Ovarian Cancer Follow-up: A preliminary comparison of two approaches.

WORD COUNT: 3002

*Corresponding author

Anne Lanceley PhD

Senior Lecturer in Women's Cancer

Dept of Women's Cancer

The UCL Elizabeth Garrett Anderson Institute for Women's Health

University College London

74, Huntley Street

London WC1E 6AU

Email: a.lanceley@ucl.ac.uk

Tel: 020 7679 6807

Fax: 02031082036

Carlo Berzuini PhD

Professor of Biostatistics

Institute of Population Health

The University of Manchester

Matthew Burnell PhD

Senior Statistician

Department of Women's Cancer

University College London

Susan Gessler PhD

Consultant Clinical Psychologist, UCLH Gynaecological Cancer Centre

Honorary Senior Lecturer, UCL Elizabeth Garrett Anderson Institute for Women's Health

Stephen Morris PhD

Professor of Health Economics

Department of Applied Health Research,

University College London

Andy Ryan PhD

Data Base Administrator

Dept of Women’s Cancer

University College London

Jonathan Ledermann MD

Professor of Medical Oncology & Director

Cancer Research UK and UCL Cancer Trials Centre

UCL Cancer Institute

Ian Jacobs MBBS

Professor, President and Vice Chancellor

University of New South Wales

Australia

Acknowledgements

The work was part funded by The Eve Appeal Gynaecological Cancer Charity and undertaken at UCLH/UCL within the ‘women's health theme’ of the NIHR UCLH/UCL Comprehensive Biomedical Research Centre supported by the Department of Health. The research activity of Prof Carlo Berzuini was partially supported by the FP7-305280 MIMOmics European Collaborative Project, as part of the HEALTH-2012-INNOVATION scheme. Prof Ian Jacobs is an NIHR Senior Research Fellow.

AL conceived the study and MB, SG, JL and IJ were involved in the design. CB, SM and MB analysed the data. CB, IJ and AL interpreted the results. AR performed the randomisation, provided data management expertise and with CB prepared figures and tables. AL drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

We are grateful to the trial participants and especially to the CNSs who provided the nurse-led service and patient activity data: Egla Aitkens, Rachel Keenan, Emma Azeem, and Marilyn Lewis. We also thank the clinical teams at University College London NHS Foundation Trust Hospital, and Southend and Basildon University Hospitals NHS Foundation Trusts for their support for the study, in particular Dr Khalil Razvi. We also thank Gemma Ogden who recruited patients and collected data and Dr Zara Eagle for data entry.

Background

Ovarian Cancer (OC) has the highest mortality rate of all gynaecological cancers, and is the fourth leading cause of cancer-related death among women. Approximately 20% of patients present with early stage disease and have a good prognosis. 70-80% of patients with advanced OC respond to primary therapy consisting of primary or delayed debulking surgery followed by platinum based combination chemotherapy, but have a >75% risk of recurrence, in most cases within three years, with two years median survival thereafter [1]. These patients have a short progression free interval and periods of remission of ever-shorter duration as tumours become increasingly resistant to chemotherapy. Many patients with recurrent disease have no or few symptoms at first but in later stages of the disease symptom burden is often heavy. On recurrence the aim of therapy shifts from cure to long term palliation to improve quality of life.

The European Society of Medical Oncology recommends follow-up every three months for two years, every four months during the third year, and every six months during years four and five or until progression. The guideline states that at each appointment a doctor takes a clinical history and performs a physical examination including pelvic examination [2], together with measurement of the serum cancer antigen 125 (CA 125) tumour marker. Guidelines indicate a CT scan if there is clinical evidence of progressive disease. However, these recommendations are not supported by any evidence, except that CA125 can accurately predict tumour recurrence. A recent UK survey [3] revealed that follow-up practices varied with most centres using a standard hospital-based protocol of appointments for 5 years with routine tests for women with ovarian cancer. A minority utilised nurse-led or telephone follow-up. The assumption that earlier treatment on detecting recurrence

and before symptoms develop would improve survival has been discredited by the MRC OV05/EORTC trial [4], which compared immediate treatment on the basis of increased CA125 concentrations versus waiting until clinical/symptomatic relapse and showed no difference in survival between the two arms.

Randomised studies are lacking on most aspects of OC follow-up care [5]. Although hospital follow-up provides opportunities for managing the disease or treatment related symptoms and optimal referral to supportive and palliative care with Clinical Nurse Specialist (CNS) involvement, clinic appointments may lead to stress and delay [6]. Urgent research has been advocated not only to develop better predictors of treatment response and indicators of treatment benefit to inform treatment plans [7], but also to determine the most appropriate provision of follow-up care [8]. Such care may have to be flexible in order to take into account fear of recurrence [9], multiple treatments and associated decision-making [10]; symptom burden [11], and new treatments that may become available for relapsed OC where earlier intervention may be indicated [5]. This study of follow-up strategies directed towards quality of life and psychological impact in addition to cost-effectiveness pre-empts the recommendation of the recent almost “empty” Cochrane review of different types of follow-up in this patient group.

Methods

We conducted a prospective preliminary RCT of individually tailored follow-up (henceforth synonymously termed individualised or intervention treatment) led by a gynaecological CNS versus conventional follow-up in 3 gynaecological cancer

centres at one metropolitan and two suburban sites, comparing cost and effects on quality of life, mood and patient satisfaction. We followed MRC guidelines for the design and testing of complex interventions [12].

Patients were consecutively approached and 113 patients (63% of 180 approached) were recruited into a follow-up period of two years. Inclusion criteria were: clinical diagnosis of OC or fallopian tube or peritoneal cancer; completed primary treatment by surgery alone or with chemotherapy irrespective of outcome with regard to remission; expected survival > 3 months; aged ≥18 years; and willingness and ability to participate. Relapse and recurrence dates, death, contacts with nurses and other members of the clinical team, reasons for contacts, clinic appointments, symptoms reported and hospital in-patient episodes were collected and recorded on a 'Patient Events' data base. The East London Research Ethics Committee approved the study (Trial registration number ISRCTN59149551) and a trial management group acted as adviser.

After informed written consent was obtained, participants were randomly allocated to receive either individual follow-up (N= 57) or conventional follow-up (N= 56) [11]. Recruitment by centre was as follows: Centre 1 - Intervention N = 33, Conventional N= 30, Total 63; Centre 2 - Intervention N = 19, Conventional N= 20, Total 39; Centre 3 – Intervention N = 5, Conventional N = 5, Total 10. We considered random allocation for every individual participant, but given the small sample size we could have easily ended up with a disproportionate number in one arm purely by chance. For purposes of independent randomisation, we divided participants into those recruited at the metropolitan centre 1 and those at the suburban centres 2 & 3 with participants in each group randomly allocated to either conventional or individualised follow-up in a 1:1 ratio. We allocated the first participant of a pair to one of the

follow-up groups using randomness derived from atmospheric noise (http://www.random.org). We allocated the remaining participant to the other group. We found later that one patient randomised to conventional follow-up was ineligible and was excluded from the study: this left 112 patients for analysis. Figure 1 shows a participant Flow-Chart.

