# Follow up After Treatment for Gynaecological Cancer

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine by

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# Contents

# Chapter 1 - Background

Gynaecological cancers affect nearly 20 000 women annually in the United Kingdom[1]. They are a diverse group of cancers that are mostly only linked by their origin in the female genital tract. As such they vary in their stage at presentation, management and prognosis. Women with ovarian cancer are more likely to present at an advanced stage of disease than women with cancers further down the genital tract, due mainly to the late development and non-specific nature of the symptoms associated with this disease. As a result the overall five-year survival for ovarian cancer is only 41%[2]. Women suffering from endometrial, cervical and vulval cancers tend to present at an earlier stage with symptoms of bleeding, discharge or pain (or through screening in the case of cervical cancer). This earlier presentation is reflected in the overall five year survival for these cancers: 75% (endometrial)[3], 64% (cervical)[4] and 58% (vulval and vaginal)[5].

Treatments vary according to the nature of disease. Ovarian cancer is primarily treated with surgery (simple hysterectomy, bilateral salpingo-oophorectomy, washings, omentectomy and debulking of tumour) and, in advanced cases with six cycles of platinum-based chemotherapy. Endometrial cancer is treated by surgery (simple hysterectomy, bilateral salpingo-oophorectomy and washings), with adjuvant brachytherapy or pelvic radiotherapy for those at higher risk of pelvic relapse. Cervical cancer is treated by surgery (radical hysterectomy and pelvic lymph node dissection) for early cases (in a third of cases adjuvant radiotherapy is required for those at high risk of relapse), but with primary chemoradiotherapy for the more advanced cases. Vulval cancer is usually treated by surgery (wide local excision with or without bilateral groin node dissection), with adjuvant radiotherapy given if there is spread of the disease to the lymph nodes or as primary treatment if there is involvement of adjacent structures such as rectum and urethra.

As might be expected for a diverse group of cancers, patterns and frequency of recurrence also vary between the different gynaecological cancers. Ovarian cancer tends to present at a later stage than the other cancers, with over half of women having disseminated disease at the time of presentation. As a result, recurrence is more common in this disease. The treatment of recurrent ovarian cancer represents a challenge, as there are no curative interventions, with options invariably including chemotherapy, with a poor long term prognosis[6]. Whilst there is no curative salvage treatment for recurrent ovarian disease, in those previously responding to platinum based chemotherapy, surgery with or without chemotherapy offers an opportunity to produce significant periods of disease remission after recurrence[7]. It is difficult to extrapolate results in other malignancies to ovarian cancer, since it has a different natural history to both non-gynaecological cancer and other gynaecological cancers.

By contrast, recurrence in endometrial (13%)[8] and cervical cancers is less common due to the earlier stage at presentation. Unlike ovarian cancer, there are potentially curative salvage treatments for a small proportion of these women. For women with recurrence after treatment for microinvasive carcinoma of the cervix, further surgical excision is usually possible. Women who are radiotherapy naïve and have localised pelvic recurrence can be cured with pelvic radiotherapy[9]. Those already treated with radiotherapy who have a central pelvic recurrence can, in certain cases, be saved by exenterative surgery. Localised recurrence in vulval cancer can be treated with further excision, if feasible, or radiotherapy if it is not.

As can be seen from this brief description, gynaecological cancers are a varied group of tumours with markedly different disease courses, treatments and prognoses. Their link is predominantly only the anatomical link of originating in the female genital tract. As such these cancers are managed individually according to the cancer site, the histology, the stage of disease and the individual patient needs.

Conversely the approach to follow up after treatment has tended to be less individualised. Traditionally, all patients who have been treated for cancer undergo long-term, even life-long, follow up in secondary specialist care. The primary rationale is that if a recurrence of the cancer is picked up early, it is more likely to be amenable to treatment and that therefore survival and/or quality of life will be improved[10 11]. It is regarded as standard practice to routinely follow up women after treatment for gynaecological cancer[11 12] but this practice puts a significant strain on financial and workforce resources[13-16]. However, it has been suggested that the use of routine review may in fact delay the detection of recurrence because some women delay presenting symptoms until their next routine appointment[17-19]. Qualitative work has shown that women find routine visits to the hospital reassuring, especially if they are experiencing unexpected symptoms[20]. Never the less, for some, feelings of anxiety and apprehension may actually deter them from attending[20].

