[f]	Various[b4]
Hospital follow-up (MS / BCN)	108.30/visit[b1]
Telephone MS	12.83/5 min call[b5]
Telephone BCN	21.50/follow-up contact[b5]
Postoperative surgery[g]	Various/procedure[b1]
Mammography/ultrasound	79.75/82.10/test[b1]
Breast biopsy	127.19/procedure[b1]
Laboratory tests	Various/test[b1]
Cardiology or lung tests	Various/test[b1]
Other diagnostics[h]	Various/procedure[b1]
Costs for in-hospital days[i]	598.89/d[b1]
Direct non-health care costs	
Paid help	10/h[b1]
Informal care	8.99/h[b1]
Costs of lost production	
Paid work (HCA)	19.22/h[b6]
Domestic tasks	8.99/h[b1]
Out of pocket costs	
Reported by patients[j]	Various[b7]
Drugs[j]	Various[b7]

[a] When necessary, cost prices were converted to 2008 by means of Dutch consumer price index numbers.

[b] Source of unit price: [1]Dutch manual for cost prices[15]; [2]tariff for health insurer; [3]calculation included cost location, wage of health care providers, material, travel costs; [4]www.farmacotherapeutischkompas.nl (including tax + recepy fee of €6.11); [5]calculations based on time per call multiplied by wage and overhead costs; [6]gross wage, female 55–65, CBS; [7]as reported by patient.

[c] Rehabilitation programme: a 12-week group programme for cancer patients combining physical exercise and psycho-education.

[d] Educational group programme (study intervention): two group sessions outside hospital by a health care psychologist and breast care nurse (including booklet).

[e] Other health care professionals such as lymph oedema therapist, alternative health practitioners.

[f] Medication was sub grouped to tranquilisers, antibiotics, antidepressants, pain killers, drugs for side-effects of treatment and other drugs.

[g] Included breast reconstruction, treatment of wounds/abscess, lymph oedema.

[h] Included CTs, MRIs, PET whole body scans, etc.

[i] Average of total costs for in-hospital days, including intake assessment and nursing.

[j] Out-of-pocket costs included costs for over the counter medication, parking costs, etc.

were used to calculate 95% confidence intervals (CI) around mean costs and effects of the four study arms. Differences between the four groups in resource use, costs and QALYs were reported descriptively and were not compared statistically to avoid problems with multiple testing and because the focus of the economic evaluation was on the combined costs and effects in order to assess cost-effectiveness.

To investigate cost-effectiveness of the four strategies, incremental cost-effectiveness ratios (ICERs) were calculated. The strategies were ranked by QALYs, from the most effective to the least effective, and if a strategy was less effective and more costly than the previous strategy, it was said to be dominated and excluded from the calculation of ICERs.[21,22] Hence, this process compared strategies in terms of observed differences in costs and effects, regardless of the statistical significance of the difference.[23] Cost-effectiveness acceptability curves (CEACs) were derived in order to show the probability of each strategy being the optimal choice, for a range of possible maximum values a decision maker is willing to pay for a QALY.[22,24] Bootstrapping was performed using Excel 2000. Other analyses were performed using the SPSS package, version 17.0® for Windows (SPSS INC 2009).

2.5. *Secondary analyses*

Secondary analyses were performed to assess the robustness of the base case results. First, an analysis was performed according to the actually applied follow-up strategy (per protocol analysis). Second, an analysis was performed excluding productivity costs. A third analysis used the friction cost method to account for costs of lost productivity.[19] It was assumed that patients had not been on sick leave in between cost diaries if in two subsequent cost diaries zero hours of lost paid work were reported. A fourth analysis included only health care related costs.

