



General practitioner organised follow-up after curative colon cancer resection is not inferior to surgeon organised follow-up. A randomised controlled trial.

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3 **General practitioner organised follow-up after curative colon cancer resection is**
4 **not inferior to surgeon organised follow-up. 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; $\Delta - 2.23$, p=0.20; EQ-5D index; $\Delta - 0.10$, p=0.48, EQ-5D VAS; $\Delta - 1.1$, 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 cancer diagnosis and with 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 significant 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 trial was stopped after 1884 follow-up months due to no impact of the primary intervention on QoL.

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

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3 general practitioners (GP's).² Increasingly, the benefits of greater involvement of
4 primary care providers in the ongoing management of chronic illnesses are recognised.
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6 ¹³ Level of follow-up care may greatly influence quality of life and costs, especially in
7 rural areas with long distances to travel for hospital services. However, such
8 considerations must be balanced against the imperative that colon cancer survivors
9 receive the best care available. Recently, the UK's National Cancer Survivorship Initiative
10 recognised the need to develop new models of cancer care that support patient self care,
11 care planning and making the best out of resources.¹⁴ In Norway, similar national
12 initiatives have been launched. In this trial, we tested the main hypothesis that colon
13 cancer patients followed-up by their GP would experience similar or higher scores on
14 quality of life measures at a lower cost than alternative hospital controls. The other aims
15 were to test for differences of harms and benefits in a follow-up program, i.e. rate of
16 serious clinical events, rate of false positive tests, time to diagnosis of recurrence, and
17 frequency of metastases surgery.

26 **Methods**

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28 This was a randomised controlled trial with institutional ethical approval and patient
29 written consent carried out in North Norway Health Authority trust using a previously
30 published protocol. ¹⁵ **The first patient was included 1st of June 2007, the last patient**
31 **included 15th of December 2011. Patients were followed until June 2012.**

35 **Participating patients, hospitals, primary and secondary care professionals**

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37 Patients were eligible if they were aged less than 75 years and had recent surgery for
38 colon cancer with Dukes' stage A, B or C. Patients receiving postsurgical adjuvant
39 chemotherapy (some Dukes' B and all Dukes' C) were also eligible. Three local hospitals
40 and one university hospital participated. Approximately 100 patients with colon cancer
41 are surgically treated annually at these four hospitals. **All 550 GPs in the region received**
42 **written information, 448 GPs consented to participate in the trial (figure 1).**

47 **Objective and hypotheses**

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49 The primary objective was to compare patients' quality of life and costs of follow-up by
50 their local GP or at the surgical outpatient clinic. The primary hypothesis was that
51 patients followed-up by their GP would experience similar or better QoL scores at a
52 lower cost. The secondary objective was to test whether the incidence of serious clinical
53 events (SCE) would be similar for patients followed-up by their GP or hospital specialist
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(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 trial 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

QoL measurements were collected at baseline and 3,6,9,12,15,18,21 and 24 months. 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

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3 also included (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial
4 difficulties).¹⁸ **Primary outcome measure in this trial was the global health status.**
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6 *The EuroQol-5D (EQ-5DTM; EuroQol Group, Rotterdam, The Netherlands):* Is a
7
8 standardized generic instrument employed to measure of health outcome. EQ-5D
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10 measures five dimensions of health-related QoL (HRQOL): mobility, self-care, usual
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12 activities, pain/discomfort and anxiety/depression. Each dimension is rated at three
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14 levels: no problems (1), some problems (2) and major problems (3).¹⁹ Based on
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16 preferences elicited from a general population, EQ-5D health states (e.g. 1-1-2-1-3) may
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18 be converted into utility scores (= index scores, IS). In this trial we used preferences
19
20 elicited from a UK population, as no similar Norwegian preferences exist.²⁰
21
22 EQ Visual Analogue Scale (EQ VAS) records the respondent's self-rated health status on
23
24 a vertically graduated (0-100) visual analogue scale.

23 **Secondary outcome measures**

24 *Cost-effectiveness*

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26 Resources used (baseline to 24 months) were registered prospectively based on reports
27
28 by the patients and on hospital EMR review. The cost elements included costs related to
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30 hospital visits, GP visits, laboratory tests, radiology examinations, colonoscopy,
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32 examinations due to suspected relapse (radiology, colonoscopy, CT of thorax and/or
33
34 abdomen, PET scan), treatment of recurrence, travelling/transportation, production
35
36 losses, co-payments and other patient/family expenses.

37 *Time to cancer diagnoses*

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39 **Time to cancer diagnoses was defined as the time from occurrence of a serious clinical**
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41 **event (SCE, dated in the GP referral or hospital EMR record) until the date of diagnoses**
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43 **of a cancer recurrence. A serious clinical event (SCEs) was defined as an episode were**
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45 **cancer recurrence was suspected. A SCE can be triggered by either symptoms reported**
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47 **(at follow-up or in between follow-up), clinical findings at follow-up or findings by**
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49 **screening test.** A SCE was defined as: Cancer suspect lesion revealed at colonoscopy,
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51 increase in CEA measurements shown by repeated measurements, blood in stool
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53 detected by the Hemofec (FOB) test, unexplained abdominal pain, unexplained weight
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55 loss of 5 kg during the last three months, cancer-suspect lesions detected by rectal
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57 examination, palpable lymphadenopathy, metastatic suspect lesions shown by chest x-
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59 occurrence of cancer related symptoms.
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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 trials 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. 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.²⁴

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-innsatsstyrte-finansiering-2012/Sider/default.aspx>.

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3 1 DRG weight: 38209 NOK. Surgeon outpatient consultation (day and night-time): DRG 923 O, weight 0.017.
4 Colonoscopy: DRG 710 O, weight 0.072. Abdominal surgery: DRG 170, weight 3.484. Liver surgery: DRG 201,
5 weight 2.850. Lung surgery: DRG 76, weight 3.21

6 ^fStatistics in Norway 2011: Average annual salary 750 000 NOK (80 000 £) hospital consultant.

7 ^gCost rates Department of Radiology and Nuclear Medicine University Hospital North Norway.

8 ^hKorner H. Soreide K. Stokkeland PJ. Soreide JA. Systematic follow-up after curative surgery for colorectal
9 cancer in Norway: a population-based audit of effectiveness, costs, and compliance. J Gastrointest Surg
10 2005 Mar;9(3):320-8.

11 ⁱEstimated from a median income of 350 000 NOK/year/patient as reported by patient subsample in
12 regular work at time of surgery.

13 14 **Statistics**

15 Descriptive statistics were performed by percentages, 2x2 contingency tables, Chi
16 Square, Fisher Exact test and t-test. The base case analyses (n=110, 600 complete
17 follow-up questionnaires/cycles) were performed on intention to treat principle.
18 Treatment arms were compared with respect to potential covariates using continuous
19 and categorical univariable analyses. The main analyses examined whether differences
20 in outcome between baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months existed in all QoL
21 outcome measures (EORTC QLQ C-30 and EQ-5D). A general linear model was
22 employed, where time (1-24 months) and intervention group (GPs versus Surgeon) were
23 predictors in analyses of variance (between groups ANOVA). **Missing items in a form
24 were treated as missing. When missing forms, missing data were imputed by the last
25 observation carried forward (LOCF).** Conditional power (CP) was defined as the chance
26 of getting statistically significant results at the end of the trial given the data so far.^{25,26}
27 We defined a CP < 15% as a sufficient threshold to stop early.²⁷ Results were expressed
28 as mean differences for continuous outcomes with corresponding standard deviations
29 (SD), 95% confidence intervals, and associated p-values. P-values were reported with
30 two decimal places with p-values less than 0.001 reported as p < 0.001. For all tests we
31 used p = 0.05 level of significance. All analyses were performed with IBM SPSS Statistics
32 v 19.0 (IBM Company SPSS 2010) and Microsoft Excel for Mac 2011.
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51 **Results**

52 110 patients surgically treated for colon cancer met the inclusion criteria and agreed to
53 participate (figure 2). The control and intervention group were matched at baseline for
54 demographic and medical characteristics (table 3). During the follow-up period 628
55 follow-up cycles (**i.e 1884 follow-up months; GP 942 months vs. surgeon 942 months**)
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were performed (GP 314 cycles vs. surgeon 314 cycles). 28 questionnaires (5%) were excluded from analyses (GP 15 vs. surgeon 13) due to incomplete data or missing information, i.e. 600 follow-up questionnaires (95%) (GP 299 vs. surgeon 301) were included in analyses. 84 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. Eleven patients withdrew during trial due to no wish of follow-up (GP 5 vs. surgeon 6), 20 patients were transferred to a new follow-up program (GP 9 vs. surgeon 11). Implementation of new national colon cancer follow-up guidelines triggered an interim analysis in June 2012 (80% of pre planned recruitment).⁷ There was at this point 4% probability (conditional power as defined in methods) of showing a significant result, 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				
Cøkum	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
Decedens	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.

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	GP	Total
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	n=55			n=55			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			156.9			76.7 (160.1,			117.1
£ (SD)			{145.0}			p<0.001)			{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			4.1			9.0 (9.1,			6.6
£ (SD)			{7.9}			p<0.001)			{8.9}
Out of pocket expenses									
Mean cost			2.7			4.3 (15.0,			3.5 (11.9)
£ (SD)			{7.7}			p=0.10)			
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			66.4			70.1 (112.2,			68.2
£ (SD)			{100.1}			p=0.67)			{106.1}
NGICG follow-up tests									
Blood samples	203	0.67	3.3	300	1.0	5.1	503	0.83	4.2

			(5.1)			(6.8)			(6.0)
Chest x ray	150	0.50	12.2	128	0.43	10.6	278	0.46	11.4
			(12.2)			(12.1)			(12.2)
CEUS	110	0.37	56.2	99	0.33	51	209	0.34	53.8
			(74.0)			(72.5)			(73.2)
Colonoscopy	50	0.17	49.2	65	0.22	65.1	115	0.19	57.1
			(110.3)			(122)			(116.7)
Total	513	1.70		592	1.97		1105	1.84	
Mean cost			121.1			132.2 (166.7,			126.6
£ (SD)			(152.8)			p=0.39)			(159.8)
Work loss									
Patients in paid work (n)	17			12			29		
Days off work mean (SD)	215			198 (190,			208		
	(168)			p=0.79)			(219)		
^c Mean cost			2440			1884 (2092,			2086
£ (SD)			(1906)			p=0.45)			(2014)
Serious clinical events									
Number of events	22			26			48		
^d Mean cost			261.6			573.1 (838.9,			444.0
£ (SD)			(157.7)			p=0.14)			(662.4)
Metastases surgeries									
Cancer recurrences	8			6			14		
Metastases surgeries	4			3			7		
^e Mean cost			9037.2			13316.0			10871.0
£ (SD)			(5117.5)			(1489.0,			(4366.3)
						p=0.22)			

^a Mean travel cost for hospital travels, see 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, 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	Surgeon n=55	GP n=55	Total n=110	p value
Healthcare cost per follow-up cycle £ (SD)	351 (324)	292 (332.9)	324.1 (330.0)	0.02
Healthcare cost 24 month follow-up £ (SD)	3178 (2917)	2651 (3004)	2917(2970)	0.03
Societal cost per follow-up cycle £ (SD)	1098 (324)	914 (332)	1007 (340)	< 0.001
Societal cost 24 month follow-up £ (SD)	9889 (2917)	8233 (2996.1)	9068 (3068.2)	< 0.001

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 28 follow-up cycles were excluded from analyses (incomplete or missing). 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.

