Cost-effectiveness and quality of life in surgeon versus general practitioner organised colon cancer surveillance. A randomised controlled trial.

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Cost-effectiveness and quality of life in surgeon versus general practitioner organised colon cancer surveillance. A randomised controlled trial.

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Abstract

Objective: To assess whether colon cancer follow-up can be organised by general practitioners (GPs) without decline in patient quality of life (QoL), increase in cost, or increase in time to cancer diagnoses, compared to hospital follow-up.

Design: Randomised controlled trial.

Setting: Northern Norway Health Authority Trust, 4 trusts, 11 hospitals and 88 local communities.

Participants: Patients surgically treated for colon cancer, hospital surgeons and community GPs.

Intervention: 24 month follow-up according to national guidelines at the community general practitioner office. To ensure a high follow-up guideline adherence, a decision support tool for patients and GPs were used.

Main outcome measures: Primary outcome were QoL, measured by the global health scale of EORTC-QLQC30, and EQ-5D. Secondary outcomes were cost-effectiveness and time to cancer diagnoses.

Results: 110 patients were randomised to intervention (n=55) or control (n=55), and followed by 78 GPs (942 follow-up months) and 70 surgeons (942 follow-up months), respectively. Compared to baseline, there was a significant improvement in postoperative QoL (p=0.003), but no differences between groups were revealed (mean difference at 1,3,6,9,12,15,18,21 and 24 month follow-up appointments): Global Health; Δ – 2.23, p=0.20; EQ-5D index; Δ – 0.10, p=0.48, EQ-5D VAS; Δ -1.1, p=0.44. There were no differences in time to recurrent cancer diagnosis (GP 35 days vs. surgeon 45 days, p=0.46), 14 recurrences were detected (GP 6 vs. surgeon 8) and 7 metastases surgeries performed (GP 3 vs. surgeon 4). The follow-up program initiated 1186 health care contacts (GP 678 vs. surgeon 508), 1105 diagnostic tests (GP 592 vs. surgeon 513) and 778 hospital travels (GP 250 vs. surgeon 528). GP organised follow-up was associated with societal cost savings (£8233 vs. £9889, p<0.001).

Conclusion: GP organised follow-up was associated with no decline in QoL, no increase in time to recurrent cancer diagnosis and cost savings.

Trial registration: ClinicalTrials.gov identifier NCT00572143.

Article summary:

Article focus:

- Intensive follow-up after curative colon cancer resection is associated with improved overall survival of 5-10%.
- No international consensus exist regarding the detailed content of a follow-up program for colorectal cancer .
- Quality of life (QoL), cost-effectiveness and patient safety in a GP organised follow-up program is unknown.

Key messages:

- GP organised colon cancer follow-up is associated with no decline in QoL, no increase in time to recurrent cancer diagnosis, and cost savings.

Strengths and limitations of this trial:

- Intention to treat analyses with high adherence to the national follow-up program.
- First trial assessing cost-effectiveness of a GP organised colon cancer follow-up program.
- The trail was stopped after 1884 patient follow-up months due to no impact of the intervention on global health status.
- 52% of included patients were followed for two years. This limits the interpretation of recurrence, as 80% of colon cancer recurrences occurs within three years.

Background

Colon cancer is the third most common cancer in the western world, and surgery is the only curative treatment. Around one-third of those resected will experience recurrent disease with less than two years expected survival. [1,2] Despite the generally poor outcomes among patients with recurrent disease, most patients treated with curative intent are included in some form of surveillance program involving periodic evaluation. Reviews comparing various follow-up programs have suggested that more intensive strategies tend to increase five-year survival by detecting relapse about six months earlier than less intensive strategies — at a point where the patient will be more likely to be considered a candidate for potentially curative metastases surgery. [2-4] However,

wide consensus has not been reached regarding just what an intensive follow-up strategy should entail. [5-8] New surveillance trials in progress are not likely to fully settle the issue either. [9-12] What none of the available clinical recommendations for follow-up have addressed adequately is the *setting* where this follow-up should occur: conducted by specialists who originally treated the cancer at hospitals, or in the offices of local general practitioners (GP's). [2] Increasingly, the benefits of greater involvement of primary care providers in the on-going management of chronic illnesses are recognised. [13] Level of follow-up care may greatly influence quality of life and costs, especially in rural areas with long distances to travel for hospital services. However, such considerations must be balanced against the imperative that colon cancer survivors receive the best care available. Recently, the UKs National Cancer Survivorship Initiative recognised the need to develop new models of cancer care that support patient self care, care planning and making the best out of resources.[14] In Norway, similar national initiatives have been launched. In this trial, we tested the main hypothesis that colon cancer patients followed-up by their GP would experience similar or higher scores on quality of life measures at a lower cost than alternative hospital controls. The other aims were to test for differences of harms and benefits in a follow-up program, i.e. rate of serious clinical events (SCE), time to diagnosis of SCE and cancer recurrence, and frequency of metastases surgery.

Methods

This was a randomised controlled multicentre trial carried out in North Norway Health Authority trust using a previously published protocol. [15] The first patient was included 1st of June 2007, the last patient included 15th of December 2011. Interim analyses were performed in June 2012.

Ethics and trial registration

The Regional Committee for Medical Research Ethics, North Norway approved this protocol in 2006 (P REK NORD 79/ 2006). Patients provided written consent before entering the trial. The trial was registered in ClinicalTrials.gov with identifier NCT00572143. Due to organisational delay the trial was registered 11th of December 2007, specified study start in ClinicalTrials.gov is June 2007.

Inclusion and exclusion criteria

Inclusion criteria were age less than 75 years with recent surgery for colon cancer with Dukes' stage A, B or C. Patients receiving postsurgical adjuvant chemotherapy (some Dukes' B and all Dukes' C) were also eligible. Exclusion criteria were patients older than 75 years old, patient belonging to health care trust not participating in the trial, not able to provide informed consent and Dukes D.

Hospitals, primary and secondary care professionals

Three local hospitals and one university hospital participated. Approximately 100 patients with colon cancer are surgically treated annually at these four hospitals. All 550 GPs in the region received written information, 448 GPs consented to participate in the trial.

Objective and hypotheses

The primary objective was to compare patients' quality of life and costs of follow-up by their local GP or at the surgical outpatient clinic. The primary hypothesis was that patients followed-up by their GP would experience similar or better QoL scores (on the global health scale) at a lower cost. The secondary objective was to test whether the incidence of serious clinical events (SCE) would be similar for patients followed- up by their GP or hospital specialist (control group), secondary hypothesis being that patients followed-up by their GP would have no delay in detection of relapse and the same frequency of SCEs as controls.

Description of intervention

We defined this as a complex intervention, consisting of several interconnecting parts. [16] To ensure high follow-up guideline adherence by patients allocated to GP follow-up, we used a decision support tool as part of the intervention. [17] Thus, the intervention consisted of the following parts:

1. *GP organised colon cancer follow-up:* The patients were referred to their general practitioner for postoperative follow-up according to national guidelines (table 1). Information was given about surgery, any complications, Dukes' staging, time and location of chemotherapy (for Dukes' C patients), and risk of recurrence.
2. *Patient decision-support pamphlet:* Received at the baseline consultation,

containing information about; a) Their own disease, tumour stage and risk of recurrence; b) The aim and objective of the trial; b) The current national follow-up guidelines, i.e. schedule and location of CEA measurements, chest x-ray, contrast enhanced liver ultrasound, colonoscopy and clinical examination; b) A detailed description of signs and symptoms of potential recurrence of colon cancer; c) In case of a serious clinical event between appointments, relevant phone numbers and contact information was given.

3. *GP decision-support pamphlet:* Sent at time of baseline appointment to all GPs that had a patient allocated to their practice. This pamphlet contained similar information as the patient received i.e. information about follow-up guidelines, signs and symptoms of recurrence and behavioural strategy in the case suspicion of a recurrence. In case of questions regarding the follow-up relevant contact information was given.

Patients allocated to GP follow-up could be referred back to any surgical clinic at any time during the study period. Similarly, patients in the hospital follow-up group (controls) were free to consult their GP at any time. National follow-up guidelines were applied in both study arms and patients were followed for up to two years. The follow-up period consisted of nine follow-up cycles with regular clinical examinations, CEA measurement, chest x ray, contrast enhanced liver ultrasound and colonoscopy (table 1).