Study measures

We administered three validated self-report instruments at baseline, 3, 6, 12, 18 and 24 months.

Quality of life

The European Organisation for Research and Treatment of Cancer [14] core QoL questionnaire (QLQ-C30) consists of 30-items questionnaire assessing 8 domains, and a number of specific symptoms as well as the perceived financial impact of the disease and treatment. We used the core scale with the site-specific OC module Ov-28 [15] which consists of 28 items. Higher scores for functioning subscales indicated better functioning; higher scores in symptom subscales indicated worse symptoms.

Mood

We used the 14-item self-rated Hospital Anxiety and Depression Scale (HADS) for use in the medically ill [16].

Patient satisfaction

We used the Ware Patient Satisfaction Questionnaire (PSQ-III) to measure patients' perceptions of care [17] providing a summary measure of general satisfaction along with six aspects of health care.

Use of services

We extracted data from the ‘Patient Events ‘ data base for the following types of service use during the two-year follow-up period: clinic appointments with the CNS; CNS visits while the patient was an inpatient; telephone consultations with the CNS; email consultations with the CNS; clinic appointments with the consultant gynaecological oncologist; clinical appointment with other types of consultant; clinic appointment with clinical psychologist; clinic appointment with complementary medicine team; inpatient stays. We also recorded primary care contacts and reasons by questionnaire to general practitioners.

Procedures

Conventional Arm

Follow-up of asymptomatic patients consisted of one post-treatment outpatient appointment with further appointments at three monthly intervals including complete clinical history and CA 125 and radiological imaging when symptoms or signs appeared. The doctor and other members of the clinical team including nurse specialists not otherwise involved in the study also saw patients based on need.

Intervention Arm

We allocated patients selected for individualised follow-up to one of several gynaecological cancer nurse specialists at participating hospitals. They met with the nurse immediately after their end of treatment appointment to negotiate follow-up to suit their individual situation. Contact was flexible, primarily by telephone at prearranged mutually convenient times, although some women opted for face-to-face appointments, usually at the regular gynaecological cancer clinic. In addition, contact with the nurse was made when necessary in the regular gynaecological

oncology clinic or by telephone without prearranged appointment. Patients were assessed using a holistic guide to identify signs of disease progression, symptoms warranting intervention, and psychological issues. Unless the patient had worsening symptoms needing further treatment, the nurse was responsible for the care of patients receiving individualised follow-up. The nurse would discuss with the patient's consultant and arrange any necessary investigations, for example a CT scan before a clinic appointment with the doctor. The four nurses delivering the intervention were expert in the management of OC, having completed generic cancer nursing and specialist gynaecological cancer nurse training; they were cognisant of post treatment surveillance dilemmas and "watchful waiting" for patients, including patients' preoccupation with CA 125 levels. The intervention was informed by a model of health promoting interactions [18] oriented towards improving self-efficacy [19]. In addition, nurses were familiarised with the concept of adjustment to cancer described by Brennan [20] in two workshops designed to prepare them for their role in the study. The nurses provided information and support to assist patients to manage troublesome symptoms and live with the psychological discomfort of enduring uncertainty. Adherence to the intervention treatment protocol was supported by the study protocol and the preparation and ongoing support of the nurses. One or two CNSs in each of the three sites not trained in the intervention approach provided care in the conventional arm. The researcher (AL) was engaged at each study site to encourage trained CNSs not to share the specific approach with their colleagues during the study.

Statistical analysis

Questionnaire items were organised into functional domains: 13 functional domains in QLQ-C30, 7 in QLQ-OV28, 7 in PSQ-III and the HADS domain. They were additively combined (with appropriate signs) within each of the 28 functional domains to form corresponding *functional* scores measuring discomfort on a 0-100 scale, and within each of the 4 questionnaires to form four corresponding *global* scores measuring discomfort on a 0-100 scale. Each (functional or global) score was separately modelled to depend on tumour stage (STAGE), on the current number of days spent by the patient under the intervention treatment (DAYS OF INTERVENTION, defined to be uniformly zero in the conventional treatment arm), on her age at randomisation (AGE) and on her current number of days since randomisation (TIME), allowing for quadratic AGE and TIME relationships. The model for each score also contained a pair of patient-specific - a priori correlated - random effects to allow the intercept and linear trend component of each patient's trajectory to deviate from average. By modelling the random intercepts to be unaffected by treatment we incorporated the assumption that the treatment has no baseline effect. Primary study outcomes were the effect of treatment on each global score, measured by the corresponding estimated regression coefficient of DAYS OF INTERVENTION, and the effect of treatment on the hazard of relapse, as estimated via Cox's regression adjusting for the patient's age and tumour stage.

Of secondary interest was the breakdown of treatment effect according to the 28 functional scores.

Economic analysis

We calculated the total cost of follow-up for each patient multiplying service use by

unit costs obtained from 2011/12 NHS Reference Costs [21] and summing across all types of use. We compared unadjusted service use and total costs between each group using Mann-Whitney two-sample statistics. We analysed differences in medians because the data were highly skewed. In adjusted analyses we regressed total costs per patient against treatment controlling for age at baseline (cubic function), disease stage and grade at baseline, and study site. We used a generalised linear model with gamma family and log link [22]. We adjusted for clustering by participant and calculated the marginal effect of individualised follow-up compared with conventional follow-up.

Results

Mean age of participants in the intervention arm was 62 years (range 23-92) whilst in the conventional arm the mean was 61 years (range 21-85). Clinical and demographic characteristics of participants are presented in Table 1.

At baseline there was no significant treatment effect on the global QLQ-C30 score (*p*-value = 0.3), global QLQ-OV28 score (0.34), global PSQ III score (0.4) or global HAD score (0.3). The main analysis was based on 112 patients.

Table 2 shows the estimated fixed effects for the global QLQ-C30 score (see table caption for an explanation of the content). The estimated effect of the individualised treatment, adjusted for tumour stage and age at randomisation, was −0.016, corresponding to an expected decrease in discomfort of 5.76 points per year with respect to the conventional treatment. This represents statistically significant (two-

tailed test *p*-value=0.013) evidence of a beneficial advantage of the individualised treatment according to QLQ-C30.