One-way sensitivity analyses assessed the impact of the unit prices of telephone contacts and hospital visits. The highest reported value for telephone contact (55 min) and the generic cost price for a hospital visit (€54.15) were used. Furthermore, the impact of using the Dutch EQ-5D tariff for utility scores was investigated.[25]

A series of explorative subgroup analyses compared cost-effectiveness data according to age, use of chemotherapy, levels of anxiety and support from partner. Finally, a subsample of patients for whom 18 months data were available ($n = 244$) was used in order to investigate whether cost-effectiveness results could be extrapolated to the 2nd year after treatment. In this analysis, costs and effects incurred between 12 and 18 months were discounted using, respectively, a 4% and 1.5% discount rate.[26]

3. Results

3.1. *Participants*

Data for the economic evaluation were available for 299 patients of the RCT (Table 1). Two hundred and forty non-participants of the RCT agreed to fill out baseline questionnaires for comparison with participants. Participants did not differ from non-participants with respect to education, marital status, employment status (including hours of paid work per week), HRQoL and utility scores (all p-values > 0.05). However, participants were significantly younger than non-participants [mean age 60 years (SD = 10.2), $p < 0.001$].

3.2. Resource usage and utility data

Complete hospital resource usage data were available for all 299 patients. Data on resource usage outside the hospital as collected by patient diaries were missing for 39 patients (13%) at three months, 45 patients (15%) at six months and for 55 (18%) patients at 12 months after treatment. The EQ-5D questionnaire was missing for three patients at baseline (1%), 19 patients (6%) at 3 months, 28 patients (9%) at 6 months and 37 patients (12%) at 12 months after treatment. Logistic regression analysis showed that missing EQ-5D data were not related to the interventions, HRQoL, levels of anxiety or other patient characteristics. However, missing resource usage data outside the hospital (patient diaries) were higher in patients with higher levels of anxiety ($p = 0.036$) and in patients with a low educational level ($p < 0.001$).

3.3. Effects and costs

Table 3 summarises the percentage of patients reporting *any* problems (levels (2) and (3) combined) on the five dimensions of the EQ-5D as well as index (utility) scores, at all measurement time points. Baseline differences in EQ-5D values were substantial, but not statistically significant ($p = 0.07$). Nevertheless, subsequent utility scores are presented using a regression-based adjustment as recommended by Manca and colleagues,[27] and taking into account regression to the mean effects.

Utility gains were most notable in the telephone follow-up and telephone follow-up plus EGP groups, but overall QALYs were highest for hospital follow-up plus EGP. We used the adjusted QALY for the construction of cost-effectiveness acceptability curves, which reflects the finding that baseline scores were higher for this strategy. Tables 4 and 5 show resource utilisation and costs during the study period.

3.4. Economic analysis

In the base case analysis, hospital follow-up plus EGP yielded most QALYs (0.776; 95% CI 0.753–0.799), but also incurred highest mean annual costs (€4914; 95%CI 3793–6192). The ICER of hospital follow-up plus EGP versus the next best alternative, telephone follow-up plus EGP (0.772 QALYs and €3971), amounted to €235.750/QALY. Assuming a threshold of €40.000,

Table 3 – Percentage of patients reporting any (including some and major) problems on the EQ-5D dimensions, the EQ-5D index scores at baseline, 3, 6 and 12 months after treatment and adjusted QALYs for the four study arms. EGP, educational group programme.

Measurement		% of patients reporting ANY problems			
	Dimensions of EQ-5D	Hospital f-up	Telephone f-up	Hospital f-up + EGP	Telephone f-up + EGP
Baseline	Mobility	22.2	30.3	16.0	22.2
	Self-care	5.4	5.3	2.7	3.0
	Usual activities	52.7	54.7	48.0	55.4
	Pain/discomfort	64.9	68.4	50.7	66.2
	Anxiety/depression	42.7	50.0	33.3	36.5
	Index score	0.736	0.728	0.804	0.722
3 months	Mobility	21.1	30.8	16.8	24.9
	Self-care	5.4	3.7	1.3	5.7
	Usual activities	47.0	46.8	42.7	46.8
	Pain/discomfort	63.8	60.0	42.1	51.4
	Anxiety/depression	51.1	47.4	37.9	41.9
	Index score	0.721	0.757	0.810	0.775
	Index score (adjusted)[a]	0.727	0.767	0.780	0.789
6 months	Mobility	21.6	26.3	18.1	26.4
	Self-care	4.3	0.0	0.5	8.6
	Usual activities	36.5	40.0	33.3	47.0
	Pain/discomfort	54.6	53.4	45.9	54.6
	Anxiety/depression	38.6	45.8	40.0	43.5
	Index score	0.760	0.771	0.803	0.758
	Index score (adjusted)[a]	0.766	0.780	0.776	0.770
12 months	Mobility	24.9	18.2	26.7	28.4
	Self-care	10.0	5.3	2.4	10.5
	Usual activities	34.6	37.4	36.0	33.0
	Pain/discomfort	60.8	57.6	48.0	50.0
	Anxiety/depression	34.1	40.3	36.3	33.2
	Index score	0.733	0.768	0.786	0.771
	Index score (adjusted)[a]	0.739	0.777	0.759	0.783
QALY		0.740	0.762	0.801	0.761
QALY (adjusted)[a]		0.747	0.769	0.776	0.772
Bootstrapped 95% CI		(0.707–0.778)	(0.746–0.794)	(0.753-0.799)	(0.745-0.797)