Table 1. Norwegian Gastrointestinal Cancer Group (NGICG) 2007 follow-up program.

Examination/test	**Follow-up cycle (months postoperative)**														
	1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Chest x-ray			X		X		X		X		X		X		X
Contrast enhanced liver ultrasound (CEUS)			X		X		X		X		X		X		X
Colonoscopy					X								X		
CEA measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Red: Length of trail participation (24 months, 9 follow-up cycles). CEA: carcinoembryonic antigen.

Randomisation

At study entry, patients were seen for a baseline visit by a local trial investigator at the

hospital where they received surgical treatment approximately 3-4 weeks postoperatively. At this visit, a clinical examination was performed and information about the histology and results of the surgery was shared with each patient. If the patients provided informed consent, they were randomised to follow-up either by their GP (intervention) or at the surgical outpatient clinic (controls) using a web-based randomisation service managed by the Norwegian University of Science and Technology (www.ntnu.no). The randomisation ratio was 1:1, patients were stratified according to the Dukes' staging (A,B,C) and whether they had a stoma. The local trial investigator was not involved in the subsequent follow-up appointments in any way. Recruited patients were not informed about other patients recruited in the same trial. Similarly, no information regarding trial progress and allocation was revealed to participating GPs or surgeons. However, as GP organised follow-up represented a new practice, blinding was not possible in the intervention arm.

Primary outcome measures

Quality of life

Primary outcome measure in this trial was the global health status on the EORTC QLQ C-30 questionnaire. QoL measurements were collected at baseline and 3,6,9,12,15,18,21 and 24 months, i.e:

The European Organization for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ C-30): EORTC QLQ C-30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, nausea/vomiting); and a global health status/QOL scale. Six single-item scales are also included (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).[18]

The EuroQol–5D (EQ-5D™; EuroQol Group, Rotterdam, The Netherlands): Is a standardized generic instrument employed to measure of health outcome. EQ-5D measures five dimensions of health-related QoL (HRQOL): 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).[19] Based on preferences elicited from a general population, EQ-5D health states (e.g. 1-1-2-1-3) may

be converted into utility scores (= index scores, IS). In this trial we used preferences elicited from a UK population, as no similar Norwegian preferences exist. [20]
EQ Visual Analogue Scale (EQ VAS) records the respondent's self-rated health status on a vertically graduated (0–100) visual analogue scale.

Secondary outcome measures

Cost-effectiveness

Resources used (baseline to 24 months) were registered prospectively based on reports by the patients and on hospital EMR review. The cost elements included costs related to hospital visits, GP visits, laboratory tests, radiology examinations, colonoscopy, examinations due to suspected relapse (radiology, colonoscopy, CT of thorax and/or abdomen, PET scan), treatment of recurrence, travelling/transportation, production losses, co-payments and other patient/family expenses.

Time to cancer diagnoses

Time to cancer diagnoses was defined as the time from occurrence of a serious clinical event (SCE, dated in the GP referral or hospital EMR record) until the date of diagnoses of a SCE. A SCE was defined as an episode were cancer recurrence was suspected. A SCE can be triggered by either symptoms reported (at follow-up or in between follow-up), clinical findings at follow-up or findings by screening test. Symptoms and clinical findings initiating a diagnostic check-up were defined as: Cancer suspect lesion revealed at colonoscopy, increase in CEA measurements shown by repeated measurements, blood in stool detected by the Hemofec (FOB) test, unexplained abdominal pain, unexplained weight loss of 5 kg during the last three months, cancer-suspect lesions detected by rectal examination, palpable lymphandenopathy, metastatic suspect lesions shown by chest x-ray, ultrasound of liver or CT scan, cancer suspect findings at clinical examination, occurrence of cancer related symptoms.

Data collection

At the baseline appointment, patients recruited received nine questionnaires (as part of the patient decision-support pamphlet) corresponding with the nine follow-up cycles (table 1). The questionnaires contained questions about QoL, patient satisfaction, and

cost and resource utilisation. Questionnaires were returned by mail every three months by the patients to the trial centre until 24 months postoperatively. These questionnaires were optically readable, being consecutively registered in the trial database. A research assistant was responsible for data collection, database input and patient reminders when missing questionnaires. The reminders were sent to participating patients when the questionnaires were 3 months overdue the estimated follow-up schedule. All questionnaires were dated and we could thus monitor trial progression. In case of missing information about cost elements we either reviewed the hospital EMR, or performed telephone interview with participating surgeons, GPs or patients.

Sample size calculation

In June 2007 sample size calculations were based on a significance level of 5% and power set at 80%, this indicated that we needed 136 patients to detect a 10 units QoL difference (i.e. a small to moderate improvement) on EORTC QLQ C-30 Global Health score with a standard deviation of 20. Definition of "a small to moderate improvement on QoL" (i.e 10 units on the global health score), and standard deviation estimates of QoL (colon cancer patients with localised disease), were retrieved from previous published publications.[21,22]

Economic analysis

BMJ guidelines for economic analyses alongside randomised controlled trails were employed. [23] As the trial revealed no difference in quality of life, a cost-minimisation analysis was carried out. The economic evaluation had a societal perspective. A 3% discount rate was used to discount future costs and benefits. For this publication cost elements have been converted from Norwegian kroner (NOK) into British Pounds at the rate of GBP 1£ = NOK 9,39 NOK as of the Norwegian National Bank the 27th of June 2012. Details of the unit costs assigned to health care resource use are shown in table 2. Economic evaluation data are invariably positively skewed, and it requires an alternative analysis. We used a bootstrapping technique, which makes no assumptions regarding the equality, variance or shape of the distribution, and takes into account skewness. [24,25] To adjust for skewness cost were bootstrapped with 1000 replications to estimate bias corrected confidence intervals. The bootstrapping technique was undertaken using IBM SPSS Statistics v 19.0

A one-way sensitivity analysis was used to assess the robustness of the results and impact of variance. Societal cost of 24-month follow-up was assessed for low, base and high input values, and the result expressed as a many inputs, one output tornado chart. To increase generalizability of cost between countries, unit costs from the UK were included in the sensitivity analyses. Cost for GP consultation and diagnostic testing, has been reported to be 30-40% higher than units cost applied in this trial and relevant cost elements were increased accordingly in sensitivity analyses.[26]

Table 2. Details of the unit costs assigned to health care resource use data.

Variable	Unit cost (£)*	Sensitivity analyses
Cost of travel		± 25%
Mean costs hospital travel	88 [a]	
Hotel overnight	74 [b]	
Private car rates	0.2 per km [c]	
Parking	10.6 [b]	
Taxi	1.3 per km [c]	
Bus	2.6 [c]	
Cost of GP consultation		± 25- 40%
GP consultation 20 min	18.5 [d]	
Phone consultation GP 10 min	5.3 [d]	
Emergency consultation GP 30 min	26 [d]	
Cost of surgeon outpatient consultation		± 25-40%
Surgeon outpatient consultation 30 min	69 [e]	
Phone consultation surgeon 15 min	10.6 [f]	
Emergency outpatient consultation 30 min	69 [e]	
Cost of follow-up tests		± 25-40 %
Blood samples	5 [d]	
Chest-X-ray	25 [g h]	
Contrast enhanced ultrasound liver	153 [g h]	
CT abdomen	105 [g h]	
CT thorax	105 [g h]	
Colonoscopy	293 [e h]	
PET scan	2662 [g]	
Cost related to sick leave		± 25%
Governmental reimbursement 1 day work absence	102 [i]	
Costs related to metastases surgery		± 25%
Cost of abdominal surgery	14176 [e]	
Cost of liver surgery	11596 [e]	
Cost of lung surgery	13061 [e]	

* Exchange rate 29th of June 2012: 1 £ = 9.36 Norwegian Kroner: www.dnb.no/en/currencylist?la=EN&site=DNB_NO

[a] Personal communication North Norwegian Health Administration (JN): 5 400 000 NOK budgeted annual travel expenses/950 000 annual patient travels = 88 £ per travel

[b] Local data.