Table 3 shows the estimated effects of the individualised treatment on each of the 13 QLQ-C30 functional scores, relative to the conventional treatment, adjusting for tumour stage and patient's age. The sign of all but one *t*-statistics indicates a uniform beneficial advantage of the individualised treatment, four of these statistics achieving two-tailed 5 percent statistical significance. Insufficient data information at a functional score level may explain the non-significant estimate for the effect of diarrhoea, whose 95% confidence interval is nevertheless compatible with the hypothesis that the individualised treatment is beneficial also in terms of this item.

The results from our analysis of the global QLQ-OV28 score are shown in Table 4. These data indicate only modest and non-significant evidence in favour of the individualised follow-up, after adjusting for tumour stage and patient’s age. The estimated coefficient of DAYS OF INTERVENTION is −0.0027 (two-tailed *p*-value=0.14).

A bayesian noninferiority analysis of these data can be used to further explore this finding. A bayesian analysis of the same data, based on a locally uniform prior for the model parameters, yields a bayesian 95 percent posterior credible interval of (-0.002, 0.005) for the coefficient of DAYS OF INTERVENTION. This corresponds to a 95 percent credible interval of (-0.6, 1.5) for the yearly increase in QLQ-OV28 global score attributable to the intervention treatment. We may take this to indicate that - in the worst scenario and excluding extremely unlikely events - the intervention

treatment will be responsible for a 0.6 yearly increase of the QLQ-OV28 global score, with respect to what would have been obtained via conventional treatment. The median value for the QLQ-OV28 score at one year from randomisation is about 37. We may thus interpret the data as suggesting that, if we allow for a very small margin of tolerance, the individualised treatment is non-inferior to the conventional one in terms of their impact on QLQ-OV28 quality of life.

Supplemental Table 1, indicates that there was no significant benefit of one treatment over the other in terms of global HAD score, either marginally or after adjusting for the effects of tumour stage and patient's age. In this analysis the effect of the individualised treatment gave a t-statistic of 0.221, which fails to achieve the required statistical significance level, and the corresponding 95% confidence interval spans a region of clinically negligible effect.

Table 5 reports the results from the fitting of our hierarchical mixed-effects model to the global PSQ-III score data. The estimated regression coefficient for DAYS OF INTERVENTION, adjusted for tumour stage and age at randomisation, represents significant evidence (two-tailed test p-value=0.002; 95% confidence interval -0.03 through -0.001) of a benefit of the individualised treatment over the conventional one in terms of PSQ-III. Supplemental Table 2 compares the effects of the two treatments on each of the five PSQ-III functional scores.

Effects on PSQ-III functional scores

We compared the two treatments in terms of their effects on the following five PSQ-III functional scores: general satisfaction (based on 6 items), interpersonal aspects (7

items), communication (5 items), time spent with health care professional (2 items) and access/ availability/convenience (12 items). High values of these functional scores indicate “high satisfaction”. The results from fitting a mixed model to each of these functional scores are reported in Supplemental Table 2. For each functional score, the table reports the estimated coefficient of DAYS OF INTERVENTION, as a measure of the effect of the individualised treatment relative to the conventional one, its standard error, the corresponding *t*-statistic and the 95% confidence interval. The *t*-statistic for each item except “Communication” provides stronger that 5 percent significant evidence that there is a beneficial advantage of the individualised treatment over the conventional one in terms of PSQ-III. The results for “Communication” provide fair (albeit short of 5 percent significance) evidence that the individualised treatment is superior also in terms of this particular item.

Effect of the intervention on the relapse-free time

The effect of treatment on relapse-free time was assessed via Cox’s model, taking time from randomization as the main temporal scale, and adjusting for patient’s age and tumour stage. Included in the model was an interaction between the intervention treatment and tumour stage. The results from fitting the model under an assumption of proportional hazards are summarised by Supplemental Table 3. For each unknown parameter, the table reports the estimated coefficient in the regression (COEF), its exponentiated value (relative risk), its standard error, the Z-statistic, the *p*-value for the null hypothesis of no effect and the 95 percent confidence interval for exp (COEF). The table shows modest evidence of a dependence of the risk of relapse on patient's age at randomization, and borderline-

significant evidence of an interaction between treatment and tumour stage. The sign and the Z-statistic for the intervention treatment effect represent some evidence (albeit short of nominal statistical significance) that the individualised treatment tends to reduce the risk of (and hence to delay) the relapse, at least in a non-advanced stage of the tumour. This effect appears to be moderated by an advanced stage of the tumour.

Cost analysis

In individualised follow-up patients had significantly fewer clinic appointments with the consultant gynaecological oncologist and more clinic appointments, telephone consultations and email consultations with the CNS (all p <0.01; Supplemental Table 4). There were no significant differences in other types of service use. Cost data were highly skewed (Supplemental Fig 1 and Table 5): patients in the nurse-led follow-up group had significantly lower costs in unadjusted analyses (p <0.01; Supplemental Table 4). In adjusted analyses costs were £700 lower on average for the nurse-led follow-up group, but the difference was not statistically significant at the 5% level (p = 0.07; Supplemental Table 6).

Dealing with missing data in economic analysis

Data on primary care contacts were missing for 39 (35%) patients, 24 patients in the conventional follow-up group (44%) and 15 in the nurse-led follow-up group (26%). We imputed missing data for both types of primary care contact (GP visits, practice nurse visits) simultaneously using multiple imputation by chained equations. Prediction equations were estimated using negative binomial regression since the variables with missing data were over dispersed count variables. The imputation

models included age at baseline (cubic function), disease stage and grade at baseline, study site, and numbers of clinic appointments with the CNS, CNS visits while the patient was an inpatient, telephone consultations with the CNS, email consultations with the CNS, clinic appointments with the consultant gynaecologist oncologist, clinical appointment with other types of consultant, clinic appointment with clinical psychologist, clinic appointment with complementary medicine team, inpatient stays, and total costs. Values were imputed 20 times; we re-estimated the models using alternative random number seeds and obtained similar results. The imputed data were used to create a new total cost variable including GP and practice nurse visits for all participants and the impact of nurse-led follow-up compared with conventional follow-up was analysed using a generalised linear model with gamma family and log link adjusting for clustering by participant. Coefficients and standard errors were computed accounting for the variability between imputations using the combination rules by Rubin [23].

Discussion

The findings of this preliminary study provide a foundation for further research of individually tailored models of follow-up care in OC. The individualised treatment offers an advantage over conventional follow-up in terms of the QoL aspects represented in QLQ-C30 and in PSQ-III, and is equivalent to conventional treatment for mood represented in HADS. It is also desirable as regards relapse free time and symptomatic reporting of relapse.