[a] *adjusted for baseline differences.*

Table 4 – Mean resource use per patient over 12 months (in number of contacts or tests unless stated otherwise). EGP, educational group programme, MS, medical specialist, BCN, breast care nurse.

Resource category	Hospital f-up mean (SD)	Telephone f-up mean (SD)	Hosp + EGP mean (SD)	Tel + EGP Mean (SD)
Direct health care resources				
General practitioner	1.7 (2.7)	1.6 (3.1)	1.5 (2.8)	0.8 (1.7)
Physiotherapist	7.0 (14.5)	8.6 (16.2)	10.1 (19.8)	8.5 (16.0)
Revalidation	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)	0.2 (0.4)
Other health care professionals	1.5 (3.4)	3.0 (7.2)	2.1 (3.6)	2.1 (3.7)
Home care domestic	8.9 (32.3)	7.3 (27.8)	6.2 (27.1)	3.7 (11.7)
Home care nursing	0.4 (1.4)	1.1 (5.2)	0.4 (1.5)	0.6 (2.0)
Visits MS	5.5 (2.4)	2.6 (1.8)	5.3 (2.0)	2.9 (2.4)
Visits BCN	0.5 (1.3)	0.7 (1.4)	0.5 (1.4)	0.6 (1.2)
Telephone MS	0.2 (0.5)	0.1 (0.6)	0.2 (0.8)	0.1 (0.3)
Telephone BCN	0.1 (0.5)	2.4 (1.2)	0.1 (0.3)	2.3 (1.0)
Mammography/ultrasound	1.6 (1.1)	1.7 (1.0)	1.5 (0.8)	1.7 (1.0)
Breast biopsy	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	0.1 (0.4)
Laboratory tests	11.8 (23.9)	5.7 (16.0)	4.6 (8.8)	4.4 (13.7)
Cardiology and lung tests	0.3 (1.1)	0.0 (0.1)	0.1 (0.4)	0.1 (0.2)
Other diagnostics	1.2 (2.1)	0.6 (1.2)	0.9 (1.6)	0.5 (0.9)
In-hospital days	0.6 (2.5)	0.1 (0.4)	0.1 (0.9)	0.1 (0.3)
Direct non-health care resources				
Paid help (in h)	18.4 (50.7)	6.9 (26.4)	16.5 (37.8)	7.7 (23.9)
Informal care (in h)	21.7 (65.9)	45.8 (136.6)	19.7 (38.5)	37.1 (125.9)
Productivity loss				
Paid work (in h)	60.3 (151.3)	85.2 (228.4)	98.0 (238.9)	68.9 (188.5)
Domestic tasks (in h)	32.7 (105.1)	45.9 (123.4)	25.5 (77.8)	14.7 (27.9)

as is argued for by the Dutch Council for Public Health and Health Care,[28] hospital follow-up plus EGP was not considered cost-effective and, therefore, telephone follow-up plus EGP was the preferred strategy (Table 6). As both hospital and telephone follow-up without EGP incurred higher costs and less QALYs than telephone follow-up plus EGP they were judged inferior.

Fig. 1 shows the cost-effectiveness acceptability curves and indicates that for a range of QALY threshold values (€0–€80.000), the probability that telephone follow-up plus EGP was cost-effective ranged between 49% and 62%.

3.5. *Secondary analyses*

Per protocol analysis, analysis excluding productivity costs or using the friction cost method to value productivity losses, as well as the analysis from a health care perspective all showed that telephone follow-up plus EGP was the preferred follow-up strategy, assuming a QALY threshold of €40.000. One-way sensitivity analyses showed that changing unit prices for telephone follow-up and hospital visits did not alter conclusions. The use of the Dutch EQ-5D tariff for utility scores also did not affect the results (Table 6).