**Current Evidence**

A systematic review by this author[21] in 2005 demonstrated no prospective studies of follow up after any of the gynaecological cancers. An updated literature search of Medline up to August 2010 (table 1) demonstrated no prospective studies other than Rustin et al[22] on the role of CA125 testing during follow up after ovarian cancer. Due to the lack of prospective studies, there are no data, other than in Rustin et al, on issues such as quality of life or meaningful economic evaluation.

**Endometrial Cancer**

There are no prospective studies, either observational or randomized.

Nine papers and one letter provide an analysis of the benefit of routine follow-up on survival[13,15,16,23-29] Rates of recurrence varied from 8.5-19% of patients

[23]. Some of the papers limited themselves to early stage disease whereas others included patients with stage III disease (table 2).

Allsop, Agboola, Berchuck, Gaducci, Gordon, Owen, Podczaski, Salveson, Sartori and Shumsky all address the issue of whether routine follow-up produces improvements in clinical outcome, with survival as the endpoint[13,15,16,23-28]. Two of these papers[26,29] conclude that there is a survival benefit from detection of recurrence at an asymptomatic stage. However, methodologically, both of these papers are very weak. No correction has been made in either for lead-time bias; the comparison is in survival times from detection of recurrence until death. There is also no attempt to correct for any differences in the known prognostic factors in the two groups. Hence the assertion from these two authors that there may be a survival benefit from routine follow-up is not reliable.

The remainder all correct for lead time bias[13,15,16,23-25,27,28], by calculating survival as the time period from the original diagnosis to death rather than from recurrence of disease to death. They all conclude that there is no benefit in survival from detection of asymptomatic recurrence at routine follow-up, as opposed to symptomatic recurrence or interval detection. However all these papers are of poor methodological quality. They rely on restrospective collection of information and there is a risk that there may be a high proportion of patients with recurrence in amongst the patients that were lost to follow-up. The papers are heterogeneous, and comparison between them is difficult. The stage of disease varies and the strategies for follow-up (both the frequency and the use of routine investigations) show large variation. This may in part explain why there is such a large variation in the proportion of patients that were asymptomatic at the time of recurrence (8%-54%)[15,25]. Despite this, none of them show any benefit from routine clinical review. However it is possible that small differences in survival would not have been detected in view of the small numbers of patients with recurrent disease in these papers (table 2).

A recent systematic review of follow up after primary treatment for endometrial cancer identified sixteen non-comparative retrospective studies[8]. This review set out to determine the most appropriate strategy for the follow up of patients with endometrial cancer who are disease free at the end of treatment. They pooled data to determine the risk of recurrence (13% overall and 3% for low risk disease). On pooled data, with one study excluded that would skew the results[30], 70% of women were symptomatic at the time of detection of recurrence. No justification is given for the exclusion of the paper, which showed 100% of patients to be symptomatic at the time of recurrence.

**Cervical Cancer**

There are no prospective studies, either observational or randomized.

Ten papers[14,31,32-36,29,37,38] were identified that considered the impact of follow-up after cervical cancer on survival in terms of survival benefit from detection of asymptomatic recurrence (table 4). All are retrospective case series analyses.

Zola reviewed 327 consecutive women with recurrent cervical cancer across eight institutions, identified from a central database[38]. The cases ranged from stage Ib1 to stage IV. They found a significant difference in median overall survival between women who were detected at an asymptomatic stage (109 months) compared to those who were symptomatic (37 months, log rank p=0.0001). This paper contains the largest number of recurrences of any of the papers identified, but no data is given nor corrections made for any differences in prognostic features between the two groups. No data is provided as to whether the distribution of stages is similar across the two groups, let alone any other recognised prognostic indicators. Failure to consider prognostic indicators potentially introduces length time bias since it is likely that women with more indolent disease will have a longer time period with asymptomatic disease recurrence. This then creates the potential for women with more indolent disease to have a greater chance of having any

recurrence detected at an asymptomatic stage. Since indolent disease has better survival than more aggressive disease any difference in survival detected may be a reflection of type of disease rather than benefit from earlier detection. Hence it is likely that the difference demonstrated by Zola is an overestimate since the figure has to be subject to length time bias. Furthermore, this difference is made even more marked since this paper deals with a wider range of FIGO stages than the other papers identified. If these are not evenly distributed between the two groups then it will markedly bias the results.