[c] Norwegian National Bureau of Patient Travels: http://www.pasientreiser.no/andre-spraak/english.

[d] The Norwegian Medical Association: Norwegian Policy Document for Governmental Reimbursements in Primary Care (Fastlegetariffen) 2011: www.legeforeningen.no/normaltariff/Fastlegetariff_2010.pdf. *Cost of GP consultation:* 136 NOK (20 min consultation) + 386 NOK per patient annually. Assuming 10 consultations per patient annually = 38 NOK/consultation. In total 174 NOK per consultation = 18.5 £.
[e] Norwegian Health Authorities. Reimbursement and DRG weighting in Norwegian Hospitals 2012: http://www.helsedirektoratet.no/publikasjoner/regelverk-innsatsstyrt-finansiering-2012/Sider/default.aspx.
1 DRG weight: 38209 NOK. *Surgeon outpatient consultation (day and night-time):* DRG 923 O, weight 0.017. *Colonoscopy:* DRG 710 O, weight 0.072. *Abdominal surgery:* DRG 170, weight 3.484. *Liver surgery:* DRG 201, weight 2.850. *Lung surgery:* DRG 76, weight 3.21
[f] Statistics in Norway 2011: Average annual salary 750 000 NOK (80 000 £) hospital consultant.
[g] Cost rates Department of Radiology and Nuclear Medicine University Hospital North Norway.
[h] Korner H. Soreide K. Stokkeland PJ. Soreide JA. Systematic follow-up after curative surgery for colorectal cancer in Norway: a population-based audit of effectiveness. costs. and compliance. J Gastrointest Surg 2005 Mar;9(3):320-8.
[i] Estimated from a median income of 350 000 NOK/year/patient as reported by patient subsample in regular work at time of surgery.

Statistics

Descriptive statistics were performed by percentages, 2x2 contingency tables, Chi Square, Fisher Exact test and t-test. The base case analyses (n=110, 600 complete follow-up questionnaires/cycles) were performed on intention to treat principle. Treatment arms were compared with respect to potential covariates using continuous and categorical univariable analyses. The main analyses examined whether differences in outcome between baseline, 3, 6, 9, 12, 15, 18, 21 and 24 moths existed in all QoL outcome measures (EORTC QLQ C-30 and EQ-5D). A general linear model was employed, where time (1-24 months) and intervention group (GPs versus Surgeon) were predictors in analyses of variance (between groups ANOVA). Missing items in a form and when missing forms, missing data were imputed by the last observation carried forward (LOCF). Conditional power (CP) was defined as the chance of getting statistically significant results at the end of the trial given the data so far. [27,28] We defined a CP < 15% as a sufficient threshold to stop early.[29] Results were expressed as mean differences for continuous outcomes with corresponding standard deviations (SD), 95% confidence intervals, and associated p-values. P-values were reported with two decimal places with p-values less than 0.001 reported as $p < 0.001$. For all tests we used $p = 0.05$ level of significance. All analyses were performed with IBM SPSS Statistics v 19.0 (IBM Company SPSS 2010) and Microsoft Excel for Mac 2011.

Results

110 patients surgically treated for colon cancer met the inclusion criteria and agreed to participate (figure 1). The control and intervention group were matched at baseline for

demographic and medical characteristics and there were no significant differences between groups (table 3).

Trial flow and dropouts

85 patients (75%) (GP 41 vs. surgeon 44) were followed for 12 months, 58 patients (52%) (GP 29 vs. surgeon 29) were followed for 24 months . 32 patients were defined as lost (surgeon 17 vs. GP 15), of those 14 patients had cancer recurrence (surgeon 8 vs. GP 6). 20 patients (surgeon 9 vs. GP 11) were transferred to the new national colon cancer surveillance program (figure 1).

Response rate

We received 636 of the expected 657 questionnaires (response rate 96%), of those 600 (91%) questionnaires (GP 299 vs. surgeon 301) were included in final cost and QoL analyses. 21 (4%) of questionnaires (surgeon 11 vs. GP 10) were not returned and 36 questionnaires (surgeon 18 vs. GP 18) were excluded from analyses due to insufficient identification.

Interim analyses

New national colon cancer surveillance guidelines were gradually implemented from 2010, with different frequency of consultations (3 month vs. 6 months interval) and radiological modalities (chest x ray vs. CT chest). [7] This could bias the cost-effectiveness and QoL analyses, and an interim analysis was performed in June 2012 (80% of pre planned recruitment, 1884 follow-up months). There was at this point 4% probability (i.e. conditional power) of showing a significant impact of the intervention on QoL global health score, which meant that further trial continuation were not justified.

Table 3. Baseline demographics and clinical characteristics.

Variable	Surgeon (%) n=55	GP (%) n=55	Total (%) n=110	p value
Age group				
< 50	2 (3·6)	6 (10·9)	7 (6·3)	0.10
50-59	8 (14·5)	6 (10·9)	14 (12·7)	0.56
60-69	23 (41·8)	24 (43·6)	47 (42·7)	0.84
70-75*	22 (40·0)	19 (34·5)	41 (38·0)	0.55

Mean age (SD)	66·7 (7·3)	64·0 (8·7)	65·4 (8·1)	0.09
Gender				
Male	32 (58·2)	33 (60·0)	65 (59·1)	0.84
Female	23 (41·8)	22 (40·0)	45 (40·9)	0.84
Education				
Primary	20 (36·3)	18 (32·7)	38 (34·5)	0.68
Secondary	21 (38·1)	25 (45·4)	46 (41·8)	0.49
University < 4yrs	8 (14·5)	5 (9·0)	13 (11·8)	0.37
University > 4 yrs	6 (10·9)	7 (12·7)	13 (11·8)	0.76
Income level				
Median (£)	32-42 000	32-42000	32-42000	
Main activity				
Employment	12 (21·8)	17 (30·9)	29 (26·3)	0.27
Home	3 (5·4)	9 (16·3)	11 (10·0)	0.06
Out of work	0 (0)	1 (1·8)	1 (0·9)	
Pensioner	40 (72·7)	28 (50·9)	68 (61·8)	0.01
Location of surgery				
University hospital (n=1)	34 (61·8)	37 (67·3)	71 (64·5)	0.55
Local hospital (n=3)	21 (38·1)	18 (32·7)	39 (35·4)	0.55
Clinical characteristics				
Tumour location				
Køkum	13 (23·6)	13 (23·6)	26 (23·6)	1.0
Ascendens	9 (16·3)	5 (9·1)	14 (12·7)	0.25
Transversum	4 (7·2)	5 (9·1)	9 (8·1)	0.72
Decendens	1 (1·8)	4 (1·8)	5 (4·5)	0.15
Sigmoid	28 (50·9)	28 (50·9)	56 (50·9)	1.0
Elevated preoperative CEA	19 (34·5)	23(41·8)	42(38·1)	0.55
Type of surgery				
Laparoscopic surgery	14 (25·5)	11 (20·0)	25 (22·7)	0.49
Open surgery	41 (74·5)	44 (80·0)	85 (77·3)	0.49
Tumor stage				
Dukes A	12 (21·8)	11 (20·0)	24 (21·8)	0.81
Dukes B	25 (45·5)	30 (54·5)	55 (50·0)	0.34
Dukes C	18 (32·7)	14 (25·5)	32 (29·0)	0.40
New surgery due to complications	6 (10·9)	9 (16·4)	15 (13·6)	0.40
Permanent stoma	8 (14·5)	7 (12·7)	15 (13·6)	0.78
6 months chemotherapy regime	18 (32·7)	14 (25·5)	32 (29·1)	0.40

* Patients < 75 years were included in survey. P values calculated with chi square, t test and fisher exact test when appropriate.

Quality of life

There was no significant effect on the QoL main outcome measures. However, on the EORTC QLQ C-30 subscales, there were significant effects in favour of GP follow-up, i.e. role functioning (p=0.02), emotional functioning (p= 0.01) and pain (p=0,01) (Table 4, Figure 3 A, B, C).

Table 4. Health related quality of life (ERTOC QLQ-C30 and EQ-5D) outcome variables and estimated differences.