Subgroup analyses showed that for patients with high levels of anxiety, hospital follow-up *plus* EGP is the most cost-effective if society would be willing to pay at least €33.269 for one QALY gain compared to hospital follow-up. Age, level of education and chemotherapy treatment did not influence cost-effectiveness results. Telephone follow-up plus EGP was also the most cost-effective strategy in the analysis with a time horizon of 18 months.

4. Discussion

4.1. *Key findings*

This comprehensive economic evaluation provided a detailed insight into the cost-effectiveness of four follow-up strategies for breast cancer patients during their first year after treatment. Hospital follow-up plus EGP yielded most QALYs, but was also the most costly follow-up strategy of the study. The ICER of hospital follow-up plus EGP versus the next best alternative, telephone follow-up plus EGP, amounted to €235.750/QALY. Hospital follow-up plus EGP was not considered to be cost-effective and telephone follow-up plus EGP was the preferred follow-up strategy. The probability of telephone follow-up plus EGP being the most cost-effective ranged from 60% when applying a more conservative threshold value of €20.000 to 58% with a threshold of €40.000. Secondary and sensitivity analyses showed that these results were robust. However, for patients with high levels of anxiety after treatment, hospital follow-up plus EGP was the preferred strategy in terms of cost-effectiveness.

The detailed cost analysis showed that health care costs were lower if some first year hospital follow-up visits were replaced by nurse-led telephone follow-up. This was mostly due to reduced costs for visits, concomitant laboratory tests and other diagnostics. Moreover, the combination of nurse-led telephone follow-up plus EGP was conducive to cost reductions. It may be speculated that a combination of frequent contacts with a BCN, together with a comprehensive education about signs and symptoms of possible treatment

Table 5 – Mean costs per patient (in Euros) over 12 months. EGP, educational group programme, MS, medical specialist, BCN, breast care nurse.

Cost category	Mean costs in 12 months (Euros)			
	Hospital f-up	Telephone f-up	Hospital f-up + EGP	Telephone f-up + EGP
Direct health care costs				
General practitioner	81	77	63	50
Physiotherapist	172	212	249	209
Revalidation	114	237	108	219
Educational group programme (EGP)	0	0	135	135
Other health care professionals	218	305	303	318
Home care (domestic and nursing)	226	219	166	111
Medication	23	20	18	23
Visits MS	712	357	666	350
Visits BCN	59	83	57	67
Telephone MS	3	3	2	1
Telephone BCN	2	52	2	49
Postoperative surgery	83	55	42	0
Mammography/ultrasound	131	137	123	139
Breast biopsy	9	12	14	10
Laboratory tests	92	47	69	41
Cardiology or lung tests	12	0	2	1
Other diagnostics	148	69	135	65
Costs for in-hospital days	362	53	82	43
Subtotal health care costs	2447	1938	2236	1831
(95% bootstrapped CI)	(1974–3014)	(1604–2303)	(1864–2713)	(1468–2196)
Direct non-health care costs				
Paid help	184	69	165	77
Informal care	195	412	177	333
Subtotal	379	481	342	410
(95% bootstrapped CI)	(196–609)	(256–807)	(232–473)	(201–682)
Costs of lost production				
Paid work	1159	1637	1884	1325
Domestic tasks	294	412	230	133
Subtotal	1453	2049	2114	1458
(95% bootstrapped CI)	(848–2163)	(1159–3111)	(1202–3321)	(692–2344)
Out of pocket costs				
Reported by patients	130	177	202	257
Drugs	10	27	20	15
Subtotal	140	204	222	272
(95% bootstrapped CI)	(89–209)	(141–277)	(133–340)	(144–417)
Subtotal non-healthcare costs	1972	2734	2678	2140
(95% bootstrapped CI)	(1308–2713)	(1706–3873)	(1642–3941)	(1171–3317)
Total costs	4419	4672	4914	3971
(95% bootstrapped CI)	(3410–5501)	(3489–6033)	(3793–6192)	(2975–5186)

side-effects, may have led to fewer contacts with (more specialised) health care professionals.

