Economic evaluation of flap fixation techniques after mastectomy

European Journal of Surgical Oncology 49 (2023) 107003

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Economic evaluation of flap fixation techniques after mastectomy: Results of a double-blind randomized controlled trial (SAM-trial)

L. De Rooij [a], M.L. Kimman [b], M.A. Spiekerman van Weezelenburg [a,*], S.M.J. van Kuijk [b], R.W. Y. Granzier [a], K.F.H. Hintzen [a], C. Heymans [a], L.L.B. Theunissen [a], E.R.M. van Haaren [a], A. Janssen [a], Y.L.J. Vissers [a], G.L. Beets [c,d], J. van Bastelaar [a]

[a] Department of Surgery, Zuyderland Medical Center, Sittard, the Netherlands
[b] Department of Clinical Epidemiology and Medical Technology Assessment, Care and Public Health Research Institute (CAPHRI), Maastricht University Medical Center, Maastricht, the Netherlands
[c] Department of Surgery, Netherlands Cancer Institute, Amsterdam, the Netherlands
[d] GROW School for Oncology and Developmental Biology, University of Maastricht, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Flap fixation
Seroma formation
Cost-effectiveness

ABSTRACT

Background: An economic evaluation was performed alongside an RCT investigating flap fixation in reducing seroma formation after mastectomy. The evaluation focused on the first year following mastectomy and assessed cost-effectiveness from a health care and societal perspective.
Methods: The economic evaluation was conducted between 2014 and 2018 in four Dutch breast clinics. Patients with an indication for mastectomy or modified radical mastectomy were randomly assigned to: conventional closure (CON), flap fixation with sutures (FFS) or flap fixation with tissue glue (FFG). Health care costs, patient and family costs and costs due to productivity losses were assessed. Outcomes were expressed in incremental cost-effectiveness ratios (ICERs): the incremental cost per quality-adjusted life year (QALY). Bootstrapping techniques, sensitivity and secondary analyses were employed to address uncertainty.
Results: The FFS-group yielded most QALYs (0.810; 95%-CI 0.755–0.856), but also incurred the highest mean costs at twelve months (€10.416; 95%-CI 8.231–12.930). CON was the next best alternative with 0.794 QALYs (95%-CI 0.733–0.841) and mean annual costs of €10.051 (95%-CI 8.255–12.044). FFG incurred fewer QALYs and higher costs, when compared to the CON group. The ICER of FFS compared to CON was €22.813/QALY. Applying a willingness to pay threshold in the Netherlands of €20.000/QALY, the probability that FFS was cost-effective was 42%, compared to 37% and 21% for CON and FFG, respectively.
Conclusion: The cost-effectiveness of FFS following mastectomy, versus CON and FFG, is uncertain from a societal perspective. Yet, from a health care and hospital perspective FFS is likely to be the most cost-effective intervention.

1. Introduction

With an incidence of 3%–85%, seroma formation is a common complication after mastectomy [1,2]. Seroma can cause pain, discomfort, wound complications, delay of adjuvant therapy and additional out-patient clinic visits are generally required to treat seroma related complications [3,4]. Depending on the severity of the complications, aspiration of seroma, long-term wound treatment, or even surgical intervention with hospital admission may be necessary.

Recently, clinical research has been conducted to optimize seroma related outcomes in mastectomy. These papers have focused on reducing post mastectomy dead space using various surgical techniques such as flap fixation and flap quilting [5–7]. No specific method of skin flap dissection has proven to be beneficial in reducing seroma formation over others [8,9]. Studies on skin flap fixation show promising results with regard to reducing the need for seroma aspirations in clinically significant seromas [10–16]. The seroma reduction after mastectomy (SAM) trial, a double blind, randomized controlled trial (RCT) compared two methods of flap fixation to a conventional cohort, i.e. flap fixation using sutures and flap fixation using tissue glue. This trial demonstrated that

* Corresponding author. Zuyderland Medical Center, Department of Surgery, P.O. Box 5500, 6130 MB, Sittard, the Netherlands.
E-mail address: m.spiekermanvanweezelenburg@zuyderland.nl (M.A. Spiekerman van Weezelenburg).

https://doi.org/10.1016/j.ejso.2023.107003
Received 7 June 2023; Received in revised form 14 July 2023; Accepted 31 July 2023
Available online 2 August 2023

flap fixation using sutures was most effective in reducing seroma aspirations in patients undergoing mastectomy [17].

Apart from establishing the effectiveness on clinical outcomes, it is important to evaluate broader outcomes of potential flap fixation methods. An important element in this evaluation are the effects on patient's health-related quality of life (HRQoL) in relation to its costs. While flap fixation with sutures is clinically most effective, impact on HRQoL is unknown and it may be associated with higher costs due to a longer duration of the surgical procedure. An economic evaluation can support health policy makers in making evidence-based decisions on allocation of scarce resources [18]. This type of evaluation focuses on the difference in costs between a (new) treatment and usual care or other competing treatments, in relation to the difference in health benefits, so as to assess its cost-effectiveness (i.e. value for money). The present study reports on the results of the economic evaluation of the SAM trial to identify the most cost-effective method to reduce seroma formation and its sequelae after mastectomy.

2. Methods

2.1. Study design, setting and patient selection

The SAM trial was conducted between June 2014 and July 2018 in four breast clinics in the Netherlands (Atrium Medical Center Heerlen, Orbis Medical Center Sittard (later Zuyderland Medical Center after the merger of the former two), Albert Schweitzer Hospital Dordrecht and St. Jans Gasthuis Hospital Weert. Patients with an indication for simple mastectomy or modified radical mastectomy (MRM) due to invasive breast cancer or ductal carcinoma in situ (DCIS) were eligible for inclusion. Patients undergoing breast conserving therapy or primary breast reconstruction were not eligible for the trial. After informed consent, patients were randomly assigned to one of three arms: 1) conventional closure (CON), 2) flap fixation with sutures (FFS), or 3) flap fixation with tissue glue (FFG). Additional data collection for the present economic analysis started in November 2016.