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) (table 7). Five patients died (all deaths caused by disseminated colon cancer) during the follow-up period (GP 1 vs. surgeon 4).

Table 7. Clinical presentation of colon cancer recurrence by trial group

Case no	Sex	Presenting problem	Routine/interval	Diagnostic tests	Metastatic site	Time to diagnoses (days)	Metastases surgery	Time to surgery (days)
GP group								
1	F	Elevated CEA	routine	CEUS PET CT	Disseminated	27	no	inoperable
2	M	Abdominal pain	interval	CEUS	Liver	21	no	inoperable
3	M	Elevated CEA	routine	CEA CT thorax CT abdomen	Disseminated	71	no	inoperable
4	M	Metastatic lesion detected at CEUS	routine	CEUS CT thorax CT abdomen	Liver	4	yes	38
5	F	Abdominal pain, normal CEA, CT and CEUS, disseminated cancer detected at laparotomy	interval	CEUS CT thorax CT abdomen	Disseminated	270	yes	270
6	M	Abdominal tenderness	interval	Anorectoscopy Ct thorax CT abdomen	Local recurrence	2	yes	30
Surgeon group								
7	M	Metastatic lesion detected chest x-ray	routine	CT thorax CT abdomen	Lung	45	yes	62
8	M	Stoma bleeding	interval	Colonoscopy CT thorax CT abdomen	Local and lymph node recurrence	10	no	inoperable
9	M	Weight loss Night sweating	routine	CT Thorax CT abdomen	Lung	45	no	inoperable
10	M	Metastatic lesion detected at chest-x ray	routine	CT Thorax CT abdomen	Lung	4	yes	42
11	M	Metastatic lesion detected CEUS	routine	MR liver CT thorax CT abdomen	Liver	3	yes	43
12	F	Abdominal pain	interval	CT abdomen CT thorax	Disseminated	16	no	inoperable
13	M	Elevated CEA	routine	CT thorax CT abdomen CT liver	Liver Lung	30	no	inoperable
14	F	Occult blood in faeces	interval	CT thorax CT abdomen CEUS	Liver	31	yes	35

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 a 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 2004.²⁸⁻³⁰ However, 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^{31,32 33} with no

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3 increase in the frequency of SCE.³⁴ Nevertheless, the quality of primary care cancer
4 management is still debated.³⁵⁻³⁷

6 **Strengths and limitations**

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8 Our trial has several strengths. Firstly, this is the first randomised trial addressing the
9 economical implications and time to recurrent cancer diagnoses in a GP organised colon
10 cancer follow-up program. We have shown that GP organised follow-up, even with
11 increased frequency of health care contacts, was associated with cost savings and no
12 decline in quality of life. Secondly, poor guideline compliance has been shown to
13 represent a problem in cancer follow-up programs.³⁸ However, tools to support
14 decision making in cancer are on way forward. In this study, a decision support
15 pamphlet was part of the intervention and the patient and the GP organising the follow-
16 up received a decision support tool. Detailed instructions of forthcoming follow-up
17 consultations and test were given. We believe this decision support tool contributed to a
18 **high follow-up guideline adherence** (table 6, GP 592 tests vs. surgeon 513 tests). Thirdly,
19 we have shown that the rate of SCE and time to diagnosis of cancer recurrence is
20 comparable between groups. In our opinion, this is an indicator of adequate quality in a
21 GP organised follow-up program.

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32 There exist some limitations. Firstly, **it might be argued that we were missing important**
33 **information by choosing another endpoint than survival.** However, this trial was
34 designed primarily to evaluate whether general practice follow-up results in effect on
35 patient specific quality of life and cost effectiveness. We acknowledge that this choice of
36 endpoint might impact the observed frequency of serious clinical events and time to
37 cancer diagnoses, as a higher number of SCE and cancer recurrences would have
38 occurred with a longer follow-up time. Nevertheless, during our trial length of 1884
39 follow-up months we observed fewer recurrences than anticipated (15,4%), however
40 this might be related to the decreasing rate of colon cancer recurrences at a national
41 level (unpublished data Cancer Registry of Norway). Similarly, costs will be impacted by
42 a longer follow-up time. However, when health care cost of follow-up is analysed
43 separately (table 5, figure 3), cost spending are significantly lower in the GP group
44 compared to the surgeon group. Secondly, **generalisability and** cost transferability
45 across jurisdictions might be challenging, as elements of cost data may vary from place
46 to place.³⁹ **It might be argued that this is a single country trial with limited**
47 **generalizability. However, we do not think this is the case.** Comparable follow-up trials
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3 have been performed in countries like USA, Canada, UK, Australia, Netherlands.^{28,33,34,40}
4 These surveys are commonly cited and thus accepted as generalizable. In Norway, the
5 GP has a traditional gatekeeper function and plays a central role managing resource use
6 in secondary care. **Similarly**, many European countries have a health care organisation
7 where the GP plays a central role as gatekeeper to access of secondary health care
8 service. In our trial, guidelines for dealing with aspects of generalizability and
9 transferability were applied, and variations in units costs were included in the
10 sensitivity analyses (see figure 4).³⁹ **Finally, the trial was stopped after 1884 follow-up**
11 **months due to no significant effect of the intervention on Global health score and**
12 **implementation of a new national follow-up program. This might be a potential**
13 **limitation. However, it would have been unethical to spend large resources over years to**
14 **complete a trial with a 4% probability of proving the primary hypotheses.**

23 **Implication for patients, decision makers and clinicians**

24
25 Colon cancer in numbers is the third largest cancer type worldwide and a considerable
26 number of patients are enrolled in a post surgical surveillance program, resulting in
27 significant societal cost. However, as there is no evidence based consensus of how to
28 design cost-effective follow-up programs, differences in tests, test frequency and level of
29 care will have high impact on societal cost spending. For many patients, follow-up leads
30 to a number of long distance travels to hospital, causing high societal cost. Thus, from an
31 economical perspective, GP organised follow-up is cost-effective due to a better
32 coordination of care. In a time with escalating health care cost, especially in cancer care,
33 these aspects are of increasing importance. From a patient perspective, GP organised
34 follow-up is associated with high quality of care. Our study demonstrates that a
35 decentralised follow-up has no negative impact on quality of life, length to cancer
36 diagnoses and follow-up guideline adherence. Finally, patients surgically treated often
37 have other chronic illnesses, and there is a trend towards higher involvement of primary
38 care in treating these conditions as described in the chronic care model.¹³ From a
39 hospital perspective, a transfer of follow-up programs to primary care have economical
40 and organisational implications. GP organised follow-up may be an effective way of
41 reducing the burden on busy hospital clinics.

54 **Conclusion**

55 The present study suggests that colon cancer follow-up can safely be performed by GPs,
56 with no negative impact on quality of life and to a lower cost. However, solid evidence is
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3 missing regarding the optimal follow-up program that maximise survival. **We believe**
4 **new methods of comparative effectiveness research in combination with emerging data**
5 **from randomised trials must be used to settle these controversies.** ⁴¹
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8 **Contribution**

9
10 KMA and ROL conceived and designed the research idea, and were responsible for the
11 overall administration and direction of the study, the analysis and interpretation of data.
12
13 KMA and SOS designed the statistical analyses. KMA did the statistical analyses. KMA did
14 the economic analysis with assistance from JN, who contributed to the design, data
15 analysis, and interpretation of the findings. TN, RA and SD helped with patient
16 recruitment and randomization, and to do the trial and interpreted the findings. UR
17 advised on the trial protocol, unit cost and reimbursement practice in primary care. BV
18 advised on protocol writing and pre trial sample size calculations and manuscript
19 revision. KMA wrote the first draft. All authors read and approved the final manuscript.
20
21 KMA had full access to all the data in the study and had final responsibility for the
22 decision to submit for publication.
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28 **Competing interest**

29
30 All authors have completed the ICMJE uniform disclosure form at
31 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author)
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8 **Data sharing**

9 No additional data available.

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26 **Figure legends:**
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30 **Figure 1.** Participating trial hospitals and communities.

31 Three hospital trusts and the University Hospital of North Norway trust are located within the Northern-
32 Norwegian Health Region, serving a population of 470 000. Median travel time with car from primary care
33 communities to hospital were 2 hours. Two patients were randomised to follow up at their GP located in
34 Longyear City, Spitsbergen (not shown on map), 2 hours flight from the university hospital.
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38 **Figure 2.** Flow of participants.

39 Patients were enrolled in the 2007 NGICG (Norwegian Gastrointestinal Cancer Group, table 1) follow-up
40 program in both trial arms. The program are divided in 3 months cycles i.e.; clinical examination at 1
41 (baseline), 3,6,9,12,15,18,21 and 24 months, carcinoembryonic antigen (CEA) measurement at 3 months
42 intervals, chest x-ray and contrast enhanced liver ultrasound every 6 months, and colonoscopy 1 time
43 during 24 months (table 1).
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49 **Figure 3 A, B, C.** Health related quality of life 1-24 postoperative month.

50 EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.
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54 **Figure 4.** Cost of follow-up.