Outcome variable	Mean (SD)			Estimated mean difference (95% CI)	p *
	Baseline	12 months	24 months		
Global health status					
Surgeon	70.7 (22.5)	75.9 (19.2)	85.0(16.8)		
GP	70.4 (20.8)	81.3 (17.0)	86.5 (16.2)	- 2.23 (-5.7 – 1.2)	0.20
Physical functioning					
Surgeon	80.5 (23.6)	88.8 (15.0)	88.0 (17.0)		
GP	74.5 (24.9)	90.6 (16.6)	93.3 (16.0)	- 2.4 (-5.7 - 0.8)	0.14
Role functioning					
Surgeon	62.5 (37.3)	83.8 (26.5)	90.3 (18.6)		
GP	62.7 (37.5)	91.6 (22.1)	93.7 (20.7)	- 5.1 (-9.7 – (-0.5))	0.02
Emotional functioning					
Surgeon	87.4 (18.1)	87.7 (16.1)	87.7 (16.9)		
GP	85.8 (23.2)	91.9 (15.8)	94.4 (17.3)	- 3.7 (-6.8 – (-0.6))	0.01
Cognitive functioning					
Surgeon	87.0 (20.6)	86.5 (22.8)	90.3 (15.0)		
GP	72.4 (31.8)	91.1 (17.0)	93.0 (21.3)	-1.7 (- 5.0 – 1.4)	0.27
Social functioning					
Surgeon	70.7 (30.5)	87.0 (23.8)	90.4 (15.6)		
GP	72.4 (31.8)	91.6 (17.3)	93.0 (21.3)	-4.2 (-8.4 - (-0.009))	0.04
Fatigue					
Surgeon	32.3 (26.1)	19.2 (17.1)	14.6 (23.4)		
GP	36.9 (28.0)	22.2 (19.9)	18.3 (20.8)	0.24 (-3.7 – 4.2)	0.9
Nausea and vomiting					
Surgeon	6.0 (12.4)	2.8 (8.5)	0.9 (3.9)		
GP	6.5 (14.1)	3.5 (9.9)	4.3 (10.3)	-0.8 (-2.8 – 1.2)	0.4
Pain					
Surgeon	22.3 (26.6)	11.1 (21.9)	9.6 (16.9)		
GP	19.1 (28.2)	9.3 (14.0)	2.8 (14.7)	4.5 (0.8 - 8.2)	0.01
Dyspnoea					
Surgeon	18.1 (26.3)	14.2 (20.2)	10.5 (19.4)		
GP	24.0 (32.7)	12.1 (23.3)	7.2 (21.2)	3.0 (-1.2 – 7.2)	0.1
Insomnia					
Surgeon	22.9 (25.4)	18.5 (25.7)	17.5 (25.7)		
GP	28.6 (34.5)	14.7 (23.4)	23.6 (25.0)	2.9 (-1.7 – 7.5)	0.2
Appetite loss					
Surgeon	15.5 (23.1)	3.7 (10.6)	1.7 (7.6)		
GP	20.9 (31.7)	1.9 (7.9)	4.1 (11.2)	0.8 (-2.9 – 3.9)	0.6
Constipation					
Surgeon	27.4 (32.0)	21.2 (29.9)	10.5 (19.4)		
GP	18.6 (33.5)	7.8 (16.5)	15.2 (19.6)	5.1 (0.8 - 9.4)	0.01
Diarrhoea					
Surgeon	24.4 (29.6)	21.2 (25.3)	24.5 (24.4)		
GP	31.0 (33.6)	22.5 (26.8)	23.6 (28.6)	-1.0 (-5.7 - 3.5)	0.6
Financial difficulties					
Surgeon	9.8 (26.2)	9.2(20.4)	7.0 (21.0)		
GP	6.9 (21.2)	1.9 (7.9)	4.1 (11.2)	2.7 (-0.4 - 5.8)	0.08
EQ-5D Index score					
Surgeon	0.83 (0.16)	0.85(0.20)	0.90 (0.14)		
GP	0.79 (0.22)	0.87(0.18)	0.89 (0.13)	- 0.10 (-0.039-0.018)	0.48

EQ-5D VAS score					
Surgeon	72.2 (18.9)	78.2 (16.2)	82.4 (16.6)		
GP	67.4 (17.4)	79.0 (14.6)	83.5 (14.8)	-1.10 (-3.9-1.7)	0.44

* Adjusted general linear model from 1800 follow-up months, i.e. 600 QoL questionnaires (GP 299 vs. surgeon 301).

Cost-effectiveness

There were no significant difference on primary QoL measure (Global health status), and a cost minimisation analyses were performed. A total of 778 travels (consultations, radiological investigations, colonoscopy) to hospital were registered, 528 in the surgeon group and 250 in the GP group, respectively. A total of 1186 health-care contacts (regular appointments, emergency appointments, phone consultations) were registered, 678 in the GP group versus 508 in the surgeon group (table 5). Mean cost of follow-up per patient per follow-up cycle was £292 in GP group and £351 in surgeon group (p=0.02) (figure 4). Overall mean societal cost per patient for 24 months follow-up were £ 9889 in the surgeon group and £ 8233 in the GP group (p<0.001, table 6).

Table 5. Resource use in a colon cancer follow-up program.

Cost variable	Surgeon n=55			GP n=55			Total n=110		
	n	n/ cycle	cost/ cycle	n	n/ cycle	cost/ cycle	n	n/ cycle	cost/cycle
Follow-up months	903			897			1800		
Hospital travels									
Car	189	0.62	[a]	113	0.37	[a]	302	0.50	[a]
Taxi	37	0.12		22	0.07		59	0.09	
Bus	96	0.31		33	0.11		129	0.21	
Airplane	0	0		8	0.02		8	0.01	
Express boat	43	0.14		12	0.04		55	0.09	
Extra travel due to poor logistics	104	0.34		52	0.17		156	0.26	
Travel assistant	59	0.19		10	0.03		69	0.11	
Hotel	7	0.02	1.7 (11)	8	0.02	2.0 (12)	15	0.02	1.8 (11.6)
Total	528 [a]	1.75		250 [a]	0.83		778 [a]	1.29	
Mean cost £ (SD)			156.9 {145.0}			76.7 (160.1, p<0.001)			117.1 (157.7)
GP office travels									
Car	155	0.51	[b]	317	1.06	[b]	472	0.78	[b]
Taxi	7	0.02		14	0.05		21	0.03	
Bus	17	0.06		35	0.12		52	0.08	
Travel assistant	0	0		15	0.05		15	0.02	

Total	179	0.59		381	1.27		560	0.93	
Mean cost £ (SD)			4.1 (7.9)			9.0 (9.1, p<0.001)			6.6 (8.9)
Out of pocket expenses									
Mean cost £ (SD)			2.7 (7.7)			4.3 (15.0, p=0.10)			3.5 (11.9)
Health care contacts									
GP consultations	156	0.52	9.6 (17.8)	329	1.10	20.6 (19.9)	485	0.80	15.1 (19.6)
GP phone consultation	61	0.20	1.0 (3.9)	94	0.31	1.7 (4.3)	155	0.25	1.4 (4.1)
GP emergency consultations	23	0.08	1.9 (12.2)	37	0.12	3.2 (14.4)	60	0.1	2.6 (13.3)
Surgeon outpatient consultations	227	0.75	52.3 (93.8)	185	0.61	43.3 (104.1)	412	0.68	47.8 (99.0)
Surgeon phone consultations	41	0.14	1.45 (5.7)	33	0.11	1.2 (4.4)	74	0.12	1.32 (5.1)
Total	508	1.68		678	2.26		1186	1.97	
Mean cost £ (SD)			66.4 (100.1)			70.1 (112.2, p=0.67)			68.2 (106.1}
NGICG follow-up tests									
Blood samples	203	0.67	3.3 (5.1)	300	1.0	5.1 (6.8)	503	0.83	4.2 (6.0)
Chest x ray	150	0.50	12.2 (12.2)	128	0.43	10.6 (12.1)	278	0.46	11.4 (12.2)
CEUS	110	0.37	56.2 (74.0)	99	0.33	51 (72.5)	209	0.34	53.8 (73.2)
Colonoscopy	50	0.17	49.2 (110.3)	65	0.22	65.1 (122)	115	0.19	57.1 (116.7)
Total	513	1.70		592	1.97		1105	1.84	
Mean cost £ (SD)			121.1 (152.8)			132.2 (166.7, p=0.39)			126.6 (159.8)
Work loss									
Patients in paid work (n)	17			12			29		
Days off work mean (SD)	215 (168)			198 (190, p=0.79)			208 (219)		
[c] Mean cost £ (SD)			2440 (1906)			1884 (2092, p=0.45)			2086 (2014)
Serious clinical events									
Number of events	22			26			48		
[d] Mean cost £ (SD)			261.6 (157.7)			573.1 (838.9, p=0.14}			444.0 (662.4)
Metastases surgeries									