2.2. Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee (ethics committee of Zuyderland Medical Center, Netherlands) and with the 1964 Helsinki declaration and its later amendments. This trial was approved by the institutional ethics committee (14-T-21).

2.3. Study intervention

For all participants, regardless of study arm, mastectomy was performed as follows: the nipple-areola complex was removed and dissection of the skin flaps was performed using electrocautery. The breast tissue, including the prepectoral fascia, was removed from the pectoral muscle. For skin closure the edges were sutured using absorbable monofilament sutures (Monocryl 3.0 or V-loc 30 cm), depending on the surgeon's preference.

Directly following mastectomy, patients in arm 1 (CON) underwent conventional wound closure and no flap fixation was performed. If assigned to arm 2 (FFS), the skin flaps were sutured on to the pectoral muscle using polyfilament absorbable sutures (Vicryl 3.0). These sutures were placed at 4–5 cm intervals in two or three rows, depending on the extent of the skin flaps. In arm 3 (FFG), the skin flaps were anchored using fibrin tissue glue (ARTISS, Baxter). For details of the trial design and protocol execution we refer to the publication of the SAM trial [17].

The economic evaluation was performed and reported according to the Dutch guidelines for economic evaluation [19] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement [20]. A cost-utility analysis, comparing costs and QALYs of the three techniques, was performed from a societal perspective and with a time horizon of one year.

2.4. Outcome assessment

2.4.1. Measure of effect

The quality-adjusted life year (QALY) is the outcome of choice for an economic evaluation. The QALY is a measure of life expectancy weighted by HRQoL, the latter being presented as a utility score [21]. The EuroQol 5 dimensions 5 levels (EQ-5D-5L) was used to assess HRQoL [22]. The EQ-5D-5L is a 5-item patient-reported questionnaire that comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated at five levels: no problems (1), some problems (2), moderate problems (3), severe problems (4) and inability to perform task or extreme anxiety or pain (5). Based on Dutch tariffs, EQ-5D-5L health states can be converted into utilities [23]. A utility represents the value of a patient's health state and is measured on a continuous scale anchored between 0 and 1, in which 0 means worst imaginable health state and 1 perfect health. The utilities are used for the QALY calculations.

The EQ-5D-5L was completed at baseline, three, six and twelve months after surgery. The utilities at the various time-points were used to compute QALYs by means of the area under the curve method, where the utility of a particular health state is multiplied by the time spent in this specific health state [18].

2.4.2. Measure of costs

Costs were divided into three cost categories: health care costs, patient and family costs, and costs due to productivity loss [19]. Hospital information systems were used to retrieve information on all health care consumed in the hospital (e.g. procedure, readmission, additional hospital visits or postoperative surgery). Since health care use associated with mastectomy is intertwined with use related to breast cancer treatment in general, a predetermined set of rules was used to select resource use related to the mastectomy. One of the rules was that only outpatient clinic visits, readmission and/or postoperative surgery or complications related to mastectomy were included, based on inspection of the patient's medical file. Health care use outside the hospital (e.g. general practitioner visits, physical therapy, informal care, and quantities of lost paid work) was assessed using resource use surveys, completed by participants. The survey was an adapted version of the validated Medical Cost Questionnaire (iMCQ) developed by the institute for Medical technology Assessment (iMTA) in The Netherlands [24]. The iMCQ is a generic instrument for measuring medical costs with a re-call period of three months and includes questions related to frequently occurring contacts with health care providers. It can be complemented with additional items that are relevant for specific study populations. For this study, patients were asked to only report resource use or out-of-pocket costs that were related to the mastectomy procedure.

The iMCQ was completed at three, six and twelve months. Resource use for months seven to nine were interpolated using the six and twelve-months data, under the assumption that data obtained from these cost diaries would be representative of the in-between period [25]. At baseline, patients completed a generic resource use survey, focused on health and non-health care resource use in the three months before mastectomy, not necessarily related to breast cancer.

Unit cost prices were primarily obtained from the Dutch governmental manual for health care cost analysis. If not available, average cost prices from the providers were used [19]. Intervention costs consisted of costs of the surgery and material costs (i.e. sutures or tissue glue). Costs for (conventional) surgery, postoperative surgery, and readmission were based on average cost prices of the treating breast clinics. Surgery costs for each intervention only differed in terms of operating time. Data on operating times were collected to calculate the exact cost price of each intervention; each additional minute costs €14. Productivity costs included productivity losses due to absence from work and were valued using the friction cost method [19,26]. In the Netherlands, a friction period of 85 days is recommended for economic evaluations [19]. The friction period is the time needed to replace an employee who is absent due to an illness. Informal care (received) and domestic activities were valued using the proxy good method using the average hourly wage of domestic help as a proxy. Cost prices per unit of resource use are presented in Table 1. All cost prices were converted to 2017 Euros by means of price index numbers [27]. Discounting of costs (and effects) was not performed due to the follow-up period of one year.

Table 1
Unit prices. All unit prices are expressed in Euros at 2017 values.