55 Mean cost of follow-up per patient per 3 month follow-up cycle with error bars (95% confidence
56 intervals). In a general linear model, mean difference between groups was 60.0 £ (95 CI interval: 7.0 –
57 113.0, p = 0.02).
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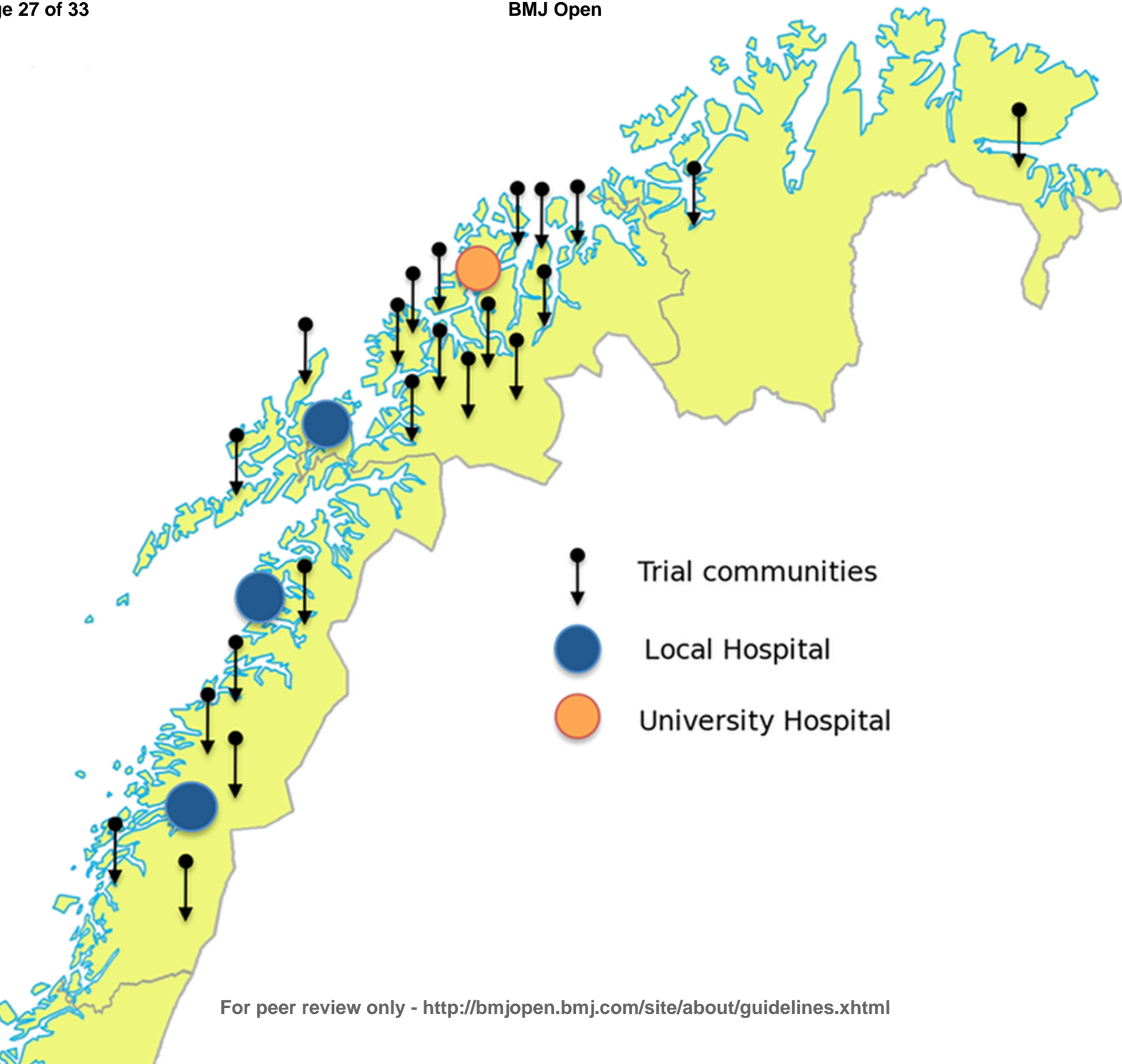
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Figure 5. Sensitivity analyses.

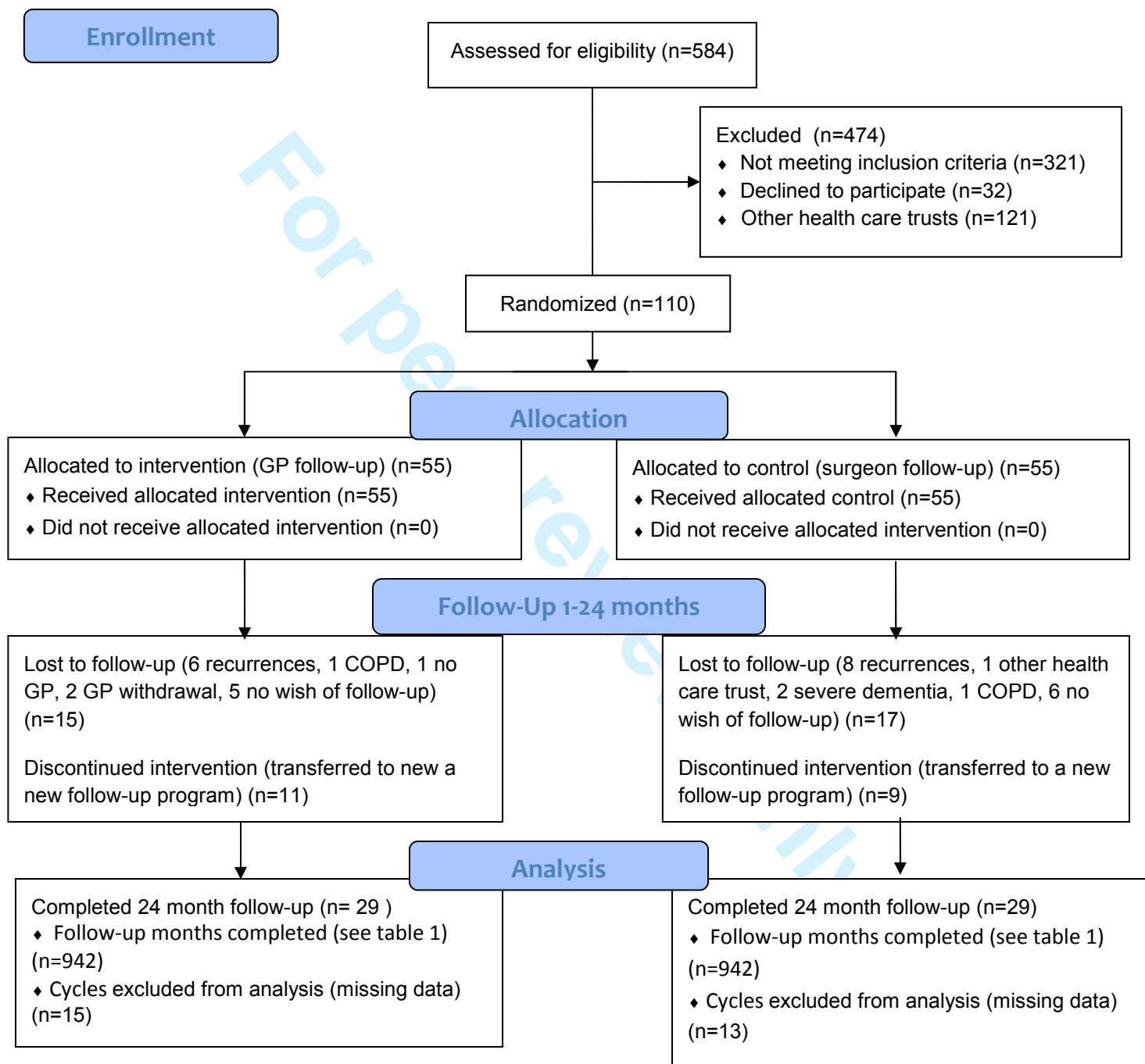
Societal cost per patient (£) for 24-month colon cancer follow-up. Most critical variable in terms of impact is listed at the top of the graph, and the rest ranked according to their impact thereafter. As unit cost from the UK, like cost for GP consultation and diagnostic testing, has been reported to 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.

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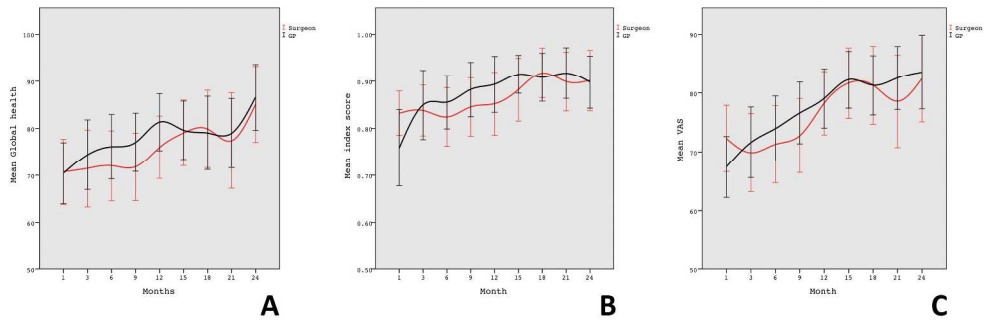
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Trial Flow Diagram