Cancer recurrences	8	6	14	
Metastases surgeries	4	3	7	
[e] Mean cost £ (SD)	9037.2 (5117.5)	13316.0 (1489.0, p=0.22)	10871.0 (4366.3)	

[a] Mean travel cost for hospital travels, se table 2. [b] Values calculated with a median distance GP office 30 km. [c] Value represent the mean cost (standard deviation) relating to the subsample who were in paid work at time of surgical treatment. NGICG: Norwegian Gastrointestinal Cancer Group. Follow-up cycle = 3 months. CEUS: Contrast enhanced liver ultrasound. [d] Value represent the mean cost (standard deviation) of work up tests (CEA, chest x-ray, colonoscopy) relating to the subsample who experienced a serious clinical event. [e] Value represent the mean cost (standard deviation) relating to the subsample who performed metastases surgery.

Table 6. Cost of colon cancer follow-up

Cost Variable (mean, £)	**Surgeon n=55**	**GP n=55**	**Total n=110**	**p value**
Healthcare cost/follow-up cycle	351	292	324.1	0.02
Bootstrapped 95% c.i	315 - 386	255 - 327	296 - 348	
Mean difference £	58			
Healthcare cost/24 month follow-up	3178	2651	2917	0.03
Bootstrapped 95% c.i	2833 - 3485	2228 - 3006	2660 - 3147	
Mean difference £	529			
Societal cost/ follow-up cycle	1098	914	1007	< 0.001
Bootstrapped 95% c.i.	1062 - 1139	877 - 954	981 - 1034	
Mean difference £	184			
Societal cost/24 month follow-up	9889	8233	9068	< 0.001
Bootstrapped 95% c.i.	9569 - 10194	7904 - 8619	8823 - 9320	
Mean difference £	1656			

In estimation of health care and societal cost, cycles with complete cost data (n=600 i.e. 1800 follow-up months) were included in analyses (as defined in table 1). Cost data from 57 follow-up cycles were excluded from analyses (incomplete ID or not returned forms). Cost of sick leave was adjusted for baseline characteristic. Cost of serious clinical events and metastases surgeries were adjusted for the percentage of events. Fu: follow-up. C.i: confidence interval, based on 1000 stratified bootstrap samples.

Sensitivity analyses

The single factor with greatest impact on overall societal costs was sick-leave followed by cost of follow-up tests and cost of hospital travels. Variances in cost related to GP office travels and follow-up appointments had minor impact on overall cost in a follow-up program (figure 5).

Time to cancer diagnoses

48 serious clinical events (SCE) occurred, mean time until diagnosis of a serious clinical event was 45 days in the surgeon group and 35 days in the GP group (p=0.46). Of patients with SCE, 14 patients had cancer recurrence and 7 patients (50%) were offered metastases surgery. Median time to diagnoses of recurrence was 21 days in the GP group (range 2-270 days) and 30 days in the surgeon group (range 3-45 days). Five patients died (all deaths caused by disseminated colon cancer) during the follow-up period (GP 1 vs. surgeon 4).

Discussion

Summary of findings

A representative population of patients surgically treated for colon cancer participated in this trial, with an expected normal variance of demographic factors and colon cancer severity. In this study patients were followed for up to two years, i.e. the period with most cancer recurrences and serious clinical events, which again would impact QoL and costs of follow-up. We have shown that a decentralised colon cancer follow-up program will not impair QoL, on the contrary we observed a significant improvement in the following QoL subscales; role functioning, emotional functioning and pain. This is the first trial evaluating the economical implications of a GP organised follow-up program after curative resection for colon cancer. Despite a higher frequency of health care contacts in primary care, a decentralised GP organised follow-up program was associated with total cost savings due to decreased cost of primary care consultations and less hospital travels. Importantly, our result shows that GP follow-up was not associated with increased time to diagnosis of SCE and thus cancer recurrence (35 versus 45 days, p=0.46), and the frequency of a SCE was similar in both groups.

Comparison with existing literature and on going trials

Although intensive follow-up is associated with improved survival, there are still international controversies on how to best organise follow-up of colon cancer patients. These controversies are mirrored in the wide variation of national follow-up guidelines.

[4-7] Two systematic reviews, comparing follow-up trials have been published. [2,3] Due to the variation in the follow-up programs included in these reviews, it is not possible to infer the best combination of consultations, blood tests, colonoscopy, radiological investigations and level of care to maximise the outcomes. [2] Large randomised trials are under way (COLOFOL, GILDA, FACS) but results are most likely years away. [9-11] Few published surveys have evaluated the effect of a GP organised follow-up program. Two surveys have reported on quality of life in a primary care based follow-up program, and a single cost-effectiveness analysis of intensified hospital based follow-up was published in 2004. [30-32] Surveys have assed cost of follow-up in a Norwegian setting. In a retrospective survey 314 patients were assessed with regards to cost, compliance and success rate of curative surgery. It was concluded that the cost of one successful curative surgery was $ 25 289, and that further implementation of such a program should be debated. [33] Harms and unintended effects of a follow-up program is poorly explored. Especially is the rate of false positive tests in a follow-up program unknown. Current surveillance is often based on serial CEA measurements, this biomarker has several pitfalls and shortcomings. I a recent survey, it is shown that the diagnostic accuracy of serial measurement of CEA is low, and is impacted by the cut off value.[34] These aspects are of high importance when designing a follow-up program, as false positive test probably has a negative impact on the patients quality of life. Finally, its there exist considerable variance in follow-up strategies, internationally and at a national level.[35] This makes outcome comparison between different follow-up strategies challenging. For other cancer conditions more cost-effective ways of organising follow-up is extensively described and evaluated. For breast cancer patients, nurse lead telephone and GP organised follow-up is cost-effective [36,3738] with no increase in the frequency of SCE.[39] Nevertheless, the quality of primary care cancer management is still debated. [40-42]

Strengths and limitations

Our trial has several strengths. Firstly, this is the first randomised trial addressing the economical implications and time to recurrent cancer diagnoses in a GP organised colon cancer follow-up program. We have shown that GP organised follow-up, even with increased frequency of health care contacts, was associated with cost savings and no decline in quality of life. Secondly, poor guideline compliance has been shown to represent a problem in cancer follow-up programs. [43] However, tools to support

decision making in cancer are on way forward. In this study, a decision support pamphlet was part of the intervention and the patient and the GP organising the follow-up received a decision support tool. Detailed instructions of forthcoming follow-up consultations and test were given. We believe this decision support tool contributed to a high follow-up guideline adherence (table 6, GP 592 tests vs. surgeon 513 tests). Thirdly, we have shown that the rate of SCE and time to diagnosis of cancer recurrence is comparable between groups. In our opinion, this is an indicator of adequate quality in a GP organised follow-up program.