Cost category	Unit prices in Euro (2017)[a,b]
Health care costs	
General practitioner	34/visit[b,1]
Hospital visit (OPD or ER)	75/visit[b,1]
Physiotherapist/lymph edema therapist	34/visit[b,1]
Other health care professionals[c]	34/visit[b,1]
Home care domestic	24[b,1]
Home care nursing	51[b,1]
Medication[d]	Various[b,2]
Surgery (mastectomy)[e]	
Mastectomy conventional (CON)	1.850[b,3]
Mastectomy + fixation with sutures[f] (FFS)	1.993[b,3]
Mastectomy + fixation with tissue glue[g] (FFG)	1.972[b,3]
Postoperative surgery[h]	834[b,3]
Postoperative readmission (per night)[i]	599[b,3]
Negative pressure wound therapy[j]	695[b,4]
Medical devices[k]	Various[b,5]
External breast prosthesis	211[b,6]
(Prosthesis) bra	62[b,6]
Wound dressings	Various[b,5]
Compression stockings	288[b,7]
Clothes	Various[b,5]
Mobility enhancing devices	Various[b,5]
Patient and family costs	
Paid help	20/hour[b,1]
Informal care	14[b,1]
Out of pocket costs[l]	Various[b,5]
Costs of lost production	
Paid work	32[b,8]

OPD = outpatient department, ER = emergency room, CON = conventional closure, FFS = flap fixation with sutures, FFG = flap fixation with tissue glue.

[a] When necessary, cost prices were converted to 2017 by means of Dutch consumer price index numbers.

[b] Source of unit price: [1] Dutch manual for cost prices; [2] www.farmacotherapeutischkompas.nl (including tax); [3] At the medical center in which this study was conducted; [4] Based on MediReva; [5] As reported by patient; [6] Specialized breast cancer prosthesis and bra store: Ankie Care 4 You; [7] Skin and edema therapy Heuvelland; [8] Based on friction cost method.

[c] Other health care professionals such as ergonomic physical therapy or alternative health practitioners.

[d] Medication was subgrouped to anxiolytics, antibiotics and pain killers.

[e] Costs for the operation time of 90 min and one night hospital admission.

[f] Costs of the average additional sutures used in the FFS group and additional operating time of 10 min were added to the standard costs.

[g] Costs of one dose tissue glue were added to the standard costs.

[h] Surgical treatment of complications such as postoperative bleeding, wounds/abscess or (infected) seroma.

[i] In case of complications requiring readmission for operative treatment or treatment with intravenous antibiotics.

[j] Based on costs for negative wound pressure therapy pump and 21 days of treatment.

[k] Medical devices were subgrouped to external breast prosthesis, (prosthesis) bra, wound dressings, compression stockings, clothes and mobility enhancing devices such as wheelchair or walking stick. Costs were noted by the participants. For external breast prostheses, bras and compression stockings a fixed price was used.

[l] Out-of-pocket costs included costs for parking or transportation costs, etc.

2.5. Analysis

The base case analysis of the economic evaluation was performed in agreement with the intention to treat principle. Stochastic regression imputation with fully conditional specification using predictive mean matching was used to replace missing values with plausible estimates so as to generate a dataset from which representatives means could be calculated [28]. If patients completed less than two evaluations, they were considered lost to follow-up and no data were imputed. Relevance of possible baseline differences were assessed using clinical and economic judgement and no statistical testing, conform the Consolidated Standard of Reporting Trials [29].

The patient's utilities at the various time-points were used to compute QALYs by means of the area under the curve method, where the utility of a particular health state is multiplied by the time spent in this specific health state [18]. Costs are calculated by multiplying individual level resource use data with cost prices.

Mean resource use, costs, and QALYs acquired over the one-year study period were reported using descriptive statistics [30]. To calculate 95% confidence intervals (CI) around mean costs and effects of the three study arms, non-parametric bootstrap simulations with 1000 replications were used. The bootstrap method estimates the sampling distribution of a statistic through a large number of simulations based on sampling with replacement [31].

To investigate the cost-effectiveness of the three techniques the incremental cost-effectiveness ratios (ICERs) were calculated. Because we included more than two techniques, techniques were first ranked by QALYs from the most effective to the least effective. A technique that was less effective and more costly than the previous technique was said to be dominated and excluded from calculation of the ICERs [18]. The ICER was defined as the incremental costs of the most effective technique, compared to the next best alternative, divided by the incremental QALYs. Non-parametric bootstrapping with 5000 replicates of the joint distribution of costs and QALYs, identified the probability of each technique being the most cost-effective, for various ceiling ratios for the ICER, presented in a cost-effectiveness acceptability curve (CEAC) [32]. Ceiling ratios reflect the maximum price health policymakers are willing to pay for an additional QALY. In the Netherlands, the Council for Public Health and Health Care proposes an informal ceiling ratio between €20.000 and €80.000 per QALY, depending on the burden of disease [33].

In addition to the base case analysis of the economic evaluation, secondary and sensitivity analyses were performed to assess the robustness of results. An analysis from a health care perspective was performed in which costs due to productivity loss and patient and family costs were excluded. Another analysis focused exclusively on hospital costs and included costs related to surgery, postoperative surgery, readmission and the use of negative pressure wound therapy. Finally, an analysis was performed where patient-reported costs were adjusted to baseline differences between groups in the three months preceding randomization using the Delta adjustment method. In this analysis individual baseline costs were subtracted from the costs at the follow-up measurements [34].

Bootstrapping was performed using Excel 2019. Other analyses were performed using SPSS (IBM SPSS statistics for Windows, Version 25).

3. Results

3.1. Participants

Within the SAM trial, 153 patients were asked to complete the EQ-5D and the resource use surveys, of whom 146 completed at least 2 assessments and could be included in the economic evaluation. These 146 patients were evenly assigned to one of the three study arms (Fig. 1). The mean age of the participants was 65.4 years (range 29–92), 25% of the patients were in paid employment and 18% received neoadjuvant

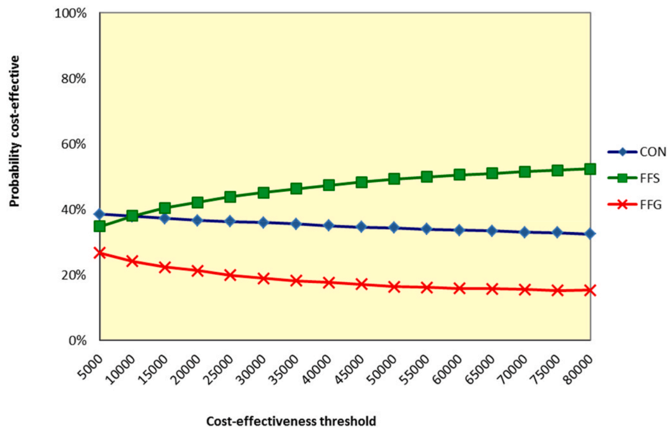

Fig. 1. Flowchart SAM trial.

chemotherapy. Demographic and clinical characteristics were comparable between the three groups (Table 2). While total costs were comparable between groups, there were noticeable differences between the groups in the number of visits to the physical therapist and in the number of hours of informal care, home care and paid help received in the three months before the study intervention (Appendix A).