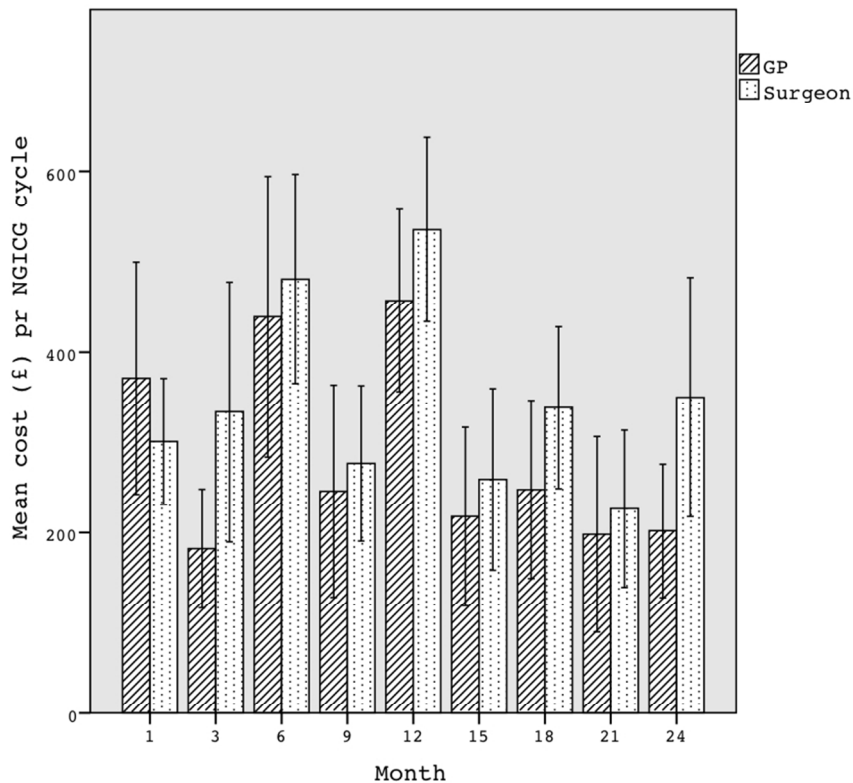
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Health related quality of life 1-24 postoperative month.
EORTC QLQ C30 Global Health (A), EQ-5D index score (B) and EQ-5D visual analog scale (C).
444x150mm (150 x 150 DPI)

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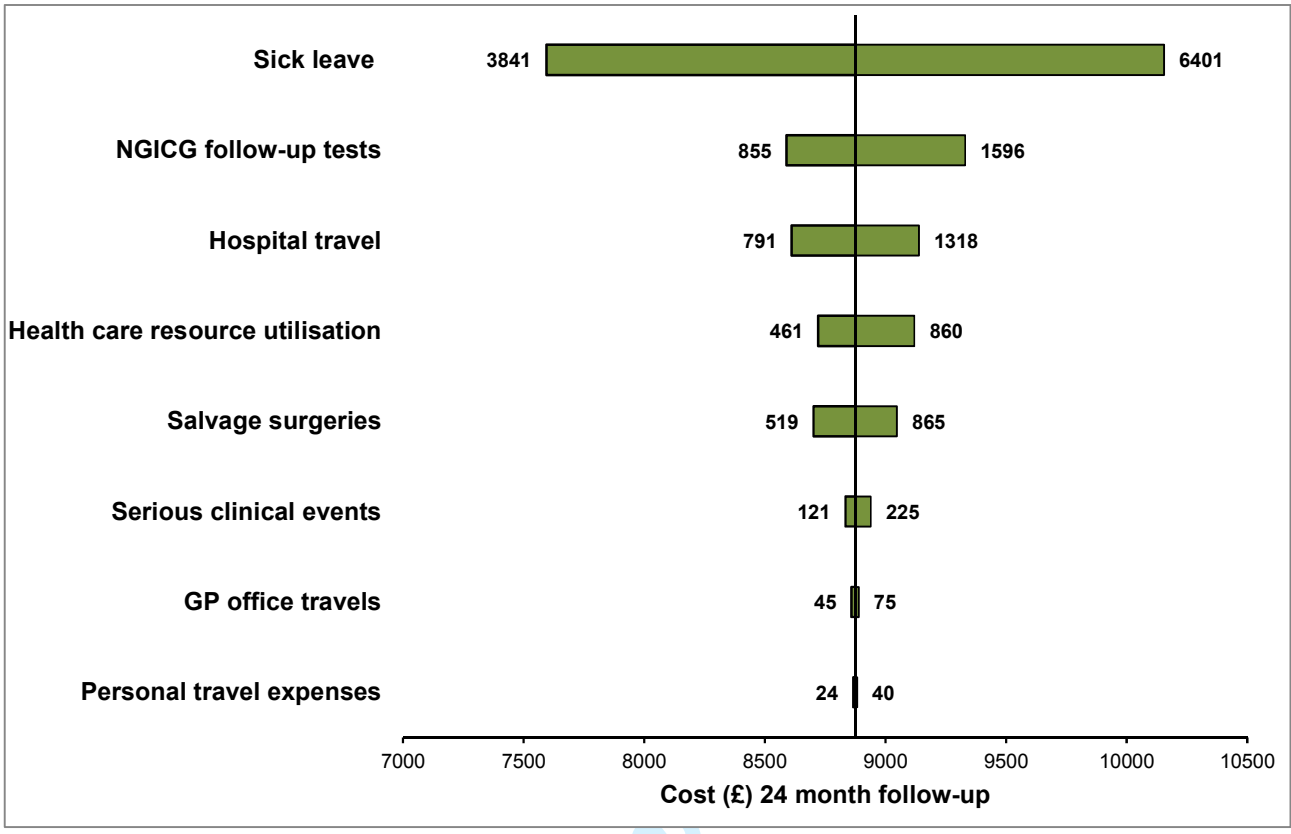
Cost of follow-up.

Mean cost of follow-up per patient per 3 month follow-up cycle with error bars (95% confidence intervals).
 In a general linear model, mean difference between groups was 60.0 £ (95 CI interval: 7.0 – 113.0, p = 0.02).

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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	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
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	NA

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2		assessing outcomes) and how	
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4		11b If relevant, description of the similarity of interventions	5
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	10
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	11
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	11
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	4
13		14b Why the trial ended or was stopped	11
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15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	OK
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	OK
17		by original assigned groups	
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19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	OK
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	OK
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	OK
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	OK
26			
27	Discussion		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18-19
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	19
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18
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32	Other information		
33	Registration	23 Registration number and name of trial registry	2
34	Protocol	24 Where the full trial protocol can be accessed, if available	23
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	21
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38 *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

39 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

40 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002391.R1
Article Type:	Research
Date Submitted by the Author:	28-Jan-2013
Complete List of Authors:	Augestad, Knut Magne; University Hospital of North Norway, Norwegian National Center of Integrated Care and Telemedicine Norum, Jan; Northern Norway Regional Health Authority trust, Dehof, Stefan; Helgeland Hospital, Mo i Rana, Department of Surgery Aspevik, Ranveig; Helgeland Hospital, Mo i Rana, Department of Surgery Ringberg, Unni; Nordbyen Primary Care Office, Nestvold, Torunn; Nordland Hospital Trust, Bodø, Department of Surgery Vonen, Barthold; Nordland Hospital Trust, Bodø, Department of Surgery Skrøvseth, Stein; University Hospital North Norway, Norwegian National Center of Integrated Care and Telemedicine Lindsetmo, Rolv-Ole; University Hospital North Norway, Department of Gastrointestinal Surgery
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Surgery, Evidence based practice, Health services research, Health economics, Gastroenterology and hepatology
Keywords:	colorectal cancer, follow-up, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, health service research, SURGERY

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Manuscripts

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

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42 Word count: 3650
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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; $\Delta - 2.23$, p=0.20; EQ-5D index; $\Delta - 0.10$, p=0.48, EQ-5D VAS; $\Delta - 1.1$, 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,

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3 wide consensus has not been reached regarding just what an intensive follow-up
4 strategy should entail.⁵⁻⁸ New surveillance trials in progress are not likely to fully settle
5 the issue either.⁹⁻¹² What none of the available clinical recommendations for follow-up
6 have addressed adequately is the *setting* where this follow-up should occur: conducted
7 by specialists who originally treated the cancer at hospitals, or in the offices of local
8 general practitioners (GP's).² Increasingly, the benefits of greater involvement of
9 primary care providers in the on-going management of chronic illnesses are recognised.
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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 UK's 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	X	X	X	X	X	X
Contrast enhanced liver ultrasound (CEUS)			X	X	X	X	X	X	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 trial 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

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3 hospital where they received surgical treatment approximately 3-4 weeks
4 postoperatively. At this visit, a clinical examination was performed and information
5 about the histology and results of the surgery was shared with each patient. If the
6 patients provided informed consent, they were randomised to follow-up either by their
7 GP (intervention) or at the surgical outpatient clinic (controls) using a web-based
8 randomisation service managed by the Norwegian University of Science and Technology
9 (www.ntnu.no). The randomisation ratio was 1:1, patients were stratified according to
10 the Dukes' staging (A,B,C) and whether they had a stoma. The local trial investigator was
11 not involved in the subsequent follow-up appointments in any way. Recruited patients
12 were not informed about other patients recruited in the same trial. Similarly, no
13 information regarding trial progress and allocation was revealed to participating GPs or
14 surgeons. However, as GP organised follow-up represented a new practice, blinding was
15 not possible in the intervention arm.
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25 26 27 **Primary outcome measures**

28 *Quality of life*

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30 Primary outcome measure in this trial was the global health status on the EORTC QLQ C-
31 30 questionnaire. QoL measurements were collected at baseline and 3,6,9,12,15,18,21
32 and 24 months, i.e:
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37 *The European Organization for Research and Treatment of Cancer QoL Questionnaire*
38 *(EORTC QLQ C-30):* EORTC QLQ C-30 incorporates nine multi-item scales: five functional
39 scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue,
40 pain, nausea/vomiting); and a global health status/QoL scale. Six single-item scales are
41 also included (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial
42 difficulties).¹⁸
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49 *The EuroQol-5D (EQ-5D™; EuroQol Group, Rotterdam, The Netherlands):* Is a
50 standardized generic instrument employed to measure of health outcome. EQ-5D
51 measures five dimensions of health-related QoL (HRQoL): mobility, self-care, usual
52 activities, pain/discomfort and anxiety/depression. Each dimension is rated at three
53 levels: no problems (1), some problems (2) and major problems (3).¹⁹ Based on
54 preferences elicited from a general population, EQ-5D health states (e.g. 1-1-2-1-3) may
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3 be converted into utility scores (= index scores, IS). In this trial we used preferences
4 elicited from a UK population, as no similar Norwegian preferences exist.²⁰
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6 EQ Visual Analogue Scale (EQ VAS) records the respondent's self-rated health status on
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8 a vertically graduated (0–100) visual analogue scale.
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10 11 12 13 **Secondary outcome measures**

14 *Cost-effectiveness*

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

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

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54 At the baseline appointment, patients recruited received nine questionnaires (as part of
55 the patient decision-support pamphlet) corresponding with the nine follow-up cycles
56 (table 1). The questionnaires contained questions about QoL, patient satisfaction, and
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3 cost and resource utilisation. Questionnaires were returned by mail every three months
4 by the patients to the trial centre until 24 months postoperatively. These questionnaires
5 were optically readable, being consecutively registered in the trial database. A research
6 assistant was responsible for data collection, database input and patient reminders
7 when missing questionnaires. The reminders were sent to participating patients when
8 the questionnaires were 3 months overdue the estimated follow-up schedule. All
9 questionnaires were dated and we could thus monitor trial progression. In case of
10 missing information about cost elements we either reviewed the hospital EMR, or
11 performed telephone interview with participating surgeons, GPs or patients.
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20 **Sample size calculation**

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

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

^dThe 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 £.