There exist limitations. Firstly, it might be argued that we were missing important information by choosing another endpoint than survival. However, this trial was designed primarily to evaluate whether general practice follow-up results in effect on patient specific quality of life and cost effectiveness. We acknowledge that this choice of endpoint might impact the observed frequency of serious clinical events and time to cancer diagnoses, as a higher number of SCE and cancer recurrences would have occurred with a longer follow-up time. Similarly, costs will be impacted by a longer follow-up time. However, when health care cost of follow-up is analysed separately (table 5, figure 3), cost spendings are significantly lower in the GP group compared to the surgeon group. Secondly, generalizability and cost transferability across jurisdictions might be challenging, as elements of cost data may vary from place to place.[44] It might be argued that this is a single country trial with limited generalizability. However, we do not think this is the case. Comparable follow-up trials have been performed in countries like USA, Canada, UK, Australia, Netherlands. [30,38,39,45] These surveys are commonly cited and thus accepted as generalizable. In Norway, the GP has a traditional gatekeeper function and plays a central role managing resource use in secondary care. Similarly, many European countries have a health care organisation where the GP plays a central role as gatekeeper to access of secondary health care service. In our trial, guidelines for dealing with aspects of generalizability and transferability were applied, and variations in units costs were included in the sensitivity analyses (see figure 4).[44]

Finally, the trial was stopped after 1884 follow-up months due to no significant effect of the intervention on global health score and implementation of a new national follow-up program. This is a limitation, as it will impact the interpretation of cancer recurrence.

However, it would have been unethical to spend large resources over years to complete an intervention with a 4% probability of showing a significant impact on global health score.

Implication for patients, decision makers and clinicians

Colon cancer in numbers is the third largest cancer type worldwide and a considerable number of patients are enrolled in a post surgical surveillance program, resulting in significant societal cost. However, as there is no evidence based consensus of how to design cost-effective follow-up programs, differences in tests, test frequency and level of care will have high impact on societal cost spending. Therefore, the cost driving elements in a colon cancer follow-up program have to be critically evaluated.

From a societal perspective, this survey has important implications. It may be argued that there are limited benefits from having GPs organising the follow-up program, as the radiological examinations and the colonoscopy have to be be performed in-hospital anyway. However, we believe the most important factors causing a less costly GP follow-up are: *Better coordination of care:* As shown in table 5, GP organised follow-up leads to fewer hospital travels. We believe this is mainly caused by improved coordination of care, for instance by performing multiple radiological test at the same hospital visit. Interestingly the GP group had fewer extra travels (GP 52 travels versus Surgeon 102 travels) due to poor logistics (table 5). *Cost of GP consultation vs. hospital consultation:* The societal cost of GP consultations is lower compared to cost of hospital consultations, due to a more costly hospital infrastructure. *Complex and chronic conditions:* Patients surgically treated often have other chronic illnesses, and there is a trend towards higher involvement of primary care in treating these conditions as described in the chronic care model. [13] *Sick leave:* Although not statistical significant, patients in the GP group return to work 17 days (mean) earlier compared to patients in the surgeon group.

In a time with escalating health care cost, especially in cancer care, improved coordination of care are of increasing importance.

From a patient perspective, GP organised follow-up is associated with high quality of care and leads to fewer time consuming hospital travels . Our study demonstrates that a decentralised follow-up has no negative impact on quality of life, length to cancer diagnoses and follow-up guideline adherence.

From a hospital perspective, a transfer of follow-up programs to primary care have

economical and organisational implications. GP organised follow-up may be an effective way of reducing the burden on busy hospital clinics.

Conclusion

The present study suggests that colon cancer follow-up can safely be performed by GPs, with no negative impact on quality of life and to a lower cost. However, there exist limitations. 13% (n=14) patients had colon cancer recurrence, this low recurrence rate is most likely caused by limited long term follow-up as most recurrences occur within 3 years. Furthermore, the best combination of consultations, radiological test, blood samples and colonoscopy that optimizes cancer survival is still unknown. We therefore argue that cost driving elements of colon cancer surveillance should be critically evaluated, when designing and implementing follow-up programs, as cancer surveillance represents a huge financial burden for society. Finally, little is known about the potential harms of follow-up, especially when it comes to the impact of false positive tests. Further research is needed to settle these controversies, and new methods of decision-analytic modeling in combination with emerging data from on-going randomised trials must be applied.[46]

Contribution

KMA and ROL conceived and designed the research idea, and were responsible for the overall administration and direction of the study, the analysis and interpretation of data. KMA and SOS designed the statistical analyses. KMA did the statistical analyses. KMA did the economic analysis with assistance from JN, who contributed to the design, data analysis, and interpretation of the findings. TN, RA and SD helped with patient recruitment and randomization, and to do the trial and interpreted the findings. UR advised on the trial protocol, unit cost and reimbursement practice in primary care. BV advised on protocol writing and pre trial sample size calculations and manuscript revision. KMA wrote the first draft. All authors read and approved the final manuscript. KMA had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: The study was funded by a research grant from Northern Norwegian Health Authorities. The authors declare that they have no conflicts of interest.

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Data sharing

No additional data available.

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Figure legends:

Figure 1. Flow of participants.

Patients were enrolled in the 2007 NGICG (Norwegian Gastrointestinal Cancer Group, table 1) follow-up program in both trial arms. The program are divided in 3 months cycles i.e.; clinical examination at 1 (baseline), 3,6,9,12,15,18,21 and 24 months, carcinoembryonic antigen (CEA) measurement at 3 months intervals, chest x-ray and contrast enhanced liver ultrasound every 6 months, and colonoscopy 1 time during 24 months (table 1).

Figure 2 A, B, C. Health related quality of life 1-24 postoperative month.

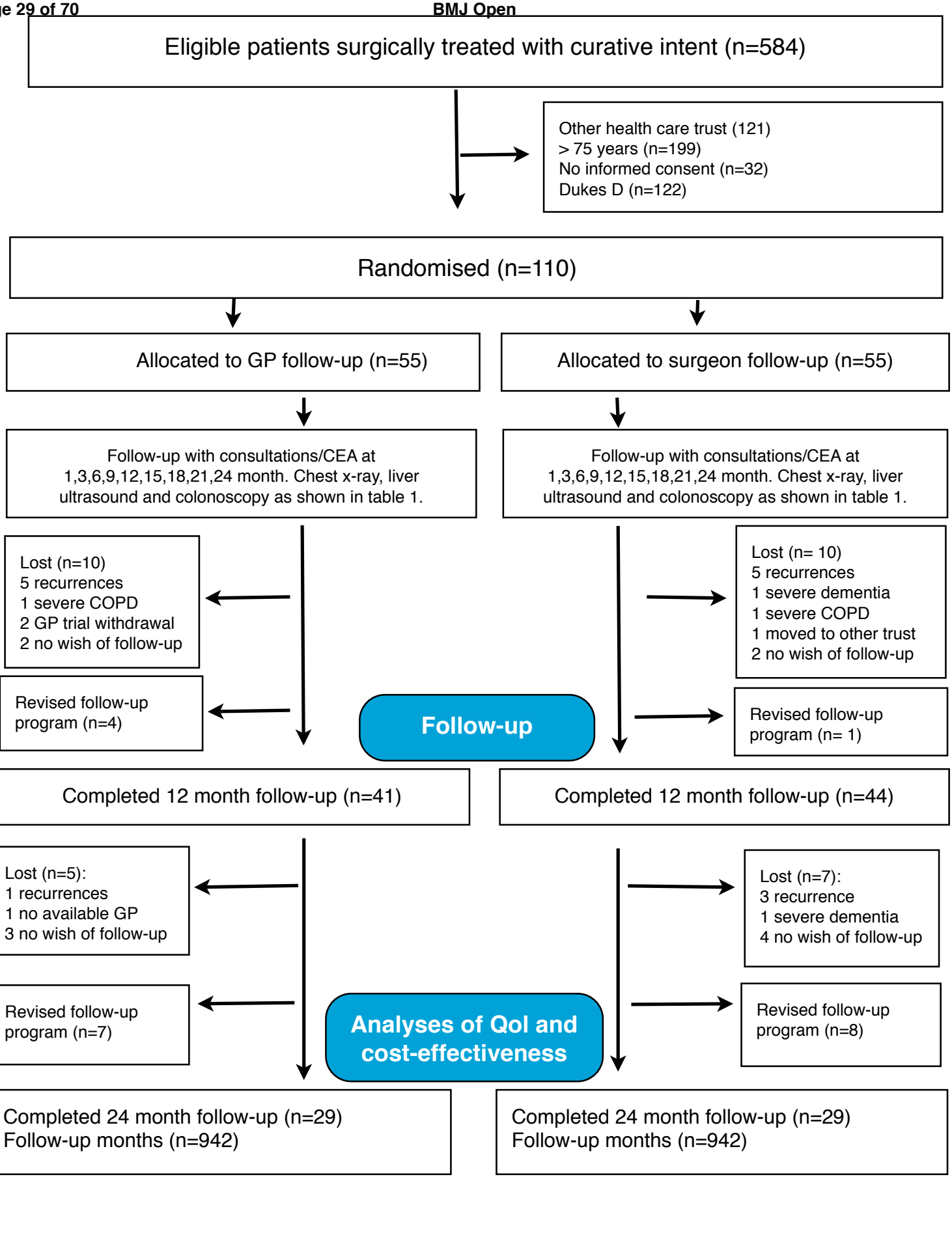
EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.