For effective communication it has been argued that patient and clinician must share a common representation or model of the condition [24]. If patients represent their

OC illness and symptom experience differently from the clinician managing their care, they may become disaffected with the service and doubt the quality of its clinical decision-making and treatment, thereby delaying the implementation of an effective treatment plan. Leventhal's theory may explain the overall QoL benefit in the individualised group, confirming our hypothesis that nurses would develop close knowledge of individual patients and collaborate with them to relieve their symptoms, alleviate their distress and help their adjustment to an uncertain future. The regular surveillance focus of the conventional arm, with less continuity of medical personnel and arguably less time for patients to discuss their recovery, symptoms or fears of recurrence, may have caused greater dissonance than the intervention group [25].

In the study we considered the practical issues of implementation for example: trial procedures including the willingness of medical staff to recruit patients; the willingness of eligible participants to be randomised; examination of potential adverse effects of the intervention; performance of a basic economic analysis to inform a larger trial; and assessment of the overall acceptability of the intervention. Despite a commitment to enrol consecutive patients more patients than we anticipated were deemed unsuitable for the study by their consultant and some were simply judged too sick with multiple co-morbidities. This is an important finding as it highlights a potential limitation to individualised follow-up programmes in OC. Characteristics of patients who were not offered enrolment in this study will form the basis of a future paper exploring barriers to individualised follow-up schemes.

Other limitations of this preliminary work may have influenced our results. No pre-defined criteria were used to establish whether the follow-up model warranted

progression to a larger RCT study. It is a recognised challenge in intervention studies that aspects of the intervention cannot be controlled and usual methods of avoiding bias when applied are likely to have partial success. Patients' expectations of continuity and responsiveness are a potential a source of bias. Nurses trained to deliver the intervention are likely to be invested in its success and consequently they may have made a special effort to be attentive and fulfil patients' expectations of continuity and responsiveness to their difficulties. The two-year period of follow-up and involvement of four nurses across three study sites may have offset these effects.

In a future work we plan to study the role of post-randomization processes (nurse reaction to emotional challenge [26] and compliance with protocol [27]) and mediating variables (number of contacts) in the treatment mechanism), for a better understanding of how the individualised treatment works, and for a fuller assessment of the evidence in its favour. This will involve the use of causal inference "analysis of mediation" methods [28]. These data might identify nurse skills as one cause – and therapeutic alliance as a main mediator – of the benefits of individualised treatment. Analysis of the data along these lines might (1) produce statistically more significant results in favour of the individualised treatment, (ii) allow us to identify early predictors of treatment outcome, (iii) provide compelling evidence of the need to develop the conditions for nurses to be able to engage patients.

The UK National Cancer Survivorship Initiative has outlined plans for improved care of those living with and after cancer [29], including pathways of follow-up care based on risk of recurrence and late effects [30]. Setting up an evidence-based framework

of effective new care models must be a priority [31] and prospective studies are needed to evaluate the quality of life issues and psychological impact of different follow-up approaches in addition to investigating survival outcomes and cost-effectiveness. Interventions are likely to include nurse-led, telephone and patient initiated follow-up and the relative merits of these strategies should be prospectively evaluated.

These preliminary results highlight the effect on outcome of the quality and focus of the nurse-patient relationship and the need for training and support to deliver flexible individualised follow-up. OC incidence is stable but OC mortality rates are predicted to fall by over 40% (42.6%) to 5 deaths per 1,000 women by 2030 [32] as therapy improves. The increasingly chronic nature of OC with more use of targeted and maintenance treatments, makes it important to assess the value women place on QoL as part of long-term survivorship assessment and to provide models of care that are respectful of individual patient choice and which educate and support women in the surveillance of their disease and management of their symptoms.

This pilot trial provides evidence to suggest that an individualised approach to OC follow up can improve quality of life and delay diagnosis of relapse in a cost effective protocol. This approach requires validation in further studies and if confirmed could be an important development in OC care in the UK NHS and other healthcare systems.

References

1. GLOBOCAN 2008. Estimated incidence, mortality and 5-year prevalence: women. http://globocan.iarc.fr/factsheet.asp#WOMEN.

2. Aebi S, Castiglione M. Epithelial ovarian carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 2008; 19 (Suppl 2): M. ii14–6.
3. Leeson S, Stuart N, Sylvestre Y, et al. Gynaecological cancer follow up: A national survey of current practice in the UK. BMJ Open 2013;3: e002859
4. Rustin GJ, van der Burg ME, Griffin CL, et al: Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet.* 2010; 376:1155-63.
5. Clarke T, Galaal K, Bryant A, Naik R. Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD006119. DOI: 10.1002/14651858.CD006119.pub3.
6. Olaitan A, Murdoch J, Anderson R, et al. A critical evaluation of current protocols for the follow up of women treated for gynaecological malignancies *Int J Gynecol Cancer.* 2001; 22: 36-53.
7. Friedlander M, Butow P, Stockler M, et al. Symptom control in patients with recurrent ovarian cancer: measuring the benefit of palliative chemotherapy in women with platinum refractory/resistant ovarian cancer. *Int J Gynecol Cancer.* 2009; 19: S44-8.
8. Lydon A, Beaver K, Newbery C et al. Routine follow-up after treatment for ovarian cancer in the United Kingdom (UK): patient and health professional views. *Eur J Oncol Nurs.* 2009; 13: 336-43.
9. Howell D, Fitch MI, Deane KA. Women's experiences with recurrent ovarian cancer. *Cancer Nurs.* 2003; 26:10-7.

10. Anderson C, Carter J, Nattress K, et al. “The booklet helped me not to panic": a pilot of a decision aid for asymptomatic women with ovarian cancer and with rising CA-125 levels. *Int J Gynecol Cancer.* 2011; 21: 737-43.
11. McCorkle R, Dowd M, Ercolano E, et.al. Effects of a nursing intervention on quality of life outcomes in post-surgical women with gynecological cancers. *Psychooncology.* 2009; 18: 62-70.
12. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: new guidance: MRC, 2008.
13. http://www.random.org
14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993; 85: 365-76.
15. Greimel E, Bottomley A, Cull A, et al. EORTC Quality of Life Group and the Quality of Life Unit. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer.* 2003; 39:1402-8.
16. Zigmond AS, Snaith RP. The hospital anxiety and d*epression scale. Acta Psychiatr Scand.* 1983; 67: 361-70.
17. Ware JE Jr, Davies-Avery A, Stewart AL. The measurement and meaning of patient satisfaction. *Health Med Care Serv Rev.* 1978; 1:1, 3-15.
18. Tones K, Tilford S. *Health Education: Effectiveness, Efficiency and Equity* London: Chapman Hall; 1994.
19. Bandura A. Self-efficacy: toward a unifying theory of behaviour change *Psych Rev.* 1977; 84: 191-215.
20. Brennan J. Adjustment to cancer - coping or personal transition? *Psychooncology.* 2001; 10:1-18.