Table 2
Baseline characteristics of participants (n = 153)[a].

Baseline characteristics	CON (n = 54)	FFS (n = 48)	FFG (n = 51)	All participants (n = 153)
Age (years) [range]	65.2 [34–88]	65.6 [33–90]	65.5 [29–92]	65.4 [29–92]
Level of education (%)				
Low	16 (30)	18 (38)	21 (41)	55 (36)
Middle	22 (41)	22 (46)	14 (28)	58 (38)
High	11 (20)	7 (15)	11 (22)	29 (19)
Missing	5 (9)	1 (1)	5 (9)	11 (7)
Main daily activity				
Paid employment (%)	15 (28)	11 (23)	12 (24)	38 (25)
Average hours of paid employment per week	24.6 ± 11.0	23.5 ± 16.2	20.6 ± 10.5	23.0 ± 12.3
Tumor stage (%)				
cT0	3 (6)	0	0	3 (2)
cTx	0	0	2 (4)	2 (1)
cTIs	6 (11)	5 (10)	2 (4)	13 (9)
cT1-2	38 (70)	35 (73)	41 (80)	114 (75)
cT3-4	7 (13)	8 (17)	6 (12)	21 (14)
cN0	39 (72)	37 (77)	37 (73)	113 (74)
cN1	12 (22)	8 (17)	12 (24)	32 (21)
cN2	2 (4)	2 (4)	2 (4)	6 (4)
cN3	1 (2)	1 (2)	0	2 (1)
Health score				
Charlson comorbidity index	5.4 ± 2.1	5.2 ± 2.1	5.7 ± 2.6	5.4 ± 2.3
Neoadjuvant therapy (%)	13 (24)	8 (17)	6 (12)	27 (18)
Procedure (%)				
Mastectomy	4 (7)	7 (15)	2 (4)	13 (9)
Mastectomy + SN	30 (56)	25 (52)	34 (67)	89 (58)
MRM	20 (37)	16 (33)	15 (29)	51 (33)

CON = conventional closure, FFS = flap fixation with sutures, FFG = flap fixation with tissue glue, cT0 = benign tumors, Is = in situ, SN = sentinel node, MRM = modified radical mastectomy.

[a] Continuous variables are presented as mean ± SD. Categorical variables in absolute numbers (%).

Completion rates of the resource use surveys were 95% for the first three assessments and 89% for the assessment at twelve months. Hospital resource use data were available for all patients for the twelve months of the study.

3.2. Costs and effects

The closure time of FFS was on average 10 min longer than CON and FFG, with a mean closure time of 25 min (standard deviation 7 min). Therefore, total costs for the FFS procedure were €1.993 compared to €1.972 and €1.850 for FFG and CON, respectively (Table 1).

In Tables 4 and 5 mean resource use and mean costs per patient over the study period of twelve months are presented. Following the intervention, costs for hospital visits, postoperative surgery, and postoperative readmission were slightly higher in the CON and FFG group compared to FFS. Costs for domestic home care were highest in the CON group, but costs for nursing home care lowest. Overall, health care related costs were €5.489 (95% CI 4.318–7.109) for FFS, €5.508 (95% CI 4.631–6.413) for FFG, and €5.530 (95% CI 4.641–6.468) for CON. Non-health care costs (patient and family costs and productivity costs) were highest for FFS (Table 5). Overall, mean total costs per patient at twelve months follow-up were €10.051 (95% CI 8.255–12.044) for the CON group, €10.416 (95% CI 8.231–12.930) for the FFS group, and €10.248 (95% CI 8.564–11.777) for the FFG group. Hence, mean costs were highest for FFS and lowest for CON, but differences were small.

Regarding HRQoL, improvements were most notable in the FFS group. Patients receiving this technique cumulated a mean QALY gain of 0.810 (95% CI 0.755–0.856) compared to 0.794 (95% CI 0.733–0.841) QALYs for CON and 0.781 (95% CI 0.728–0.830) QALYs for FFG (see Table 3).

3.3. Cost-effectiveness

The FFS group yielded most QALYs (0.810) and incurred highest mean costs at twelve months follow-up (€10.416). Conventional wound closure (CON group) was the next best alternative with 0.794 QALYs and mean annual costs of €10.051. Flap fixation using tissue glue (FFG group) was dominated by CON, meaning it was more costly than CON and less effective. Using FFS instead of CON means paying €22.813 per QALY gained (Table 6). Bootstrapped results were plotted in the cost-effectiveness acceptability curve (Fig. 2). The probability that FFS was cost-effective was 42%, compared to 37% and 21% for CON and FFG, respectively, assuming a ceiling ratio of €20.000. From Fig. 2 it can be concluded that if one would be willing to pay (a maximum of) €80 000 per QALY gained, the probability that the FFS would be cost-effective would be 52%.

Secondary analyses, from a health care and hospital perspective, showed that FFS dominated both CON and FFG due to lower mean costs and higher mean QALYs. Applying a €20.000 ceiling ratio, the probability of FFS being the most cost-effective intervention, compared to the

Table 3
EQ-5D-5L index scores at baseline, three, six and twelve months after treatment and QALYs for the three study arms.