Conceptually the cost differences between follow-up strategies were small. Mean cost differences from the societal perspective between telephone follow-up plus EGP and current clinical practice (hospital follow-up), were €448 for 1 year. However, by extrapolating these figures to the breast cancer population in the Netherlands[1] this may represent an important overall cost difference.

4.2. *Comparison with other studies*

To our knowledge, there are no earlier such publications on cost-effectiveness of follow-up for the first year after treatment. Although similar studies have been conducted, these either compared traditional follow-up to different alternative strategies,[29,30] or involved a different follow-up time period.[31] Grunfeld and colleagues showed that follow-up performed by the general practitioner did not increase the use of other health care services, and reduced costs substantially.[30] Koinberg and colleagues compared specialist nurse and medical specialist follow-ups and found that specialist nurse follow-up was approximately 20% less expensive.[29]

Beaver and colleagues conducted a cost-minimisation study, comparing traditional hospital follow-up with nurse-led telephone follow-up, and concluded that telephone follow-up may reduce the burden on busy hospital clinics but would not necessarily lead to cost savings. While women

Table 6 – Results of the base case analysis (societal perspective) and secondary analyses. Most cost-effective follow-up strategy in bold.

	Study arms in order of descending QALYs	Mean costs (bootstrapped 95% CI)	Mean QALYs (bootstrapped 95% CI)	ICER	Probability cost-effective λ = €20.000	Probability cost-effective λ = €40.000	Probability cost-effective λ = €80.000
Base case analysis societal perspective	3-hosp + EGP (*n* = 75)	4914 (3793–6192)	0.776 (0.753–0.799)	235.750/QALY versus 4	13	17	26
	4-teleph + EGP (*n* = 74)	**3971 (2975–5186)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**60**	**58**	**49**
	2-teleph f-up (*n* = 76)	4672 (3489–6033)	0.769 (0.746–0.794)	Dominated by 4	18	20	21
	1-hosp f-up (*n* = 74)	4419 (3410–5501)	0.747 (0.707–0.778)	Dominated by 4	9	6	3
Analysis excl productivity costs	3-hosp + EGP (*n* = 75)	2800 (2319–3386)	0.776 (0.753–0.799)	71.500/QALY versus 4	24	29	35
	4-teleph + EGP (*n* = 74)	**2514 (2043–3105)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**44**	**40**	**36**
	2-teleph f-up (*n* = 76)	2626 (2129–3146)	0.769 (0.746–0.794)	Dominated by 4	29	28	26
	1-hosp f-up (*n* = 74)	2968 (2392–3611)	0.747 (0.707–0.778)	Dominated by 4	3	3	3
Friction cost method	3-hosp + EGP (*n* = 76)	3161 (2591–3771)	0.776 (0.753–0.799)	94.250/QALY versus 4	29	38	41
	4-teleph + EGP (*n* = 75)	**2784 (2175–3539)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**62**	**52**	**43**
	2-teleph f-up (*n* = 74)	3653 (2938–4635)	0.769 (0.746–0.794)	Dominated by 4	6	8	14
	1-hosp f-up (*n* = 74)	3450 (2747–4203)	0.747 (0.707–0.778)	Dominated by 4	3	2	2
Per protocol analysis	3-hosp + EGP (*n* = 84)	5178 (3986–6525)	0.776 (0.753–0.799)	530.250/QALY versus 4	1	6	17
	4-teleph + EGP (*n* = 55)	**3057 (2248–3989)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**95**	**90**	**74**
	2-teleph f-up (*n* = 65)	5170 (3763–6689)	0.769 (0.746–0.794)	Dominated by 4	2	3	7
	1-hosp f-up (*n* = 96)	4270 (3417–5122)	0.747 (0.707–0.778)	Dominated by 4	1	2	2
Analysis health care perspective	3-hosp + EGP (*n* = 75)	2210 (1842–2659)	0.776 (0.753–0.799)	98.250/QALY versus 4	56	24	32
	4-teleph + EGP (*n* = 74)	**1817 (1488–2222)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**16**	**45**	**39**
	2-teleph f-up (*n* = 76)	1926 (1608–2306)	0.769 (0.746–0.794)	Dominated by 4	30	29	27
	1-hosp f-up (*n* = 74)	2422 (1969–2976)	0.747 (0.707–0.778)	Dominated by 4	2	2	2
Cost price generic hospital follow-up	3-hosp + EGP (*n* = 75)	4552 (3380–5777)	0.776 (0.753–0.799)	185.250/QALY versus 4	19	25	33
	4-teleph + EGP (*n* = 74)	**3811 (2638–5047)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**54**	**52**	**43**
	2-teleph f-up (*n* = 76)	4518 (5022–5794)	0.769 (0.746–0.794)	Dominated by 4	14	16	19
	1-hosp f-up (*n* = 74)	4038 (3108–3424)	0.747 (0.707–0.778)	Dominated by 4	13	7	5
Highest value for telephone follow-up	3-hosp + EGP (*n* = 76)	4917 (3786–6250)	0.776 (0.753–0.799)	176.750/QALY versus 4	18	25	33
	4-teleph + EGP (*n* = 75)	**4210 (3203–5451)**	**0.772 (0.745–0.797)**	**Dominates 1 & 2**	**56**	**53**	**46**
	2-teleph f-up (*n* = 74)	4961 (3807–6197)	0.769 (0.746–0.794)	Dominated by 4	12	14	15
	1-hosp f-up (*n* = 74)	4431 (3441–5512)	0.747 (0.707–0.778)	Dominated by 4	14	8	5
Dutch tariff for EQ-5D	3-hosp + EGP (*n* = 76)	4914 (3793–6192)	0.782 (0.759 – 0.803)	Dominated by 4	10	14	20
	4-teleph + EGP (*n* = 75)	**3971 (2975–5186)**	**0.782 (0.759–0.804)**	**Dominates 1 & 2 & 3**	**65**	**63**	**56**
	2-teleph f-up (*n* = 74)	4672 (3489–6033)	0.779 (0.754–0.801)	Dominated by 4	15	18	21
	1-hosp f-up (*n* = 74)	4419 (3410–5501)	0.757 (0.727–0.791)	Dominated by 4	10	6	4