Figure 3. Cost of follow-up per cycle.

Mean cost of follow-up per patient per 3 month follow-up cycle with error bars (95% confidence intervals).

Figure 4. Sensitivity analyses of cost driving elements in surveillance.

Societal cost per patient (£) for 24-month colon cancer follow-up. Most critical variable in terms of impact is listed at the top of the graph, and the rest ranked according to their impact thereafter. As unit cost from the UK, like cost for GP consultation and diagnostic testing, has been reported to be 30-40% higher than units cost applied in this trial, relevant cost elements were increased accordingly. Cost values for serious clinical events, metastases surgeries and sick leave were adjusted for baseline characteristics.


Eligible patients surgically treated with curative intent (n=584)
Other health care trust (121)
> 75 years (n=199)
No informed consent (n=32)
Dukes D (n=122)
Randomised (n=110)
Allocated to GP follow-up (n=55)
Allocated to surgeon follow-up (n=55)
Follow-up with consultations/CEA at 1,3,6,9,12,15,18,21,24 month. Chest x-ray, liver ultrasound and colonoscopy as shown in table 1.
Follow-up with consultations/CEA at 1,3,6,9,12,15,18,21,24 month. Chest x-ray, liver ultrasound and colonoscopy as shown in table 1.
Lost (n=10)
5 recurrences
1 severe COPD
2 GP trial withdrawal
2 no wish of follow-up
Revised follow-up program (n=4)
Lost (n= 10)
5 recurrences
1 severe dementia
1 severe COPD
1 moved to other trust
2 no wish of follow-up
Revised follow-up program (n= 1)
Follow-up
Completed 12 month follow-up (n=41)
Completed 12 month follow-up (n=44)
Lost (n=5):
1 recurrences
1 no available GP
3 no wish of follow-up
Revised follow-up program (n=7)
Lost (n=7):
3 recurrence
1 severe dementia
4 no wish of follow-up
Revised follow-up program (n=8)
Analyses of QoI and cost-effectiveness
Completed 24 month follow-up (n=29)
Follow-up months (n=942)
Completed 24 month follow-up (n=29)
Follow-up months (n=942)

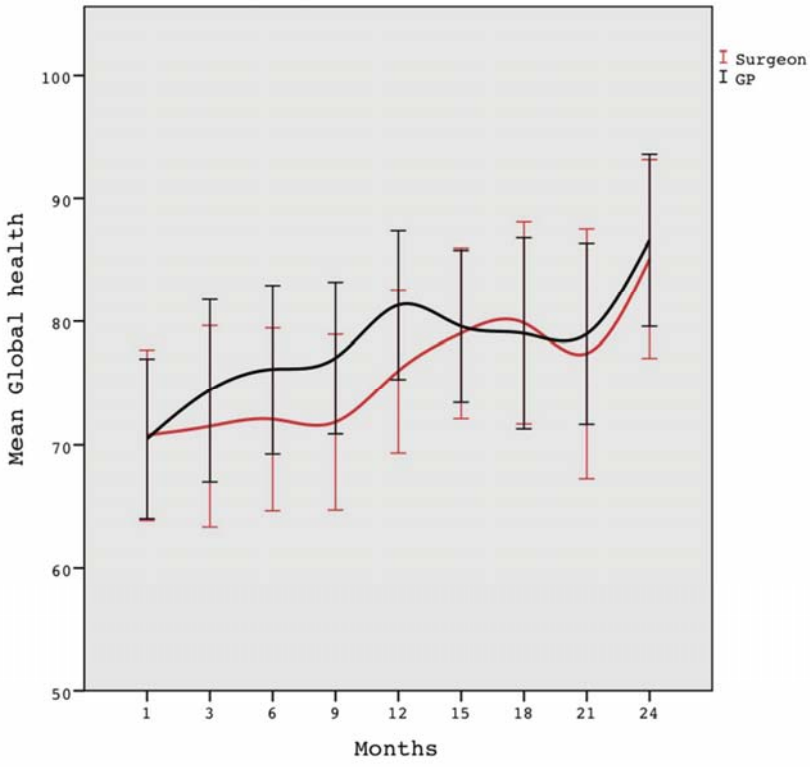
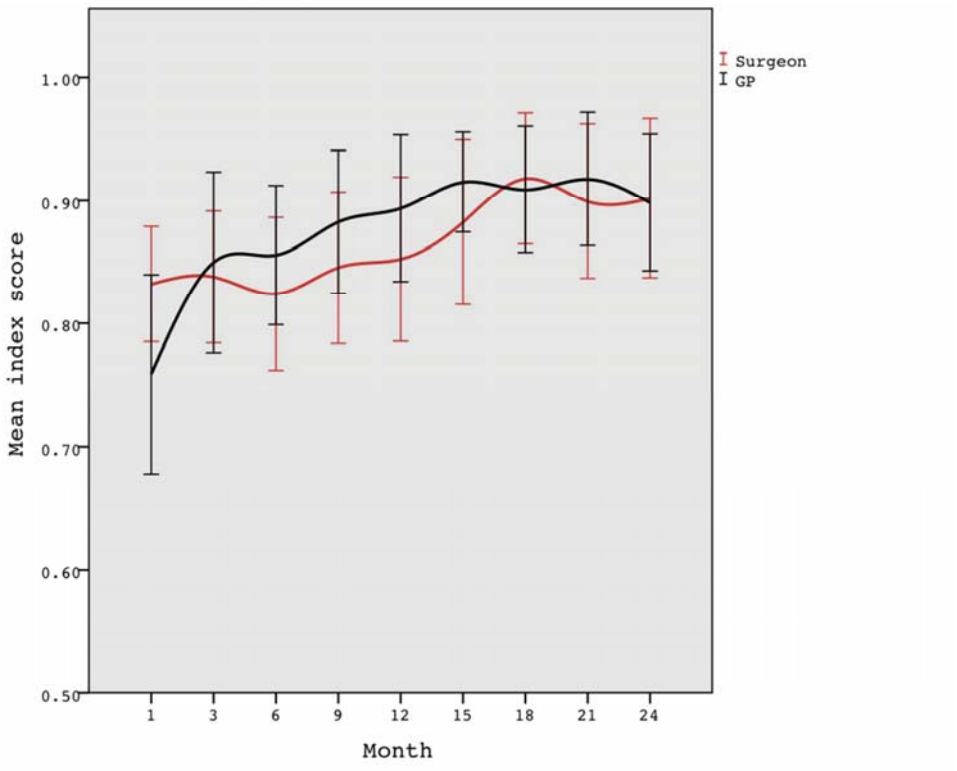


Figure 2 A, B, C. Health related quality of life 1-24 postoperative month.
EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.