Measurement	Index score of EQ-5D-5L		
	CON (n = 53)	FFS (n = 46)	FFG (n = 47)
Baseline	0.787	0.785	0.796
Three months	0.801	0.825	0.761
Six months	0.797	0.807	0.800
Twelve months	0.789	0.809	0.765
QALY (Bootstrapped 95% CI)	0.794 (0.733–0.841)	0.810 (0.755–0.856)	0.781 (0.728–0.830)

CON = conventional closure, FFS = flap fixation with sutures, FFG = flap fixation with tissue glue, QALY = Quality-adjusted life year, CI = confidence interval.

Table 4
Mean resources use per patient over twelve months (in number of contacts unless stated otherwise).

Resource category	CON (n = 53) Mean (SD)	FFS (n = 46) Mean (SD)	FFG (n = 47) Mean (SD)
Health care costs			
General practitioner	1.4 (3.0)	1.4 (2.0)	1.3 (1.7)
Additional hospital visit (OPD or ER)	1.5 (1.9)	0.9 (1.5)	1.6 (2.5)
Physical therapist/lymph edema therapist	25.6 (31.7)	28.0 (34.7)	25.0 (26.8)
Other health care professionals	4.2 (10.4)	3.9 (11.5)	3.5 (10.1)
Home care domestic (in h)	28.9 (68.5)	13.6 (36.7)	13.4 (30.7)
Home care nursing (in h)	17.6 (31.8)	22.7 (79.3)	23.1 (40.4)
Postoperative surgery	0.1 (0.3)	0.04 (0.2)	0.1 (0.4)
Postoperative readmission (in days)	0.5 (1.5)	0.2 (1.2)	0.5 (1.5)
Negative pressure wound therapy Y/N	0.1 (0.3)	0.04 (0.2)	0.04 (0.2)
Patient and family costs			
Paid help (in h)	21.5 (46.5)	37.8 (71.6)	20.6 (34.4)
Informal care (in h)	133.7 (189.7)	178.2 (264.1)	198.0 (271.8)
Productivity loss			
Paid work (loss in h)	186.5 (436.6)	107.3 (275.4)	125.9 (391.0)

CON = conventional closure, FFS = flap fixation with sutures, FFG = flap fixation with tissue glue, SD = standard deviation, OPD = outpatient department, ER = emergency room, Y/N = yes/no.

two other techniques, was 53% for the health care perspective, and 63% for the hospital perspective. Finally, when we adjusted patient-reported resources for baseline differences, the ICER dropped to €9.125 per QALY and the probability that FFS was cost-effective raised to 48% (compared to 38% and 14% for CON and FFG respectively) (see Appendix A).

4. Discussion

In this study we report on the cost-effectiveness of two techniques of flap fixation in patients undergoing mastectomy compared to a third group undergoing conventional wound closure. This analysis offers a broader perspective on tackling problems regarding seroma formation following mastectomy. Seroma is associated with increased health care utilization and reduced HRQoL, hence reducing seroma has potentially large societal benefits. When different techniques are available it is essential to balance the difference in costs with the difference in the effectiveness to ensure efficient use of scarce health care resources.

This economic evaluation showed that there were only small differences in outcomes between the three techniques. Over the year following the mastectomy, FFS yielded the most QALYs, but it was also the most costly technique. Higher costs were mainly attributed to higher costs outside the health care sector (e.g. paid help, informal care). Taking a societal perspective, the ICER amounted to €22.813/QALY. Hence, it requires €22.813 to gain a QALY when compared to the next best alternative, conventional wound closure. Taking a conservative and strict ceiling ratio of €20.000, FFS would not be considered cost-effective based on these deterministic results. When addressing the uncertainty surrounding the ICER using bootstrapping techniques FFS did have the highest probability of being the most cost-effective of the three techniques. Yet, the difference in probability between FFS and CON was small and the decision therefore highly uncertain.

The detailed cost analysis showed that patients undergoing FFS incurred lower hospital related costs. However, when taking all cost categories into account, overall costs were higher in the FFS. Notable differences between groups were the higher use of home care nursing, paid help, and informal care when flap fixation was applied compared to conventional wound closure. Patients who underwent conventional

Table 5
Mean costs per patient (in Euros) over twelve months.

Cost category	Mean costs in twelve months (Euros)		
	CON (n = 53)	FFS (n = 46)	FFG (n = 47)
Health care costs			
General practitioner	46	49	45
Additional hospital visit (OPD or ER)	116	67	123
Physical therapist/ lymph edema therapist	871	959	849
Other health care professionals	144	133	120
Home care domestic	693	326	323
Home care nursing	899	1.159	1.180
Medication	17	22	25
Antibiotics	6	2	10
Pain medication	5	10	7
Wound treatment	5	6	4
Anxiolytics	0.1	1	0
Alternative medicine	1	3	4
Surgery per fixation method	1.850	1.993	1.972
Postoperative surgery	110	36	124
Postoperative readmission	283	143	293
Negative pressure wound therapy	56	28	28
Medical devices	314	419	308
External breast prosthesis	247	295	200
(Prosthesis) bra	118	136	112
Wound dressings	4	6	1
Compression stockings	26	42	31
Clothes	49	90	74
Mobility enhancing devices	4	0	4
Subtotal health care costs (95% bootstrapped CI)	5.530 (4.641–6.468)	5.489 (4.318–7.109)	5.508 (4.631–6.413)
Patient and family costs			
Paid help	430	756	412
Informal care	1.872	2.495	2.772
Out of pocket costs	66	131	77
Subtotal (95% bootstrapped CI)	2.368 (1.694–3135)	3.380 (2.308–4.661)	3.261 (2.260–4.528)
Cost of lost production			
Paid work	2.153	1.546	1.478
Subtotal (95% bootstrapped CI)	2.153 (1.060–3.282)	1.546 (590–2.642)	1.478 (496–2.575)
Subtotal non-health care costs (95% bootstrapped CI)	4.521 (3.156–5.969)	4.927 (3.362–6.556)	4.739 (3.411–6.242)
Total costs (95% bootstrapped CI)	10.051 (8.255–12.044)	10.416 (8.231–12.930)	10.248 (8.564–11.777)