^eNorwegian Health Authorities. Reimbursement and DRG weighting in Norwegian Hospitals 2012: <http://www.helsedirektoratet.no/publikasjoner/regelverk-innsatsstyr-finansiering-2012/Sider/default.aspx>.

^f1 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

^gStatistics in Norway 2011: Average annual salary 750 000 NOK (80 000 £) hospital consultant.

^hCost rates Department of Radiology and Nuclear Medicine University Hospital North Norway.

ⁱKorner 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.

^jEstimated 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 months 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				
Cøkum	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			156.9			76.7 (160.1,			117.1
£ (SD)			(145.0)			$p<0.001$)			(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			4.1			9.0 (9.1,			6.6
£ (SD)			(7.9)			p<0.001)			(8.9)
Out of pocket expenses									
Mean cost			2.7			4.3 (15.0,			3.5 (11.9)
£ (SD)			(7.7)			p=0.10)			
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			66.4			70.1 (112.2,			68.2
£ (SD)			(100.1)			p=0.67)			(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			121.1			132.2 (166.7,			126.6
£ (SD)			(152.8)			p=0.39)			(159.8)
Work loss									
Patients in paid work (n)	17			12			29		
Days off work mean (SD)	215 (168)			198 (190,			208 (219)		
Mean cost			2440			1884 (2092,			2086
£ (SD)			(1906)			p=0.45)			(2014)
Serious clinical events									
Number of events	22			26			48		
Mean cost			261.6			573.1 (838.9,			444.0
£ (SD)			(157.7)			p=0.14)			(662.4)
Metastases surgeries									

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

^a Mean travel cost for hospital travels, see 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.

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3 4-7 Two systematic reviews, comparing follow-up trials have been published. 2,3 Due to
4 the variation in the follow-up programs included in these reviews, it is not possible to
5 infer the best combination of consultations, blood tests, colonoscopy, radiological
6 investigations and level of care to maximise the outcomes. 2 Large randomised trials are
7 under way (COLOFOL, GILDA, FACS) but results are most likely years away. 9-11 Few
8 published surveys have evaluated the effect of a GP organised follow-up program. Two
9 surveys have reported on quality of life in a primary care based follow-up program, and
10 a single cost-effectiveness analysis of intensified hospital based follow-up was published
11 in 2004. 30-32 Surveys have assessed cost of follow-up in a Norwegian setting. In a
12 retrospective survey 314 patients were assessed with regards to cost, compliance and
13 success rate of curative surgery. It was concluded that the cost of one successful curative
14 surgery was \$ 25 289, and that further implementation of such a program should be
15 debated. 33 Harms and unintended effects of a follow-up program is poorly explored.
16 Especially is the rate of false positive tests in a follow-up program unknown. Current
17 surveillance is often based on serial CEA measurements, this biomarker has several
18 pitfalls and shortcomings. In a recent survey, it is shown that the diagnostic accuracy of
19 serial measurement of CEA is low, and is impacted by the cut off value. 34 These aspects
20 are of high importance when designing a follow-up program, as false positive test
21 probably has a negative impact on the patients quality of life. Finally, there exist
22 considerable variance in follow-up strategies, internationally and at a national level. 35
23 This makes outcome comparison between different follow-up strategies challenging.
24 For other cancer conditions more cost-effective ways of organising follow-up is
25 extensively described and evaluated. For breast cancer patients, nurse lead telephone
26 and GP organised follow-up is cost-effective 36,37,38 with no increase in the frequency of
27 SCE. 39 Nevertheless, the quality of primary care cancer management is still debated. 40-42

47 **Strengths and limitations**

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

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3 decision making in cancer are on way forward. In this study, a decision support
4 pamphlet was part of the intervention and the patient and the GP organising the follow-
5 up received a decision support tool. Detailed instructions of forthcoming follow-up
6 consultations and test were given. We believe this decision support tool contributed to a
7 high follow-up guideline adherence (table 6, GP 592 tests vs. surgeon 513 tests). Thirdly,
8 we have shown that the rate of SCE and time to diagnosis of cancer recurrence is
9 comparable between groups. In our opinion, this is an indicator of adequate quality in a
10 GP organised follow-up program.
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18 There exist limitations. Firstly, it might be argued that we were missing important
19 information by choosing another endpoint than survival. However, this trial was
20 designed primarily to evaluate whether general practice follow-up results in effect on
21 patient specific quality of life and cost effectiveness. We acknowledge that this choice of
22 endpoint might impact the observed frequency of serious clinical events and time to
23 cancer diagnoses, as a higher number of SCE and cancer recurrences would have
24 occurred with a longer follow-up time. Similarly, costs will be impacted by a longer
25 follow-up time. However, when health care cost of follow-up is analysed separately
26 (table 5, figure 3), cost spendings are significantly lower in the GP group compared to
27 the surgeon group. Secondly, generalizability and cost transferability across
28 jurisdictions might be challenging, as elements of cost data may vary from place to
29 place.⁴⁴ It might be argued that this is a single country trial with limited generalizability.
30 However, we do not think this is the case. Comparable follow-up trials have been
31 performed in countries like USA, Canada, UK, Australia, Netherlands.^{30,38,39,45} These
32 surveys are commonly cited and thus accepted as generalizable. In Norway, the GP has a
33 traditional gatekeeper function and plays a central role managing resource use in
34 secondary care. Similarly, many European countries have a health care organisation
35 where the GP plays a central role as gatekeeper to access of secondary health care
36 service. In our trial, guidelines for dealing with aspects of generalizability and
37 transferability were applied, and variations in units costs were included in the
38 sensitivity analyses (see figure 4).⁴⁴
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54 Finally, the trial was stopped after 1884 follow-up months due to no significant effect of
55 the intervention on global health score and implementation of a new national follow-up
56 program. This is a limitation, as it will impact the interpretation of cancer recurrence.
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3 However, it would have been unethical to spend large resources over years to complete
4 an intervention with a 4% probability of showing a significant impact on global health
5 score.
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8 9 **Implication for patients, decision makers and clinicians**

10 Colon cancer in numbers is the third largest cancer type worldwide and a considerable
11 number of patients are enrolled in a post surgical surveillance program, resulting in
12 significant societal cost. However, as there is no evidence based consensus of how to
13 design cost-effective follow-up programs, differences in tests, test frequency and level of
14 care will have high impact on societal cost spending. Therefore, the cost driving
15 elements in a colon cancer follow-up program have to be critically evaluated.
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18 From a societal perspective, this survey has important implications. It may be argued
19 that there are limited benefits from having GPs organising the follow-up program, as the
20 radiological examinations and the colonoscopy have to be performed in-hospital
21 anyway. However, we believe the most important factors causing a less costly GP follow-
22 up are: *Better coordination of care:* As shown in table 5, GP organised follow-up leads to
23 fewer hospital travels. We believe this is mainly caused by improved coordination of
24 care, for instance by performing multiple radiological test at the same hospital visit.
25 Interestingly the GP group had fewer extra travels (GP 52 travels versus Surgeon 102
26 travels) due to poor logistics (table 5). *Cost of GP consultation vs. hospital consultation:*
27 The societal cost of GP consultations is lower compared to cost of hospital consultations,
28 due to a more costly hospital infrastructure. *Complex and chronic conditions:* Patients
29 surgically treated often have other chronic illnesses, and there is a trend towards higher
30 involvement of primary care in treating these conditions as described in the chronic care
31 model.¹³ *Sick leave:* Although not statistical significant, patients in the GP group return
32 to work 17 days (mean) earlier compared to patients in the surgeon group.
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35 In a time with escalating health care cost, especially in cancer care, improved
36 coordination of care are of increasing importance.
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39 From a patient perspective, GP organised follow-up is associated with high quality of
40 care and leads to fewer time consuming hospital travels. Our study demonstrates that a
41 decentralised follow-up has no negative impact on quality of life, length to cancer
42 diagnoses and follow-up guideline adherence.
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45 From a hospital perspective, a transfer of follow-up programs to primary care have
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3 economical and organisational implications. GP organised follow-up may be an effective
4 way of reducing the burden on busy hospital clinics.
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7 8 **Conclusion**

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

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

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28 **Figure 1.** Flow of participants.

29 Patients were enrolled in the 2007 NGICG (Norwegian Gastrointestinal Cancer Group, table 1) follow-up
30 program in both trial arms. The program are divided in 3 months cycles i.e.; clinical examination at 1
31 (baseline), 3,6,9,12,15,18,21 and 24 months, carcinoembryonic antigen (CEA) measurement at 3 months
32 intervals, chest x-ray and contrast enhanced liver ultrasound every 6 months, and colonoscopy 1 time
33 during 24 months (table 1).
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39 **Figure 2 A, B, C.** Health related quality of life 1-24 postoperative month.

40 EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.
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44 **Figure 3.** Cost of follow-up per cycle.

45 Mean cost of follow-up per patient per 3 month follow-up cycle with error bars (95% confidence
46 intervals).
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50 **Figure 4.** Sensitivity analyses of cost driving elements in surveillance.