21. Department of Health. National Schedule of Reference Costs - Year 2011-12 - NHS trusts and NHS foundation trusts: NHS own costs. London: Department of Health 2012. https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012

22. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy.* 2004; 9: 197-204.

23. Rubin, DB. *Multiple imputation for nonresponse in surveys.* New York: J Wiley & Sons; 1987.

24. Leventhal H, Leventhal EA, Breland JY. Cognitive science speaks to the "common-sense" of chronic illness management. *Ann Beh Med.* 2011; 4:152-63.

25. Frew G, Smith A, Zutshi B, et al. Results of a quantitative survey to explore both perceptions of the purposes of follow-up and preferences for methods of follow-up delivery among service users, primary care practitioners and specialist clinicians after cancer treatment. *Clin Oncol (R Coll Radiol).* 2010; 22: 874-84.

26. Sheldon, LK., Ellington, L., Barrett, R, Dudley WN, et al. Nurse responsiveness to cancer patient expressions of emotion. *Patient Educ Couns.* 2009; 76: 63-70.

27. Heaven C, Clegg J, Maguire P. Transfer of communication skills training from workshop to workplace: The impact of clinical supervision. *Patient Educ Couns.* 2006; 60: 313-325.

28. Berzuini, C., Dawid, D., Bernardinell, L. *Causality: Statistical perspectives and application.* Chichester: Wiley; 2012.

29. Jefford M, Rowland J, Grunfeld E, et al. Implementing improved post-treatment care for cancer survivors in England, with reflections from Australia, Canada and the USA. *Br J Cancer.* 2013; 108:14-20.

30. NHS Improvement-Cancer. *Effective follow up: Testing risk stratified pathways.* Leicester: NHS Improvement; 2011. www.improvement.nhs.uk.

31. Havrilesky LJ, Abernethy AP. Quality of life in ICON7: need for patients' perspectives. *Lancet Oncol.* 2013; 14: 183-185.

32. Mistry M, Parkin D, Ahmad A, et al. Cancer incidence in the UK: Projections to the year 2030. *Br J Cancer.* 2012; 105:1795–1803.

Figure and table legends

Figure 1: Patient participant flow chart

Table 1: Clinical and demographic characteristics of participants.

Table 2: Estimated fixed effects of our mixed effects regression model for the dependence of the global QLQ-C30 score on tumour stage, days since randomisation (TIME), age at randomisation (AGE) and days of intervention treatment.

Table 3: This table reports the estimated effect of the individualised treatment on each of the functional QLQ-C30 scores, in terms of score increase produced by one day of individualised treatment with respect to the conventional one.

Table 4: Analysis of the effect of the intervention treatment on the global QLQ-OV28 score.

Table 5: Analysis of the effect of the individualised treatment on the global PSQ-III score measuring
"lack of" satisfaction.

Supplementary Digital Content

Table 1: Analysis of the effect of the intervention on global HAD score. (Word file)

Table 2: Analysis of the effect of fitting the mixed model to each of the PSQ III functional scores separately. (Word file)

Table 3: Results from the fitting of Cox's proportional hazards model of the dependence of relapse-free time on treatment, adjusting for age at randomisation and tumour Stage. (Word file)

Table 4. Use of services and total cost per patient. (Word file)

Figure 1. Distribution of total cost per person in each group. (TIFF file)

Table 5. Unit costs. (Word file)

Table 6. Adjusted analysis of nurse-led follow-up on total costs. (Word file)