CON = conventional closure, FFS = flap fixation with sutures, FFG = flap fixation with tissue glue, OPD = outpatient department, ER = emergency room, CI = confidence interval.

wound closure reported high costs due to productivity loss, compared to the patients undergoing flap fixation. This may partly be explained by the slightly higher proportion of patients receiving chemotherapy treatment in this group; this requires time from work, and these hours may have been reported. The possible reporting of breast cancer related costs rather than mastectomy related costs is a particular challenge for this economic evaluation. It may not have been easy, or perhaps maybe impossible, for patients to discern mastectomy related resource use from resource use related to breast cancer in general. Even though the cost surveys included specific instructions (for every question) to include

Table 6
Results of the base case analysis (societal perspective).

	Mean costs (95% CI)	Difference in costs	Mean QALYs (95% CI)	Difference in QALYs	ICER: Diff. costs/ diff. QALYs
CON[a]	10.051	–	0.794	–	–
FFS	10.416	365	0.810	0.016	22.813
FFG	10.248	197	0.781	−0.013	Dominated

CI = confidence interval, QALYs = quality-adjusted life years, ICER = incremental cost-effectiveness ratio, CON = conventional closure, FFS = flap fixation with sutures, FFG = flap fixation with tissue glue.
[a] Conventional wound closure is comparator.

mastectomy related costs only, we expect that some patient-reported costs were due to breast cancer in general. However, there is no reason to expect that this occurred unevenly between the three groups, but it may have reduced accuracy and increased the uncertainty surrounding the ICER. To address the uncertainty surrounding patient-reported costs and assess the robustness of our findings, several secondary analyses were performed. Firstly, patient-reported cost categories were excluded in two secondary analyses (i.e. hospital and health care perspective). Notably, FFS dominated the two other techniques in both scenarios, i.e. it resulted in lower (health care and hospital) costs and in more QALYs. Furthermore, we explored the impact of adjusting for baseline differences in patient-reported costs [34]. In this analysis,

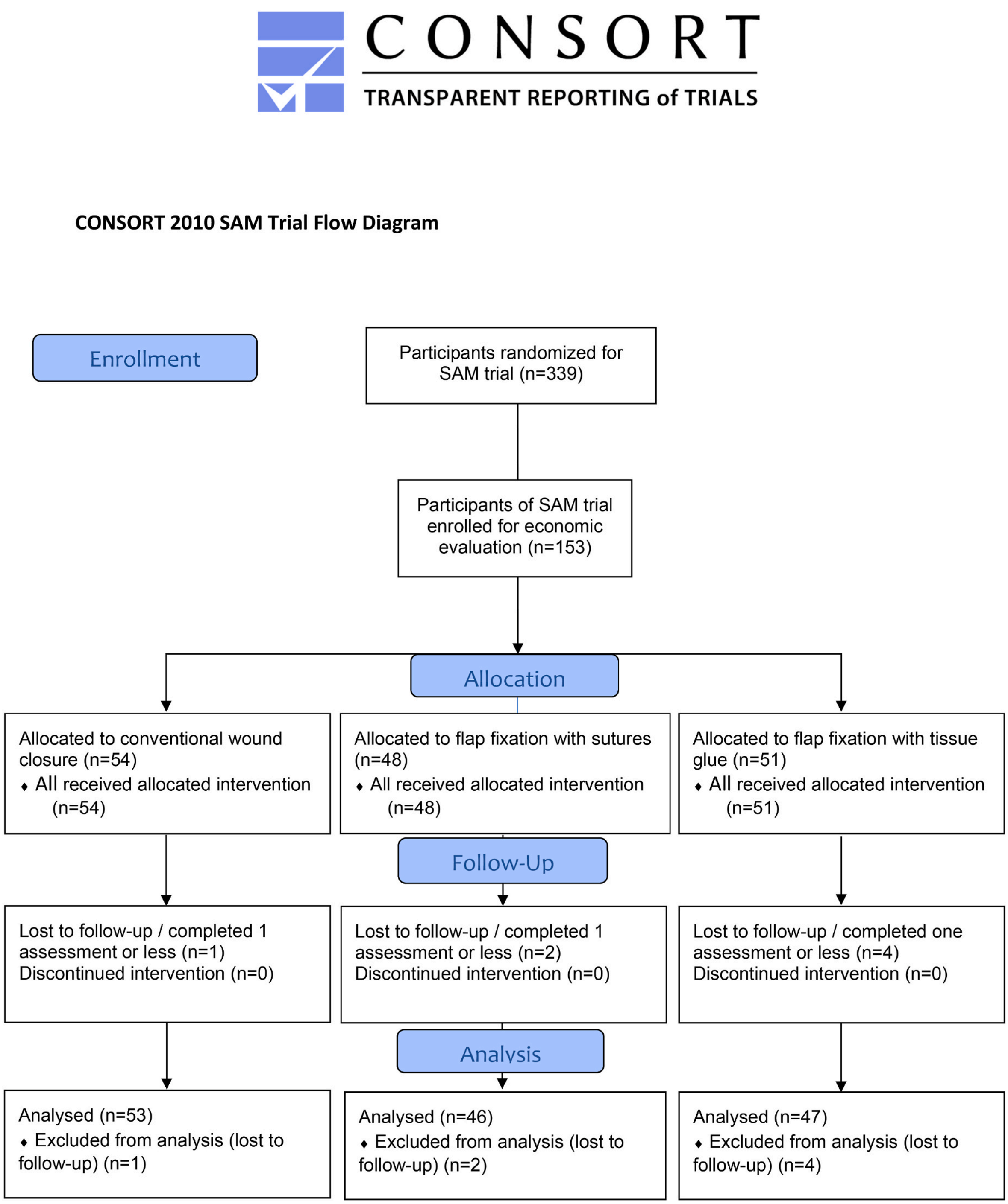

Fig. 2. The probability of cost-effectiveness of the three different techniques at different cost-effectiveness thresholds.

only the (individual) change in resource use reported was included in the cost calculations. This analysis resulted in an ICER of €9.125 per QALY and a higher probability that FFS would be the most cost-effective technique.