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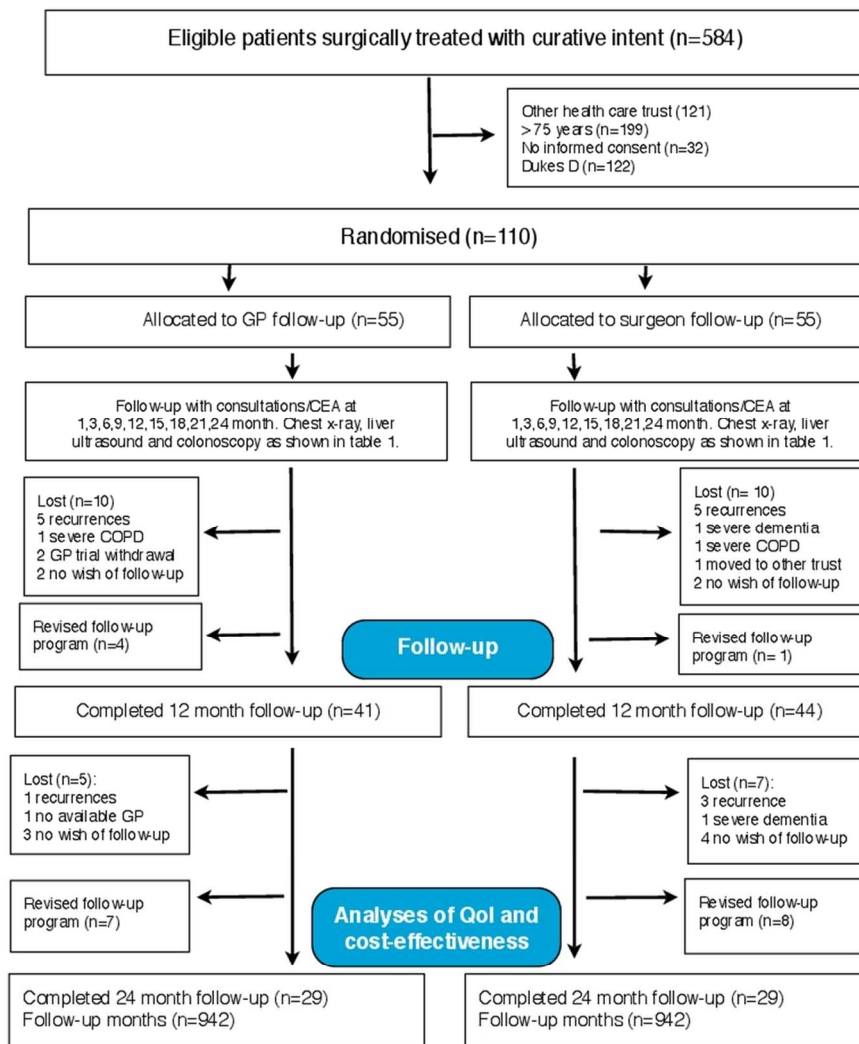


Figure 1. Flow of participants. Patients were enrolled in the 2007 NGICG (Norwegian Gastrointestinal Cancer Group, table 1) follow-up program in both trial arms. The program are divided in 3 months cycles i.e.; clinical examination at 1 (baseline), 3,6,9,12,15,18,21 and 24 months, carcinoembryonic antigen (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).

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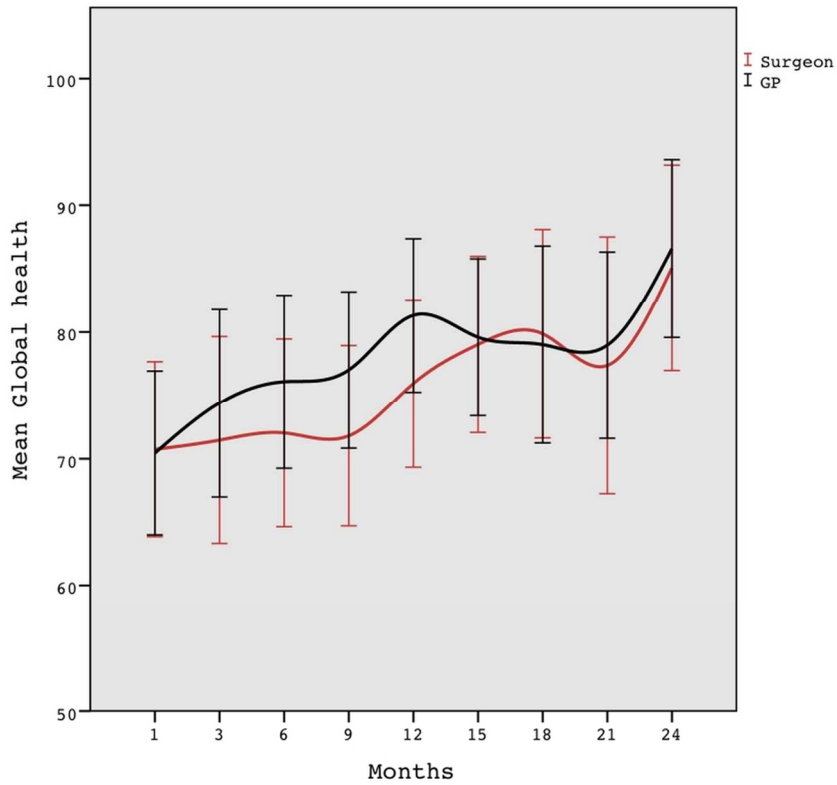


Figure 2 A, B, C. Health related quality of life 1-24 postoperative month. EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.

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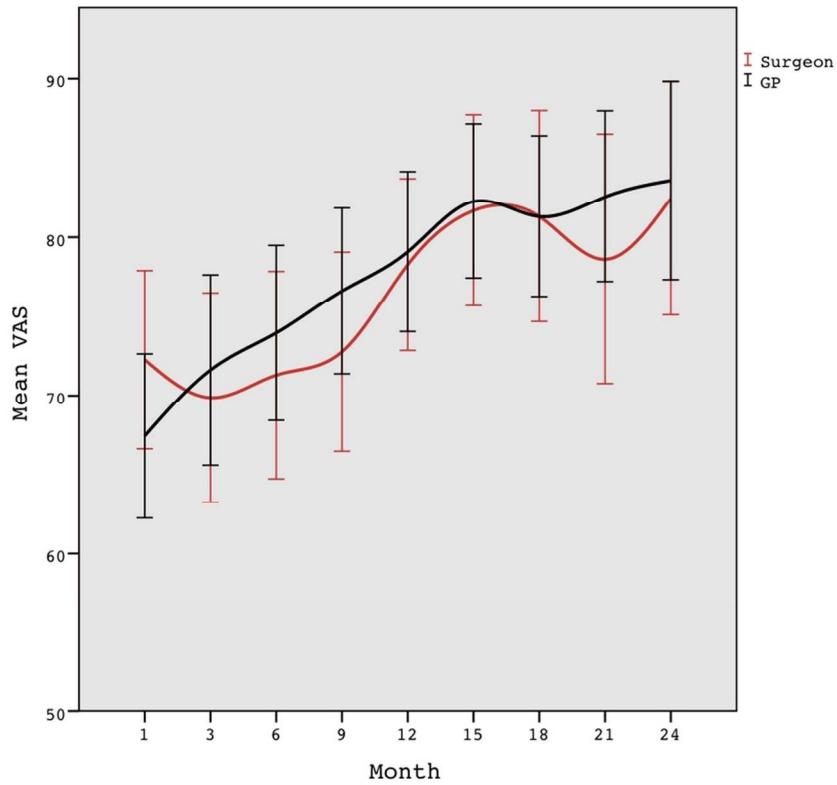


Figure 2 A, B, C. Health related quality of life 1-24 postoperative month. EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.

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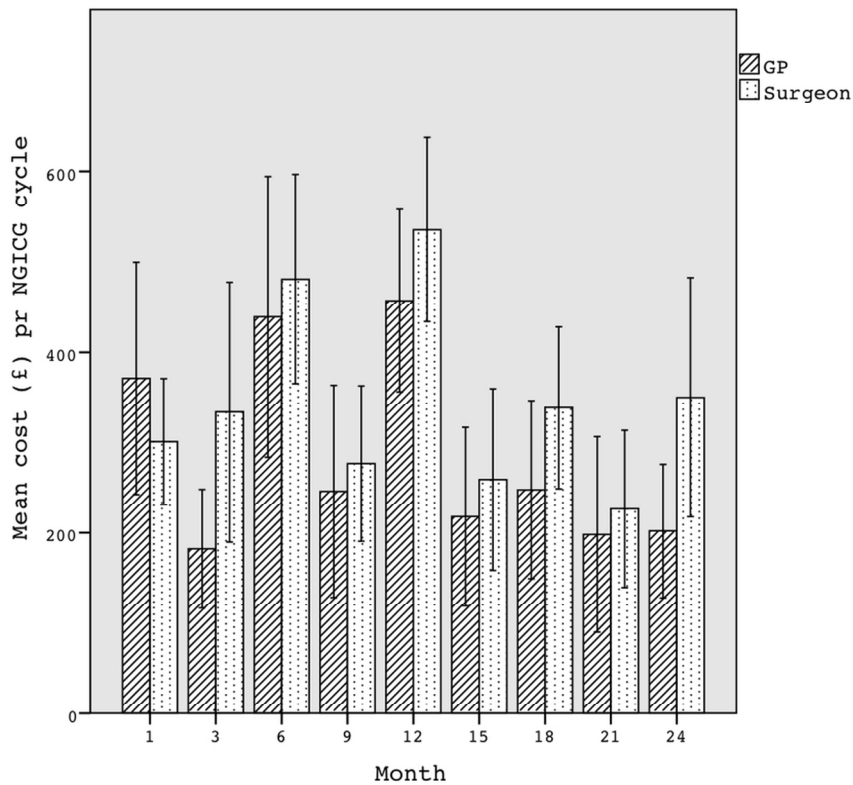


Figure 3. Cost of follow-up per cycle.
 Mean health care cost of follow-up per patient per 3 month follow-up cycle with error bars (95% confidence intervals).
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

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

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*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.

For peer review only

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7 **Cost-effectiveness and quality of life in surgeon versus general practitioner**
8 **organised colon cancer surveillance**~~General practitioner organised follow-up~~
9 ~~after curative colon cancer resection is not inferior to surgeon organised follow-~~
10 ~~up.~~ **A randomised controlled trial.**

11
12 Knut Magne Augestad, *leader health services research*^{1,2,7}, Jan Norum, *professor in*
13 *clinical oncology*^{3,7}, Stefan Dehof, *consultant in general surgery*⁴, Ranveig Aspevik,
14 *consultant in digestive surgery*⁴, Unni Ringberg, *general practitioner*⁵, Torunn Nestvold,
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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; $\Delta - 2.23$, p=0.20; EQ-5D index; $\Delta - 0.10$, p=0.48, EQ-5D VAS; $\Delta - 1.1$, 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 ~~significant~~ 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.
- ~~The trial was stopped after 1884 follow-up months due to no impact of the primary intervention on QoL.~~

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

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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 ~~ongoing~~ 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 UK's 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), ~~rate of false positive tests~~, time to diagnosis of SCE and cancer recurrence, and frequency of metastases surgery.