Figure 1

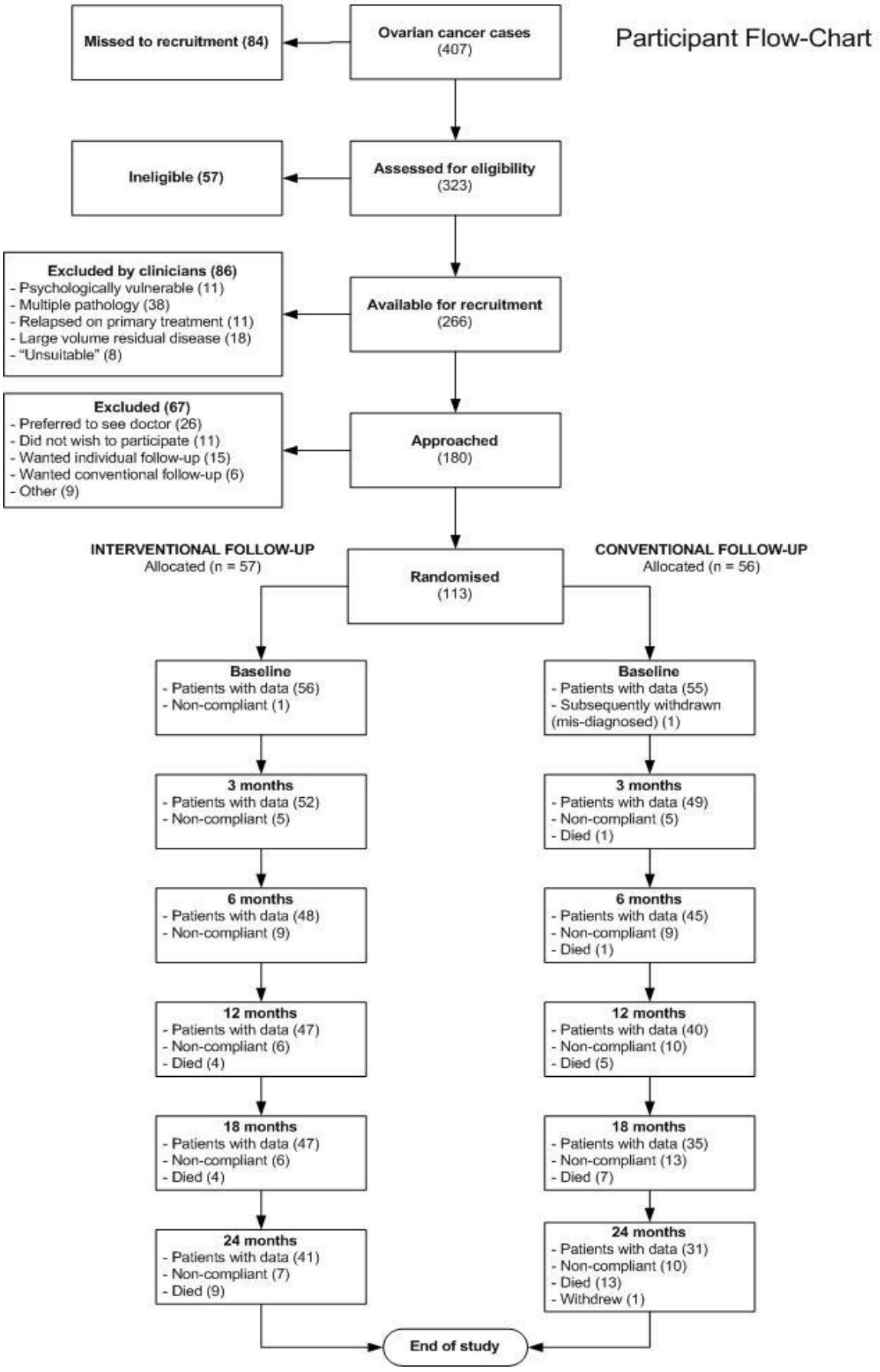

Participant Flow-Chart
Ovarian cancer cases (407)
Missed to recruitment (84)
Assessed for eligibility (323)
Ineligible (57)
Available for recruitment (266)
Excluded by clinicians (86)
- Psychologically vulnerable (11)
- Multiple pathology (38)
- Relapsed on primary treatment (11)
- Large volume residual disease (18)
- "Unsuitable" (8)
Approached (180)
Excluded (67)
- Preferred to see doctor (26)
- Did not wish to participate (11)
- Wanted individual follow-up (15)
- Wanted conventional follow-up (6)
- Other (9)
Randomised (113)
INTERVENTIONAL FOLLOW-UP
Allocated (n = 57)
CONVENTIONAL FOLLOW-UP
Allocated (n = 56)
Baseline
- Patients with data (56)
- Non-compliant (1)
3 months
- Patients with data (52)
- Non-compliant (5)
6 months
- Patients with data (48)
- Non-compliant (9)
12 months
- Patients with data (47)
- Non-compliant (6)
- Died (4)
18 months
- Patients with data (47)
- Non-compliant (6)
- Died (4)
24 months
- Patients with data (41)
- Non-compliant (7)
- Died (9)
Baseline
- Patients with data (55)
- Subsequently withdrawn (mis-diagnosed) (1)
3 months
- Patients with data (49)
- Non-compliant (5)
- Died (1)
6 months
- Patients with data (45)
- Non-compliant (9)
- Died (1)
12 months
- Patients with data (40)
- Non-compliant (10)
- Died (5)
18 months
- Patients with data (35)
- Non-compliant (13)
- Died (7)
24 months
- Patients with data (31)
- Non-compliant (10)
- Died (13)
- Withdrew (1)
End of study

Table 1

	Intervention treatment	Conventional treatment	Overall
Stage at diagnosis			
Borderline	2	2	4
I - Ic	25	18	43
II - IIc	5	6	11
III - IIIc	22	25	47
IV	3	4	7
ECOG performance status at randomisation			
0 = Fully active, able to carry on all predisease performance without restriction	35	31	66
1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature	15	14	29
2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	6	7	13
3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	1	2	3
4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	1	0	1
Co-exisiting diseases			
Cardiovascular diseases & hypertension	3	2	4
Cerebrovascular disease	2	1	3
Respiratory disorders	1	2	3
Diabetes without end-organ damage (excludes diet-controlled alone)	1	1	2
Osteoporosis	3	1	4
Obesity	4	4	8
Endocrine, nutritional & metabolic disorders	1	0	1
Digestive system disorders	5	5	10
Autoimmune diseases	1	0	1
Renal disease	1	0	1
Ethnicity			
White - British	48	42	90
White - Irish	3	4	7
White - other background	4	5	9
Asian	2	1	3
Black or black British	1	1	2
Chinese	0	1	1
Marital status			
Single	3	3	6
Married/Living with partner	31	37	68
Divorced/Separated	9	9	18
Widow	11	9	20
Employment Status			
Employed full time (including on sick leave)	18	21	39
Employed part time	14	16	30
Unemployed	3	3	6
Home-maker	9	11	20
Retired	8	9	17
Highest education level			
Less than compulsory school education	5	2	7
Compulsory school education	33	34	67
Post compulsory school education - below university	15	16	31
Post compulsory school education - university level	5	2	7

Table 1
The clinical and demographic characteristics of participants.

Tables 2-5

Parameter	Estimate	Standard error	*t*-value	95% confidence interval
Intercept	78.75	29.6	2.66	
Tumour stage	0.79	0.49	1.58	-0.17, 1.75
Time	0.032	0.013	-2.41	0.006, 0.057
$Time^2$	0.000051	0.000012	4.06	0.000031, 0.00007
Age at randomisation	0.005	0.0028	-1.79	-0.00049, 0.01
Age^2	0.00000012	0.000000064	1.96	-5.44 ×10^-9, 2.4 ×10^-7
Days of intervention treatment	-0.016	0.0074	-2.22	-0.03, -0.001

Table 2: Estimated fixed effects of our mixed effects regression model for the dependence of the global QLQ-C30 score on tumour stage, days since randomisation (TIME), age at randomisation (AGE) and days of intervention treatment.
These estimates have been obtained assuming that the score depends on TIME and AGE through a quadratic (or, as a case, linear) relationship. Dependence on DAYS OF INTERVENTION has been assumed to be linear. For each estimated parameter, this table reports point estimate, standard error, corresponding t-statistic and 95% confidence interval. Of inferential interest is the coefficient of DAYS OF INTERVENTION, representing the expected increase in QLQ-C30 discomfort produced by one day of individualised treatment with respect to that produced by one day of conventional treatment. According to this table, the sign and the magnitude of the estimate of this coefficient represent 5 percent significant evidence of a beneficial advantage of the individualised treatment over the conventional one (two-tailed p-value = 0.013, 95% confidence interval -0.03 through -0.001).