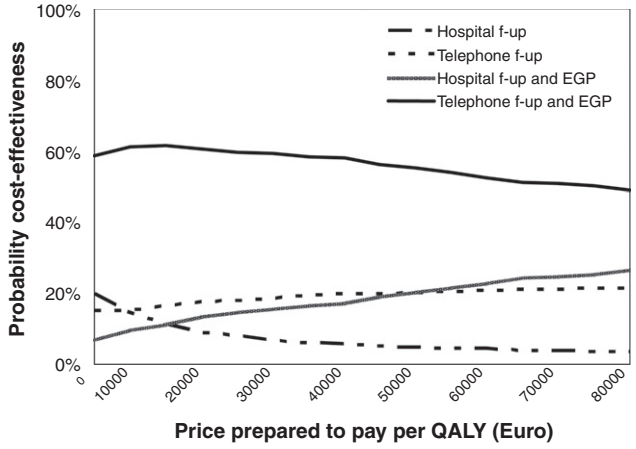

Fig. 1 – Cost-effectiveness acceptability curves for four follow-up strategies after treatment for breast cancer (base case analysis). EGP, educational group programme.

randomised to telephone follow-up reported less hospital consultations, the longer duration of telephone consultations, use of junior medical staff, and training costs of nurses resulted in higher routine costs for telephone follow-up.[31] In contrast, our study used a fixed price for hospital follow-up visits, since it was often unclear which health care provider would perform the follow-up. Furthermore, training costs of nurses were not included in the cost price of telephone follow-up, as these costs diffuse among many patients outside the study domain. Importantly, changing cost prices for hospital and telephone consultations did not alter our conclusions. Hence, our studies show similar results in terms of resource use, however, the unit cost of a hospital visit resulted in contrasting conclusions.[31]