The total costs of the intervention were highest for FFS. When interpreting the results, it should be taken into consideration that the additional costs for the surgical procedure for FSS, based on 10 min added operating time, was a conservative estimate. We added €14 per minute of operating time, which may be an overestimation since it does not take into account the fixed costs of the surgery, costs incurred regardless of the exact duration. However, the costs outside the hospital, following the intervention, ultimately led to the higher costs for FFS and impacted the results of the economic evaluation.

Overall, in the base case analysis, there was considerable uncertainty regarding the most cost-effective technique, but secondary analyses showed that FFS was the most cost-effective technique in reducing seroma aspirations following mastectomy if one would take a hospital or health care perspective.

Some limitations of our study need to be addressed. First, the importance of an economic evaluation was acknowledged after the start of the RCT, resulting in only 45% of the total number of RCT patients being included in these analyses. Hence, the study may be considered to be underpowered. However, sample size calculations in trial-based economic evaluations are rarely based on economic outcomes, but usually on a clinical outcome measure (e.g. the need for seroma aspiration in the SAM-trial). This generally does not interfere with the quality of the economic evaluation, since the analysis is typically not concerned with testing a predefined hypothesis (using traditional statistical methods), but aims to support health policymakers in making resource allocation decisions. To achieve this, the average costs and effects of comparative interventions along with indicators of uncertainty are estimated, represented by bootstrap analyses and cost-effectiveness acceptability curves [30,36,37]. Health policymakers then decide what probability of cost-effectiveness is acceptable for choosing one technique over another. Hence, this economic evaluation still provides powerful information for decision-makers. Second, patient-reported costs were collected retrospectively, potentially causing some recall bias (e.g. some resource use may have been forgotten or overestimated). Nevertheless, a recall period of three months is considered most appropriate and provides reliable data [35].

Finally, this economic evaluation had a time horizon of one year, in line with the follow-up of the SAM-trial, and therefore we have no information about the long-term cost-effectiveness of FFS. However, it is to be expected that the most relevant differences in costs and effects would show in the first year following treatment. Findings of the study reveal relatively small differences between the techniques and it is therefore not expected that long-term results would differ substantially from the findings in this trial.

This economic evaluation has several unique strengths that should be mentioned. To the best of our knowledge, this study was the first to evaluate the cost-effectiveness of multiple flap fixation techniques and conventional wound closure following mastectomy. This finally sheds a different light on an ancient problem of tackling seroma formation and its sequelae. We compared three different techniques and therefore offer a broader perspective than only comparing flap fixation versus no flap fixation. The economic evaluation reported here was conducted according to a nationally agreed design and reporting guidelines [19]. It was based on a pragmatic randomized, multicenter, controlled trial that avoids many of the selection biases and provided a vehicle to comprehensively assess resource use and HRQoL outcomes. The cost analysis was rigorous and included all relevant resource items for the health care and societal perspective, with very low missing data due to high completion rates of the surveys and the use of hospital information systems. Difficulties with skewed cost data were tackled by using appropriate bootstrap techniques. Due to the pragmatic and multicenter nature of the RCT, it is expected that the resource use and effectiveness outcomes closely reflect what would be observed in daily practice. While the study was performed in four clinics in the Netherlands, results can be generalized to other settings. The study population was representative of the breast cancer population in The Netherlands undergoing mastectomy, in terms of age, level of education and tumor stage. Further, to support transferability to other countries, volumes of resource use were reported separately for all cost categories.

5. Conclusions

Health policy makers should consider both clinical and economic outcomes when deciding on the allocation of scarce resources. Flap fixation with sutures following mastectomy has been proven clinically effective in reducing seroma formation. The economic evaluation showed that there was considerable uncertainty surrounding the cost-effectiveness from a societal perspective of FFS compared to FFG and CON. From a health care and hospital perspective, however, FFS dominated the other two techniques in terms of costs and QALYs.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Preregistration

The trial was registered after enrollment of the first participant without analysis plan. However, there is no specific explanation for this other than that through the years more importance has been given to central trial registration. Our research team can assure that after enrollment of the first participant no changes were made to the trial, analysis plan and/or study design.

CRediT authorship contribution statement

L. De Rooij: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **M.L. Kimman:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **M.A. Spiekerman van Weezelenburg:** Writing – original draft, Writing – review & editing, Visualization. **S.M.J. van Kuijk:** Formal analysis, Investigation. **R.W.Y. Granzier:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **K.F.H. Hintzen:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **C. Heymans:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **L.L.B. Theunissen:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **E.R.M. van Haaren:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **A. Janssen:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **Y.L.J. Vissers:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **G.L. Beets:** Writing – review & editing, Supervision. **J. van Bastelaar:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Visualization, Supervision.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.107003.