Functional score	Estimate x 100	Standard error	*t*-value	95% confidence interval
Physical	-2.14	0.016	-1.28	-0.052, 0.009
Role	-4.65	0.022	-2.09	-0.003, -0.089
Emotion	-1.95	0.014	-1.39	-0.046, 0.007
Social	-3.93	0.019	-2.02	-0.076, -0.002
Global	-7.66	0.033	-2.29	-0.141, -0.011
Fatigue	-2.28	0.018	-1.27	-0.058, 0.012
Nausea/vomiting	-0.18	0.009	-0.18	-0.019, 0.015
Pain	-2.83	0.018	-1.53	-0.063, 0.006
Dyspnoea	-1.12	0.019	-0.61	-0.048, 0.026
Sleep	-1.58	0.021	-0.73	-1.954, 0.025
Appetite loss	-4.34	0.015	-2.82	-0.072, -0.014
Constipation	-2.99	0.017	-0.17	-0.063, 0.003
Diarrhoea	0.8	0.011	0.68	-0.013, 0.029

Table 3: This table reports the estimated effect of the individualised treatment on each of the functional QLQ-C30 scores, in terms of score increase produced by one day of individualised treatment with respect to the conventional one.

For each effect, the table reports the point estimate, the standard error, the *t*-statistic and the corresponding 95% confidence interval. These estimates are valid under the mixed effects model described in the Statistical Analysis section.

Parameter	Estimate	Standard error	*t*-value	95% confidence interval
(Intercept)	55.2	4	13.62	
Stage	0.77	0.2	3.88	0.378, 1.162
Time	-0.014	0.0053	-2.64	-0.024, -0.003
$Time^2$	0.000012	0.000005	2.29	2.2 x 10^-6, 2.18 x 10^-5
Age	0.00074	0.00017	-4.30	4 x 10^-4, 0.001
Days of Intervention	-0.0027	0.0026	-1.06	-0.007, 0.002

Table 4: Analysis of the effect of the intervention treatment on the global QLQ-OV28 score.
For an explanation of table content see caption of Table 3. The sign of the estimated coefficient of DAYS OF INTERVENTION points to a beneficial advantage of the individualised treatment over the conventional one in terms of QLQ-OV28 quality of life, although the estimate fails to achieve 5 percent statistical significance (two-sided test *p*-value = 0.14).

Parameter	Estimate	Standard error	*t*-value	95% confidence interval
(Intercept)	-12.78	5.9	-2.16	-
Stage	0.97	0.3	0.32	-0.48, 0.68
Time	0.005	0.0026	2.02	-0.003, 0.021
$Time^2$	-3.88×10^-6	6.1-10^-6	-0.63	-1.59×10^-5, 8.13×10^-6
Age	-0.00032	0.00026	-1.25	-0.0008, 0.00018
Days of intervention	-0.009	0.0032	-2.8	-0.015, -0.003

Table 5: Analysis of the effect of the individualised treatment on the global PSQ-III score measuring "lack of" satisfaction.

For an explanation of table content see caption of Table 3. The magnitude and the sign of the estimated coefficient of DAYS OF INTERVENTION represent statistically very significant evidence of a beneficial advantage of the intervention treatment compared to the conventional one (two-tailed p-value=0.002).

Supplementary Digital Content

Parameter	Estimate	Standard error	*t*-value	95% confidence interval
(Intercept)	-10.53	5.66	-1.862	-
Stage	0.12	0.095	-1.307	-0.066, 0.3
Time	0.00089	0.0026	0.336	-0.004, 0.005
Time^2	0.0000016	0.0000026	-0.597	-3.5 ×10^-6, 6.7 ×10^-6
Age	0.000067	0.00054	0.124	-9.9 ×10^-4, 0.001
Days of intervention	0.00029	0.0013	0.221	-1.85 x 10^-8, 2.85 ×10^-8

SDC Table1: Analysis of the effect of the intervention on global HAD score
For an explanation of the content of this table see caption of Table 3. The effect of the intervention treatment on the HAD global score, adjusted for tumour stage and age at randomisation, is represented in this table by the coefficient of DAYS OF INTERVENTION. The results in this table contain no evidence of an effect of the intervention treatment on global HAD score.

Functional score	Estimate * 1000	St error *1000	*t*-value	95% confidence interval
General satisfaction	-2.25	0.85	-2.64	-3.9, -0.58
Interpersonal relationships	-2.53	0.86	-2.9	-4.2, -0.8
Communication	-0.85	0.58	-1.46	-1.98, 0.28
Time	-1.04	0.37	-2.76	-1.76, -0.31
Accessibility	-2.26	1.09	-2.07	-4.39, -0.12

SDC Table 2: Analysis of the effect of fitting the mixed model to each of the PSQ III functional scores separately.
For each score, the table reports the estimated coefficient, which measures the effect of the intervention, its standard error and the corresponding *t*-statistic and confidence intervals. The *t*-statistic for each item except Communication lies in the 5 percent region indicating that there is an effect and the coefficients are all negative indicating beneficial effect of the intervention arm.

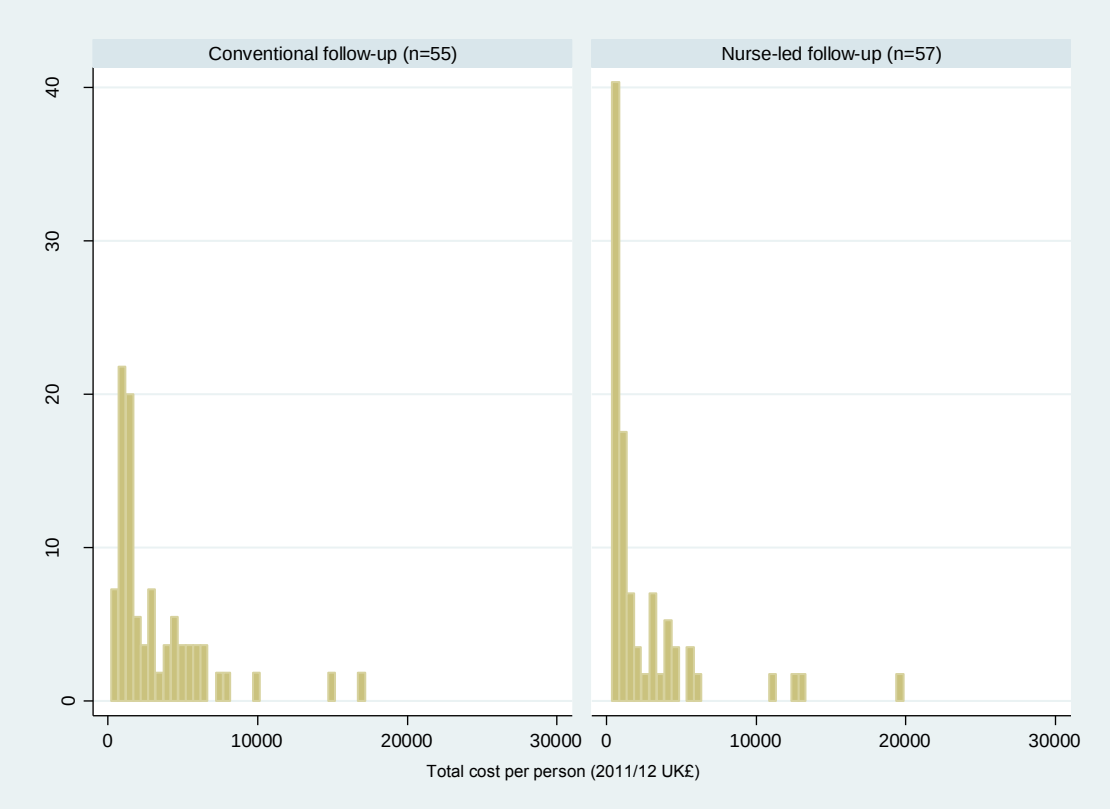
Parameters	Coef	Exp(coef)	Standard error for Coef	*z*-statistic	*p*-value	95% confidence interval for Coef
Age	0.00008	1	0.000047	1.72	0.08	(0.99, 1)
Tumour stage	0.19	1.21	0.083	2.3	0.021	(1.03, 1.43)
Intervention treatment	-4.8	0.008	2.88	-1.677	0.09	(0.000027, 2.26)
Stage x intervention	0.4	1.5	0.24	1.68	0.08	(1.03, 2.44)