Methods

This was a randomised controlled trial ~~with institutional ethical approval and patient written consent~~ 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. ~~Patients were followed until June 2012~~ 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

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7 entering the trial. The trial was registered in ClinicalTrials.gov with identifier
8 NCT00572143. Due to organisational delay the trial was registered 11th of December
9 2007. specified study start in ClinicalTrials.gov is June 2007.

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14 **Participating patients inclusion and exclusion criteria, hospitals, primary and**
15 **secondary care professionals**

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19 Inclusion criteria were Patients were eligible if they were aged less than 75 years and
20 with had recent surgery for colon cancer with Dukes' stage A, B or C. Patients receiving
21 postsurgical adjuvant chemotherapy (some Dukes' B and all Dukes' C) were also eligible.

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23 Exclusion criteria were patients older than 75 years old, patient belonging to health care
24 trust not participating in the trial, not able to provide informed consent and Dukes D.

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27 **Hospitals, primary and secondary care professionals**

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29 Three local hospitals and one university hospital participated. Approximately 100
30 patients with colon cancer are surgically treated annually at these four hospitals. All 550
31 GPs in the region received written information, 448 GPs consented to participate in the
32 trial (figure 1).

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36 **Objective and hypotheses**

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

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50 **Description of intervention**

51 We defined this as a complex intervention, consisting of several interconnecting parts. ¹⁶
52 To ensure high follow-up guideline adherence by patients allocated to GP follow-up, we
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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)
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	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 trial 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,

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7 pain, nausea/vomiting); and a global health status/QoL scale. Six single-item scales are
8 also included (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial
9 difficulties).¹⁸ ~~Primary outcome measure in this trial was the global health status.~~

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12 *The EuroQol-5D (EQ-5DTM; EuroQol Group, Rotterdam, The Netherlands):* Is a
13 standardized generic instrument employed to measure of health outcome. EQ-5D
14 measures five dimensions of health-related QoL (HRQoL): mobility, self-care, usual
15 activities, pain/discomfort and anxiety/depression. Each dimension is rated at three
16 levels: no problems (1), some problems (2) and major problems (3).¹⁹ Based on
17 preferences elicited from a general population, EQ-5D health states (e.g. 1-1-2-1-3) may
18 be converted into utility scores (= index scores, IS). In this trial we used preferences
19 elicited from a UK population, as no similar Norwegian preferences exist.²⁰
20 EQ Visual Analogue Scale (EQ VAS) records the respondent's self-rated health status on
21 a vertically graduated (0-100) visual analogue scale.
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30 **Secondary outcome measures**

31 *Cost-effectiveness*

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

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45 Time to cancer diagnoses was defined as the time from occurrence of a serious clinical
46 event (SCE, dated in the GP referral or hospital EMR record) until the date of diagnoses
47 of a ~~cancer recurrence~~SCE. A ~~serious clinical event~~ (SCE_s) was defined as an episode
48 where cancer recurrence was suspected. A SCE can be triggered by either symptoms
49 reported (at follow-up or in between follow-up), clinical findings at follow-up or findings
50 by screening test. ~~A SCE~~Syptoms and clinical findings initiating a diagnostic check-up
51 ~~was~~ere defined as: Cancer suspect lesion revealed at colonoscopy, increase in CEA
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7 measurements shown by repeated measurements, blood in stool detected by the
8 Hemofec (FOB) test, unexplained abdominal pain, unexplained weight loss of 5 kg
9 during the last three months, cancer-suspect lesions detected by rectal examination,
10 palpable lymphadenopathy, metastatic suspect lesions shown by chest x-ray,
11 ultrasound of liver or CT scan, cancer suspect findings at clinical examination,
12 occurrence of cancer related symptoms.
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15 16 17 **Data collection**

18 At the baseline appointment, patients recruited received nine questionnaires (as part of
19 the patient decision-support pamphlet) corresponding with the nine follow-up cycles
20 (table 1). The questionnaires contained questions about QoL, patient satisfaction, and
21 cost and resource utilisation. Questionnaires were returned by mail every three months
22 by the patients to the trial centre until 24 months postoperatively. These questionnaires
23 were optically readable, being consecutively registered in the trial database. A research
24 assistant was responsible for data collection, database input and patient reminders
25 when missing questionnaires. The reminders were sent to participating patients when
26 the questionnaires were 3 months overdue the estimated follow-up schedule. All
27 questionnaires were dated and we could thus monitor trial progression. In case of
28 missing information about cost elements we either reviewed the hospital EMR, or
29 performed telephone interview with participating surgeons, GPs or patients.
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36 37 **Sample size calculation**

38 In June 2007 sample size calculations were based on a significance level of 5% and
39 power set at 80%, this indicated that we needed 136 patients to detect a 10 units QoL
40 difference (i.e. a small to moderate improvement) on EORTC QLQ C-30 Global Health
41 score with a standard deviation of 20. Definition of “a small to moderate improvement
42 on QoL” (i.e 10 units on the global health score), and standard deviation estimates of
43 QoL (colon cancer patients with localised disease), were retrieved from previous
44 published publications.^{21,22}
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50 51 **Economic analysis**

52 BMJ guidelines for economic analyses alongside randomised controlled trials were
53 employed.²³ As the trial revealed no difference in quality of life, a cost-minimisation
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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.^{26,24}

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-innsatsstyrte-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 months 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 were treated as missing and when missing forms, missing data were imputed

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7 imputed by the last observation carried forward (LOCF). Conditional power (CP) was
8 defined as the chance of getting statistically significant results at the end of the trial
9 given the data so far. ^{27,28,25,26} We defined a CP < 15% as a sufficient threshold to stop
10 early.^{29,27} Results were expressed as mean differences for continuous outcomes with
11 corresponding standard deviations (SD), 95% confidence intervals, and associated p-
12 values. P-values were reported with two decimal places with p-values less than 0.001
13 reported as p < 0.001. For all tests we used p = 0.05 level of significance. All analyses
14 were performed with IBM SPSS Statistics v 19.0 (IBM Company SPSS 2010) and
15 Microsoft Excel for Mac 2011.
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20 Results

21 110 patients surgically treated for colon cancer met the inclusion criteria and agreed to
22 participate (figure 21). The control and intervention group were matched at baseline for
23 demographic and medical characteristics and there were no significant differences
24 between groups (table 3).
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28 Trial flow and dropouts

29 During the follow-up period 628 follow-up cycles (i.e 1884 follow-up months; GP 942
30 months vs. surgeon 942 months) were performed (GP 314 cycles vs. surgeon 314
31 eyes). 854 patients (75%) (GP 41 vs. surgeon 44) were followed for 12 months, 58
32 patients (52%) (GP 29 vs. surgeon 29) were followed for 24 months. Eleven patients
33 withdrew during trial due to no wish of follow-up (GP 5 vs. surgeon 6), 20 patients were
34 transferred to a new follow-up program (GP 9 vs. surgeon 11). 32 patients were defined
35 as lost (surgeon 17 vs. GP 15), of those 14 patients had cancer recurrence (surgeon 8 vs.
36 GP 6). 20 patients (surgeon 9 vs. GP 11) were transferred to the new national colon
37 cancer surveillance program (figure 1).
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45 Response rate

46 We received 636 of the expected 657 questionnaires (response rate 96%), of those 600
47 (91%) questionnaires (GP 299 vs. surgeon 301) were included in final cost and QoL
48 analyses. 21 (4%) of questionnaires (surgeon 11 vs. GP 10) were not returned and 36
49 questionnaires (surgeon 18 vs. GP 18) were excluded from analyses due to insufficient
50 identification.
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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.

28 questionnaires (5%) were excluded from analyses (GP 15 vs. surgeon 13) due to incomplete data or missing information, i.e. 600 follow-up questionnaires (95%) (GP 299 vs. surgeon 301) were included in analyses. 84 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. Eleven patients withdrew during trial due to no wish of follow-up (GP 5 vs. surgeon 6), 20 patients were transferred to a new follow-up program (GP 9 vs. surgeon 11).

Implementation of new national colon cancer follow-up guidelines triggered an interim analysis in June 2012 (80% of pre-planned recruitment).⁷ There was at this point 4% probability (conditional power) of showing a significant result, 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				
Cøkum	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)	- 2.23 (-5.7 - 1.2)	0.20
GP	70.4 (20.8)	81.3 (17.0)	86.5 (16.2)		
Physical functioning					
Surgeon	80.5 (23.6)	88.8 (15.0)	88.0 (17.0)	- 2.4 (-5.7 - 0.8)	0.14
GP	74.5 (24.9)	90.6 (16.6)	93.3 (16.0)		

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, see 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. ^a 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/_per follow-up cycle £ (SD)	351 (324)	292 (332.9)	324.1 (330.0)	0.02
Bootstrapped 95% c.i.	315 - 386	255 - 327	296 - 348	
Mean difference £		58		
Healthcare cost/_24 month follow-up £ (SD)	3178 (2917)	2651 (3004)	2917(2970)	0.03
Bootstrapped 95% c.i.	2833 - 3485	2228 - 3006	2660 - 3147	
Mean difference £		529		
Societal cost/_per follow-up cycle £ (SD)	1098 (324)	914 (332)	1007 (340)	< 0.001
Bootstrapped 95% c.i.	1062 - 1139	877 - 954	981 - 1034	
Mean difference £		184		
Societal cost/_24 month follow-up £ (SD)	9889 (2917)	8233 (2996.1)	9068 (3068.2)	< 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 28-57 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) (table 7). Five patients died (all deaths caused by disseminated colon cancer) during the follow-up period (GP 1 vs. surgeon 4).