References

[1] Kumar S, Lal B, Misra MC. Post-mastectomy seroma: a new look into the aetiology of an old problem. J R Coll Surg Edinb 1995;40:292–4.
[2] Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery; incidence and predicting factors. Am Surg 2000;66(5):444–50.
[3] Carless PA, Henry DA. Systematic review and meta-analysis of the use of fibrin sealant to prevent seroma formation after breast cancer surgery. Br J Surg 2006;93(7):810–9.
[4] Agrawal A, Ayantunde AA, Cheung KL. Concepts of seroma formation and prevention in breast cancer surgery. ANZ J Surg 2006;76(12):1088–95.
[5] Srivastava V, Basu S, Shukla VK. Seroma formation after breast cancer surgery: what we have learned in the last two decades. J Breast Cancer 2012 Dec;15(4):373–80.
[6] Van Bastelaar J, Theunissen LLB, Snoeijs M, Beets G, Vissers Y. Flap fixation using tissue glue or sutures appears to reduce seroma aspiration after mastectomy for breast cancer. Clin Breast Cancer 2017 Jul;17(4):316–21.
[7] Van Bastelaar J, van Roozendaal L, Granzier R, Beets G, Vissers Y. A systematic review of flap fixation techniques in reducing seroma formation and its sequelae after mastectomy. Breast Cancer Res Treat 2018 Jan;167(2):409–16.
[8] Currie A, Chong K, Davies GL, Cummins RS. Ultrasonic dissection versus electrocautery in mastectomy for breast cancer - a meta-analysis. Eur J Surg Oncol 2012 Oct;38(10):897–901.
[9] Khan S, Chawla T, Murtaza G. Harmonic scalpel versus electrocautery dissection in modified radical mastectomy: a randomized controlled trial. Ann Surg Oncol 2014 Mar;21(3):808–14.
[10] Ko E, Han W, Cho J, et al. Fibrin glue reduces the duration of lymphatic drainage after lumpectomy and level II or III axillary lymph node dissection for breast cancer: a prospective randomized trial. J Kor Med Sci 2009 Feb;24(1):92–6.
[11] Almond LM, Khodaverdi L, Kumar B, Coveney EC. Flap anchoring following primary breast cancer surgery facilitates early hospital discharge and reduces costs. Breast Care (Basel) 2010;5(2):97–101.
[12] Sakkary MA. The value of mastectomy flap fixation in reducing fluid drainage and seroma formation in breast cancer patients. World J Surg Oncol 2012;10:8.
[13] Ten Wolde B, van den Wildenberg FJ, Keemers-Gels ME, Polat F, Strobbe LJ. Quilting prevents seroma formation following breast cancer surgery: closing the dead space by quilting prevents seroma following axillary lymph node dissection and mastectomy. Ann Surg Oncol 2014;21:802–7.
[14] Benevento R, Santoriello A, Pellino G, et al. The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node dissection for breast cancer. A randomized controlled trial. Int J Surg 2014 Nov;12(11):1210–5.
[15] Eichler C, Fischer P, Sauerwald A, Dahdouh F, Warm M. Flap adhesion and effect on postoperative complication rates using Tissuglu® in mastectomy patients. Breast Cancer 2016;23:486–90.
[16] Vasileiadou K, Kosmidis C, Anthimidis G, Miliaras S, Kostopoulos I, Fahantidis E. Cyanoacrylate adhesive reduces seroma production after modified radical mastectomy or quadrantectomy with lymph node dissection-A prospective randomized clinical trial. Clin Breast Cancer 2017 Dec;17(8):595–600.
[17] De Rooij L, van Kuijk SMJ, Granzier RWY, Hintzen KFH, Heymans C, Theunissen LLB, et al. Reducing seroma formation and its sequelae after mastectomy by closure of the dead space: a multi-center, double-blind randomized controlled trial (SAM-Trial). Ann Surg Oncol 2020 Oct 19. https://doi.org/10.1245/s10434-020-09225-8.
[18] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. fourth ed. Oxford: Oxford: Oxford University Press; 2015.
[19] Hakkaart–van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Diemen. The Netherlands: Zorginstituut Nederland; 2015.
[20] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Cost Eff Resour Allocation 2013;11(6):f1049. https://doi.org/10.1186/1478-7547-11-6.
[21] Earnshaw J, Lewis G. NICE guide to the methods of technology appraisal: pharmaceutical industry perspective. Pharmacoeconomics 2008;26(9):725–7.
[22] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727–36. https://doi.org/10.1007/s11136-011-9903-x. Epub 2011 Apr 9. PMID: 21479777; PMCID: PMC3220807.
[23] Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value Health 2016;19:343–52.
[24] Bouwmans C, Roijen L, Koopmanschap MA, Krol M, Severens H, Brouwer W, et al. Handleiding iMTA medical cost questionnaire (iMCQ). 2013.
[25] Goossens ME, Rutten-van Mlken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. J Clin Epidemiol 2000;53(7):688–95.
[26] 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(2):171–89.
[27] Statistics Netherlands. In: Statline. Den Haag. <http://statline.cbs.nl> [accessed July 2020].
[28] van Buuren S. Flexible imputation of missing data. Chapman & Hall/CRC Interdisciplinary Statistics; 2012.
[29] Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. c332 BMJ 2010 Mar 23:340. https://doi.org/10.1136/bmj.c332. PMID: 20332509; PMCID: PMC2844940.
[30] Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999;18(3):341–64. https://doi.org/10.1016/s0167-6296(98)00039-3.
[31] Briggs Wonderling, Mooney. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997;4:327–40.
[32] Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10(8):779–87.
[33] (in Dutch) Recommendations produced by the Council for public health and health care to the minister of health, welfare and sport. Sensible and sustainable care. Zoetermeer; 2006. PDF online.
[34] van Asselt AD, van Mastrigt GA, Dirksen CD, Arntz A, Severens JL, Kessels AG. How to deal with cost differences at baseline. Pharmacoeconomics 2009;27(6):519–28. https://doi.org/10.2165/00019053-200927060-00007. PMID: 19640014.
[35] Goossens ME, Rutten-van Mölken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. J Clin Epidemiol 2000 Jul;53(7):688–95. https://doi.org/10.1016/s0895-4356(99)00177-8. PMID: 10941945.
[36] O'Sullivan AK, Thompson D, Drummond MF. Collection of health-economic data alongside clinical trials: is there a future for piggyback evaluations? Value Health 2005;8:67–79.
[37] Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting [published online]. BMJ 2011;342:d1548. https://doi.org/10.1136/bmj.d1548.