SDC Table 3: Results from the fitting of Cox's proportional hazards model of the dependence of relapse-free time on treatment, adjusting for age at randomisation and tumour Stage.
For each unknown parameter, the table reports the estimated coefficient in the regression (COEF), its exponentiated (relative risk) value, its standard error, the Z statistic and the *p*-value for the null hypothesis of no effect and the corresponding 95 percent confidence interval.

	Conventional follow-up (n=55)*		Nurse-led follow-up (n=57)*			
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	P value†	Unit cost‡
Clinic appointment with clinical nurse specialist	0.3 (1.0)	0 (0 to 0)	4.1 (3.1)	3 (2 to 7)	<0.01	95
Clinical nurse specialist visits patient in hospital	0.1 (0.3)	0 (0 to 0)	0.1 (0.4)	0 (0 to 0)	0.22	95
Telephone consultation with clinical nurse specialist	0.7 (1.3)	0 (0 to 1)	6.8 (8.4)	4 (2 to 9)	<0.01	40
Email consultation with clinical nurse specialist	0 (0)	0 (0 to 0)	1.6 (4.5)	0 (0 to 0)	<0.01	40
Clinic appointment with consultant gynaecological oncologist	10.7 (7.2)	7 (6 to 18)	3.5 (4.7)	2 (0 to 4)	<0.01	191
Clinic appointment with other type of consultant	0.5 (1.1)	0 (0 to 0)	0.5 (1.6)	0 (0 to 0)	0.16	111
Clinic appointment with clinical psychologist	0.5 (2.1)	0 (0 to 0)	0.5 (1.8)	0 (0 to 0)	0.56	137
Clinic appointment with complementary medicine team	0.2 (0.8)	0 (0 to 0)	0.6 (1.9)	0 (0 to 0)	0.49	95
Inpatient stay	0.5 (1.3)	0 (0 to 0)	0.5 (1.4)	0 (0 to 0)	0.87	1987
Visit GP at practice	5.4 (6.6)	2 (1 to 9)	3.6 (3.9)	2.5 (0 to 5)	0.27	43
Visit practice nurse at GP practice	0.9 (2.6)	0 (0 to 1)	0.7 (2.0)	0 (0 to 0)	0.62	14
Total cost (excluding GP and practice nurse visits)	3266 (3355)	1806 (1146 to 4664)	2620 (3621)	991 (745 to 2999)	<0.01	
Total cost (including GP and practice nurse visits)	3775 (3691)	2620 (1272 to 5424)	2943 (3963)	1270 (904 to 3466)	0.06	

SD = standard deviation. IQR = interquartile range. * For GP visits, practice nurse visits and total cost including GP and practice nurse visits, due to missing data the number of observations in the conventional follow-up group was n=31 and in the nurse-led follow-up group it was n=42. † Calculated using Mann-Whitney two-sample statistic. ‡ Calculated in 2011/12 UK£. See web extra material for further details.

SDC Table 4. Use of services and total cost per patient



Tests for normality on combined data: Shapiro–Wilk normality test: P <0.01.

SDC Figure 1. Distribution of total cost per person in each group

Cost component	Unit cost*	Notes
Clinic appointment with CNS	95	Specialist Palliative Care: Outpatient. Non-Medical Specialist Palliative Care Attendance, 19 years and over.
CNS visits patient in hospital	95	Specialist Palliative Care: Outpatient. Non-Medical Specialist Palliative Care Attendance, 19 years and over.
Telephone consultation with CNS	40	Non-Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Non Face to Face. Medical oncology.
Email consultation with CNS	40	Non-Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Non Face to Face. Medical oncology.
Clinic appointment with consultant gynaecological oncologist	191	Specialist Palliative Care: Outpatient. Medical Specialist Palliative Care Attendance, 19 years and over.
Clinic appointment with other type of consultant	111	Consultant Led: Follow up Attendance Non-Admitted Face to Face. Weighted mean across all attendances.
Clinic appointment with clinical psychologist	137	Non-Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Face to Face. Clinical psychology.
Clinic appointment with complementary medicine team	95	Specialist Palliative Care: Outpatient. Non-Medical Specialist Palliative Care Attendance, 19 years and over.
Inpatient stay	1987	Total - HRGs. Gynaecological Malignancy with length of stay 0 days and Gynaecological Malignancy with length of stay 1 day or more. Weighted mean across all admissions.

SDC Table 5. Unit costs

All figures taken from National Schedule of Reference Costs 2011/12*. Calculated in 2011/12 UK£.

* Department of Health. *National Schedule of Reference Costs - Year 2011-12 - NHS trusts and NHS foundation trusts: NHS own costs*. Department of Health: London, 2012. https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012 [last accessed 13 September 2013].

	Marginal effect	SE	Z score	P value	95% CI
Total cost (excluding GP and practice nurse visits)	-695	394	-1.8	0.07	-1467 to 77
Total cost (including GP and practice nurse visits)	-745	409	-1.8	0.08	-1546 to 56

SDC Table 6. Adjusted analysis of nurse-led follow-up on total costs

Controls are included for age at baseline, disease stage at baseline, disease grade at baseline and study site. The analysis excluding GP and practice nurse visits was based on complete cases; the analysis including these visits used imputed data (Online supplementary material). The marginal effect is the mean difference in total costs between the two groups adjusting for the controls. SE = standard error. CI = confidence interval.