4.3. *Concerns regarding the economic analysis*

Economic evaluations of pragmatic trials are complex and challenging. We tried to overcome the difficulties of skewed cost data by using appropriate bootstrap techniques. Furthermore, we aimed to present the cost, effectiveness and cost-effectiveness results of four strategies, including usual care. As the RCT used a factorial design, it may seem consistent to analyse and present the cost and effect data for the factorial (combined) groups. However, the interpretation of these results with respect to the economic evaluation would be less informative as the two factorial groups each represent a mixture of two follow-up strategies. Therefore, in order to facilitate interpretation, we have presented costs and effects of the four follow-up strategies separately in this economic evaluation. Effectiveness results (e.g. health-related quality of life) analysed according to the factorial design are presented in a separate paper (paper submitted).[10]

The baseline differences in EQ-5D values were, even though non-significant ($p = 0.07$), quite pronounced, while all other baseline characteristics were comparable between the four groups. Randomisation in our study was performed by an independent centre, using a computerised randomisation programme in which patients were pre-stratified by hospital and treatment modality, and no flaws in this procedure were identified. We could not explain these baseline differences and without proper adjustment they may greatly affect the cost-effectiveness analysis. We have, therefore, used recommended methods for adjustment.[27]

Some unexpected cost differences were found between the study arms that were not obviously related to the interventions. In arm 1 (hospital follow-up) costs for in-hospital days were visibly higher compared to the other three strategies. In arm 1 three patients were admitted to the hospital for more than seven days due to breast cancer related complications, and were responsible for these high costs. It seems unlikely these admissions were related to the follow-up strategy, but it would have been inappropriate to exclude these costs in the base case analysis. A secondary analysis excluding these patients showed a lower mean costs for this study arm, but did not alter conclusions (data not shown).

From the societal perspective, indirect costs due to absence from paid work or inability to perform domestic tasks accounted for a major part of the total costs of all study arms (almost 40%); however, these estimates showed large 95% confidence intervals. The present large differences in indirect costs between groups were unexpected and might be explained by relatively small sample sizes. Excluding the productivity costs in the base case analysis would have violated the pre-defined protocol and the Dutch guidelines for economic evaluation.[15] To address the uncertainty induced by the high productivity costs, a secondary analysis excluding these specific costs was also reported. This analysis showed that the ICER for hospital follow-up plus EGP versus telephone follow-up plus EGP dropped to 71.500/QALY. Additionally, an analysis was performed in which the friction cost method was applied to value productivity losses. Costs related to absence from paid work were now much lower (Table 6), since this method sets a maximum time period (friction period) for which lost hours are counted. The ICER for hospital follow-up plus EGP versus telephone follow-up plus EGP was 92.500/QALY. Hence, when excluding the productivity costs or changing the valuation method the associated ICERs were still above the Dutch QALY threshold. Telephone follow-up plus EGP remained the preferred strategy.

Finally, there may be concern that the EQ-5D is not sensitive enough in these patients to identify differences in their HRQoL. However, the EQ-5D was found to be a responsive measure in this breast cancer population, able to detect improvements and deteriorations in health.[13] The EQ-5D is also the recommended outcome measure for economic evaluations[12] and commonly used in cancer populations.[32] The use of the EQ-5D in this study, therefore, allows comparison to other studies.

4.4. *Strengths*

It is generally recognised that most breast cancer follow-up related costs are incurred in the first 2 years after treatment.[33] Also, most improvement in psychosocial status is reported for the first year after treatment.[34] Hence, the present study focused on a key time period after treatment for medical decision making. This economic evaluation was performed according to published international guidelines for trial-based economic evaluations,[12] within the framework of a

multicentre randomised controlled trial. The randomised setting prevented selection bias and due to the pragmatic nature of the trial it closely reflects the effectiveness and resource use that would be observed in daily practice. We compared four alternative strategies, which is relatively uncommon, and addressed the often proposed disadvantage of trial-based economic evaluations that they represent only a limited form of analysis by comparing few alternatives. Furthermore, we have provided detailed information on follow-up costs facilitating case-by-case calculations for the purpose of generalisability.

5. Conclusions

Results of this study may bridge an important evidence gap on cost-effectiveness of alternative follow-up strategies after breast cancer treatment. Our results and those of others[29–31] increasingly underscore the importance of critically assessing current guidelines for breast cancer follow-up. This economic analysis showed that nurse-led telephone follow-up plus an EGP may be an appropriate and cost-effective alternative to hospital follow-up for breast cancer patients during their first year after treatment.

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Conflict of interest statement

None declared.

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