165x132mm (150 x 150 DPI)



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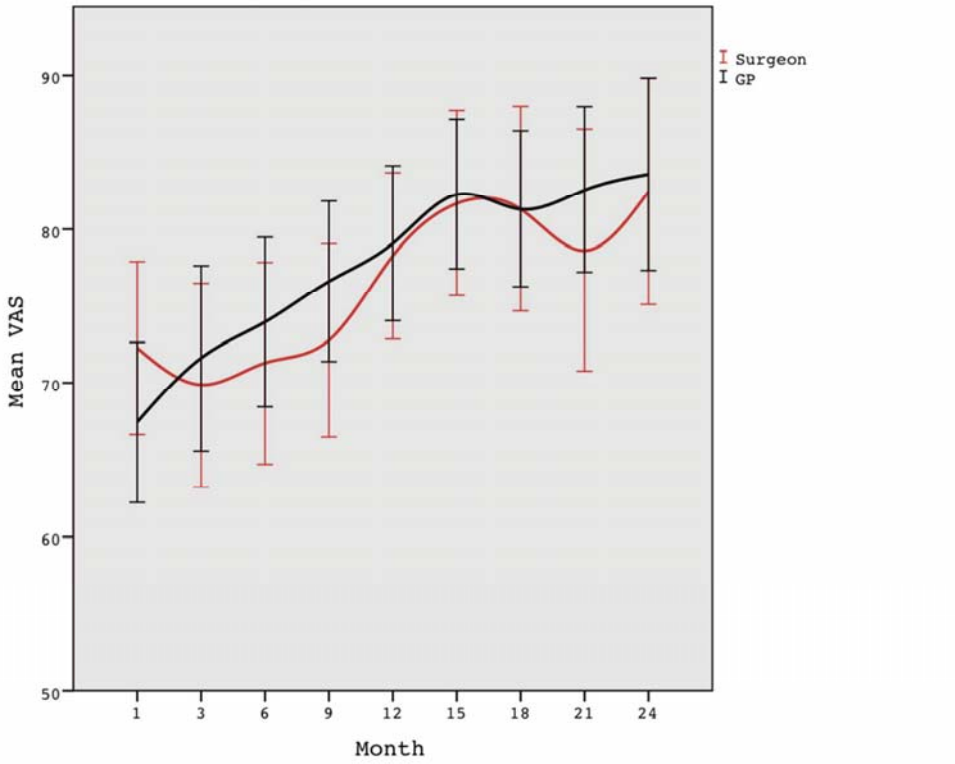

Figure 2 A, B, C. Health related quality of life 1-24 postoperative month.
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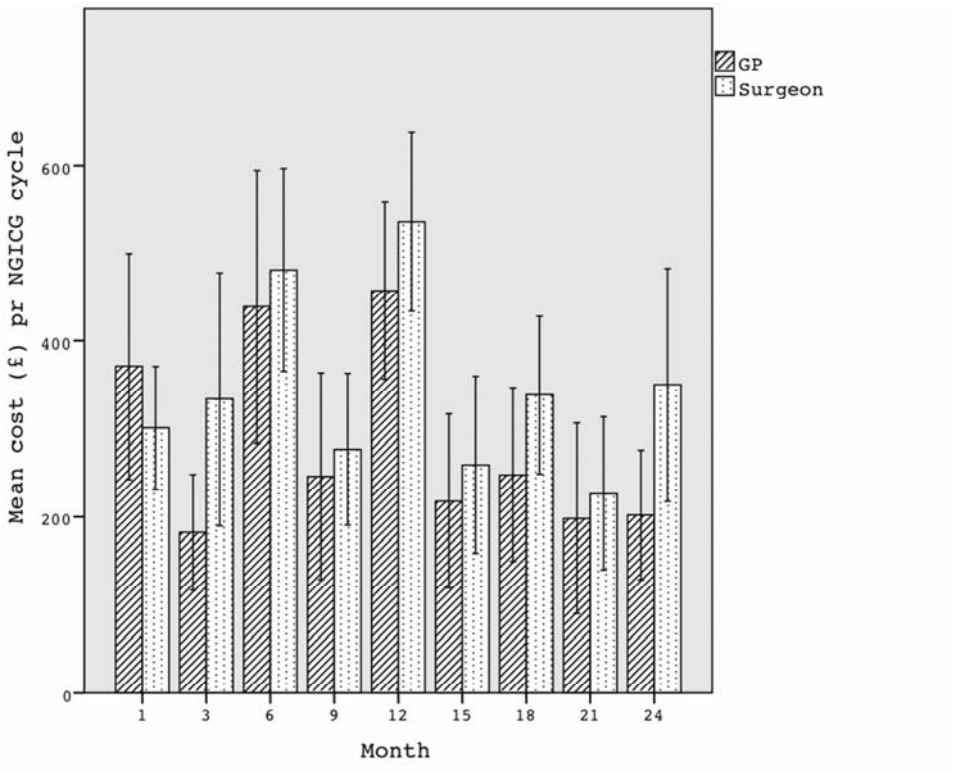
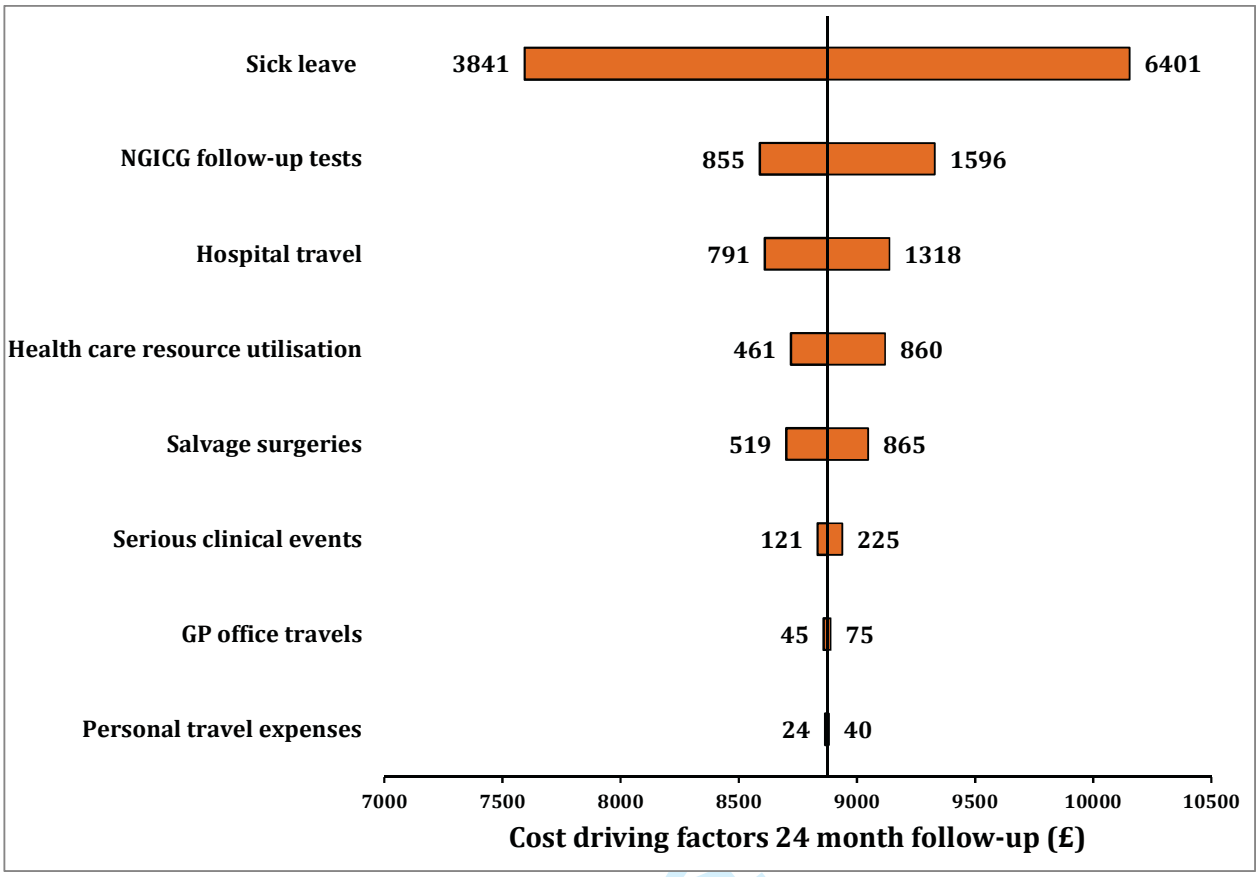


Figure 3. Cost of follow-up per cycle.
Mean health care cost of follow-up per patient per 3 month follow-up cycle with error bars (95% confidence intervals).
165x132mm (150 x 150 DPI)



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4 and 7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4 - 5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 - 6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7 - 8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11 - 12
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6 - 7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6 - 7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	No blinding

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	5 and table 1
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Economical analyses 9-10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 3
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 4 and 5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not relevant
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18 (time to diagnoses of SCE)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Figure 1, table 4 and 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19-20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-19
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Reference 15
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	23

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.