Table 7. Clinical presentation of colon cancer recurrence by trial group

Case no	Sex	Presenting problem	Routine/interval	Diagnostic tests	Metastatic site	Time to diagnoses (days)	Metastases surgery	Time to surgery (days)
GP group								
1	F	Elevated CEA	routine	CEUS PET-CT	Disseminated	27	no	inoperable
2	M	Abdominal pain	interval	CEUS	Liver	21	no	inoperable
3	M	Elevated CEA	routine	CEA CT thorax CT abdomen	Disseminated	71	no	inoperable
4	M	Metastatic lesion detected at CEUS	routine	CEUS CT thorax CT abdomen	Liver	4	yes	38
5	F	Abdominal pain, normal CEA, CT and CEUS, disseminated cancer detected at laparotomy	interval	CEUS CT thorax CT abdomen	Disseminated	270	yes	270
6	M	Abdominal tenderness	interval	Anorectoscopy CT thorax CT abdomen	Local recurrence	2	yes	30
Surgeon group								
7	M	Metastatic lesion detected chest x-ray	routine	CT thorax CT abdomen	Lung	45	yes	62
8	M	Stoma bleeding	interval	Colonoscopy CT thorax CT abdomen	Local and lymph node recurrence	10	no	inoperable
9	M	Weight loss Night sweating	routine	CT Thorax CT abdomen	Lung	45	no	inoperable
10	M	Metastatic lesion detected at chest x	routine	CT Thorax CT abdomen	Lung	4	yes	42

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11	M	Metastatic lesion detected-CEUS	routine	MR liver CT-thorax CT-abdomen	Liver	3	yes	43
12	F	Abdominal-pain	interval	CT-abdomen CT-thorax	Disseminated	16	no	inoperable
13	M	Elevated-CEA	routine	CT-thorax CT-abdomen CT-liver	Liver Lung	30	no	inoperable
14	F	Occult blood in faeces	interval	CT-thorax CT-abdomen CEUS	Liver	31	yes	35

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 a](#) 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

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7 infer the best combination of consultations, blood tests, colonoscopy, radiological
8 investigations and level of care to maximise the outcomes.² Large randomised trials are
9 under way (COLOFOL, GILDA, FACS) but results are most likely years away.⁹⁻¹¹ Few
10 published surveys have evaluated the effect of a GP organised follow-up program. Two
11 surveys have reported on quality of life in a primary care based follow-up program, and
12 a single cost-effectiveness analysis of intensified hospital based follow-up was published
13 in 2004.^{30-32,28-30} Surveys have assessed cost of follow-up in a Norwegian setting. In a
14 retrospective survey 314 patients were assessed with regards to cost, compliance and
15 success rate of curative surgery. It was concluded that the cost of one successful curative
16 surgery was \$ 25 289, and that further implementation of such a program should be
17 debated.³³ Harms and unintended effects of a follow-up program is poorly explored.
18 Especially is the rate of false positive tests in a follow-up program unknown. Current
19 surveillance is often based on serial CEA measurements, this biomarker has several
20 pitfalls and shortcomings. In a recent survey, it is shown that the diagnostic accuracy of
21 serial measurement of CEA is low, and is impacted by the cut off value.³⁴ These aspects
22 are of high importance when designing a follow-up program, as false positive test
23 probably has a negative impact on the patients quality of life. Finally, there exist
24 considerable variance in follow-up strategies, internationally and at a national level.³⁵
25 This makes outcome comparison between different follow-up strategies challenging.
26 ~~However,~~ For other cancer conditions more cost-effective ways of organising follow-up
27 is extensively described and evaluated. For breast cancer patients, nurse lead telephone
28 and GP organised follow-up is cost-effective^{36,37,38,33} with no increase in the frequency of
29 SCE.^{39,34} Nevertheless, the quality of primary care cancer management is still debated.⁴⁰⁻
30 ^{42,35-37}

Strengths and limitations

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44 Our trial has several strengths. Firstly, this is the first randomised trial addressing the
45 economical implications and time to recurrent cancer diagnoses in a GP organised colon
46 cancer follow-up program. We have shown that GP organised follow-up, even with
47 increased frequency of health care contacts, was associated with cost savings and no
48 decline in quality of life. Secondly, poor guideline compliance has been shown to
49 represent a problem in cancer follow-up programs.^{43,38} However, tools to support
50 decision making in cancer are on way forward. In this study, a decision support
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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 ~~some~~ 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. ~~Nevertheless, during our trial length of 1884 follow-up months we observed fewer recurrences than anticipated (15,4%), however this might be related to the decreasing rate of colon cancer recurrences at a national level (unpublished data Cancer Registry of Norway).~~ 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.⁴⁴³⁹ 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.

~~30,38,39,45,28,33,34,40~~ 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).⁴⁴³⁹

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7 Finally, the trial was stopped after 1884 follow-up months due to no significant effect of
8 the intervention on global health score and implementation of a new national follow-
9 up program. This might be a potential is a limitation, as it will impact the interpretation
10 of cancer recurrence. However, it would have been unethical to spend large resources
11 over years to complete a trial an intervention with a 4% probability of proving the
12 primary hypotheses. showing a significant impact on -global health score.
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17 **Implication for patients, decision makers and clinicians**

18 Colon cancer in numbers is the third largest cancer type worldwide and a considerable
19 number of patients are enrolled in a post surgical surveillance program, resulting in
20 significant societal cost. However, as there is no evidence based consensus of how to
21 design cost-effective follow-up programs, differences in tests, test frequency and level of
22 care will have high impact on societal cost spending. Therefore, the cost driving
23 elements in a colon cancer follow-up program have to be critically evaluated. For many
24 patients, follow-up leads to a number of long distance travels to hospital, causing high
25 societal cost. Thus, from an economical perspective, GP organised follow-up is cost-
26 effective due to a better coordination of care.
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31 From a societal perspective, this survey has important implications. -It may be argued
32 that there are limited benefits from having GPs organising the follow-up program, as the
33 radiological examinations and the colonoscopy have to be performed in-hospital
34 anyway. However, we believe the most important factors causing a less costly GP follow-
35 up are: Better coordination of care: As shown in table 5, GP organised follow-up leads to
36 fewer hospital travels. We believe this is mainly caused by improved coordination of
37 care, for instance by performing multiple radiological test at the same hospital visit.
38 Interestingly the GP group had fewer extra travels (GP 52 travels versus Surgeon 102
39 travels) due to poor logistics (table 5). Cost of GP consultation vs. hospital consultation:
40 The societal cost of GP consultations is lower compared to cost of hospital consultations,
41 due to a more costly hospital infrastructure. Complex and chronic conditions: Finally,
42 Ppatients surgically treated often have other chronic illnesses, and there is a trend
43 towards higher involvement of primary care in treating these conditions as described in
44 the chronic care model.¹³ Sick leave: Although not statistical significant, patients in the
45 GP group return to work 17 days (mean) earlier compared to patients in the surgeon
46 group.
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7 In a time with escalating health care cost, especially in cancer care, ~~these improved~~
8 ~~coordination of care aspects~~ are of increasing importance.

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10 From a patient perspective, GP organised follow-up is associated with high quality of
11 care ~~and leads to fewer time consuming hospital travels~~. Our study demonstrates that a
12 decentralised follow-up has no negative impact on quality of life, length to cancer
13 diagnoses and follow-up guideline adherence. ~~Finally, patients surgically treated often~~
14 ~~have other chronic illnesses, and there is a trend towards higher involvement of primary~~
15 ~~care in treating these conditions as described in the chronic care model.⁴³~~

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17 From a hospital perspective, a transfer of follow-up programs to primary care have
18 economical and organisational implications. GP organised follow-up may be an effective
19 way of reducing the burden on busy hospital clinics.
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22 23 24 **Conclusion**

25 The present study suggests that colon cancer follow-up can safely be performed by GPs,
26 with no negative impact on quality of life and to a lower cost. ~~However, there exist~~
27 ~~limitations. 13% (n=14) patients had colon cancer recurrence, this low recurrence rate~~
28 ~~is most likely caused by limited long term follow-up as most recurrences occur within 3~~
29 ~~years. Furthermore, t~~~~However, solid evidence is missing regarding the optimal follow-up~~
30 ~~program that maximise survival.~~~~he best combination of consultations, radiological test,~~
31 ~~blood samples and colonoscopy that optimizes cancer survival is still unknown. We~~
32 ~~therefore argue that cost driving elements of colon cancer surveillance should be~~
33 ~~critically evaluated, when designing and implementing follow-up programs, as cancer~~
34 ~~surveillance represents a huge financial burden for society. Finally, little is known about~~
35 ~~the potential harms of follow-up, especially when it comes to the impact of false positive~~
36 ~~tests. Further research is needed to settle these controversies, and new methods of~~
37 ~~decision-analytic modeling in combination with emerging data from on-going~~
38 ~~randomised trials must be applied. We believe new methods of comparative~~
39 ~~effectiveness research in combination with emerging data from randomised trials must~~
40 ~~be used to settle these controversies.⁴⁶⁴¹~~
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50 51 **Contribution**

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

25 All authors have completed the ICMJE uniform disclosure form at
26 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author)
27 and declare: The study was funded by a research grant from Northern Norwegian Health
28 Authorities. The authors declare that they have no conflicts of interest.
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45 (Surgical Outpatient Clinic, University Hospital of North Norway) for assistance in
46 randomisation and identification of potential trial participants. We thank Berit Marianne
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7 Bjelkåsen, Norwegian University of Science and Technology, for assistance with the web
8 based randomisation service.
9

10 11 **Data sharing**

12 No additional data available.
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14 15 **Copyright for authors**

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Figure legends:

Figure 1. Participating trial hospitals and communities.

Three hospital trusts and the University Hospital of North Norway trust are located within the Northern-Norwegian Health Region, serving a population of 470 000. Median travel time with car from primary care communities to hospital were 2 hours. Two patients were randomised to follow up at their GP located in Longyear City, Spitsbergen (not shown on map), 2 hours flight from the university hospital.

Figure 21. 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).

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8 **Figure 3-2 A, B, C.** Health related quality of life 1-24 postoperative month.
9 EORTC QLQ C30 Global Health, EQ-5D index score and EQ-5D visual analog scale.

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12 **Figure 43.** Cost of follow-up per cycle.

13 Mean health care cost of follow-up per patient per 3 month follow-up cycle with error bars (95%
14 confidence intervals). In a general linear model, mean difference between groups was 60.0 £ (95 CI
15 interval: 7.0 – 113.0, p = 0.02).

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19 **Figure 54.** Sensitivity analyses of cost driving elements in surveillance.

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