Bodurka-Bevers et al demonstrated an apparent benefit in terms of survival from routine follow-up of women who had been treated for stage 1B carcinoma of cervix[32]. Primary treatment was either by radical hysterectomy or radiotherapy. The median survival from diagnosis differed significantly between asymptomatic recurrences ($\mu$=83 months) and symptomatic recurrences ($\mu$ = 31 months) $p<0.001$. Furthermore this difference persisted when other prognostic factors (histology, grade, lesion size and lymph node status) were considered ($p<0.01$). This paper has the second highest number of cases of recurrent carcinoma (133), which may explain why this paper detected a significant difference in survival. However whilst the authors have corrected for known prognostic variables, with a retrospective paper, it is impossible to completely eliminate the possibility of length time bias producing this difference in survival.

Samlal et al also found a benefit from asymptomatic recurrence detection compared to symptomatic recurrence when comparing crude survival rates in these two groups ($p=0.04$)[36]. They looked at women with stage IB or stage IIA cervical carcinoma who had been treated by radical hysterectomy. This was a much smaller study than Bodurka-Bevers, hence there were far fewer recurrences (27) in the group of patients being studied. Missing data may have had a profound effect on these results. There was no attempt to control for known prognostic factors. Hence it is quite possible that the two groups are

not directly comparable in terms of prognosis, leading to a high risk of lead-time bias and as such the results cannot be viewed as reliable.

Morice[14] found no survival benefit from detection of recurrence at an asymptomatic stage in women who had been treated for stage I and stage II carcinoma of the cervix. This paper has a low number of recurrences, which may be due to the exclusion of 30 patients who had recurrent disease within 6 months of the completion of treatment (which seems a very high figure). This paper also reports that 3 of the 7 asymptomatic recurrences were detected on radiological examination unrelated to routine follow-up, but no explanation is given for the indication for the examinations.

Ansink et al found routine follow-up to be inefficient and ineffectual in a case series of patients with stage IB cervical carcinoma treated by radical hysterectomy[31], although no formal survival calculation is provided in the paper. Duyn found detection of recurrence at an asymptomatic stage not to be of prognostic significance[33], nor did they find any benefit from detection at routine visits as opposed to interval detection. Krebs, Lim and Satori, in studies with similar numbers of recurrences though smaller total numbers of patients, also showed no benefit[29,34,35,] (Table 4). Larson did not formally compare the survival of women with symptomatic versus asymptomatic recurrence but the data tables show survival after recurrence to be similar (13 versus 12 months)[37].

A recent systematic review has attempted to establish best practice regarding follow up based on the existing evidence[39]. Elit et al determined that there was only modest low quality evidence to inform the most appropriate follow-up strategy[39]. They identified twelve studies[14,29,31-38,40-46] that assessed the use of investigations to detect asymptomatic recurrence. Physical examination detected recurrence in this group of patients in 29-71% of cases. Chest x-ray detected asymptomatic recurrence in 20-47%, whereas CT detected asymptomatic disease in 0-34% (after exclusion of one paper with only two asymptomatic recurrences). Vault cytology found asymptomatic disease in 0-17%, but all other tests including ultrasound, MRI, intravenous pyelography

and tumour markers were not of benefit[39]. However the papers do not always specify the site of recurrence. If it is assumed that the rationale for detecting asymptomatic recurrence is to improve survival then these papers do not determine whether or not there is benefit from these investigations, since survival is also dependent on the success of any salvage treatments available at relapse. As discussed above, there are potentially curative treatments for pelvic relapse but not, for example, from lung metastases as would be detected by chest x-ray. It is also difficult to determine from the papers whether or not the investigations were performed solely with the intention of detecting asymptomatic recurrence or whether they were performed for some other reason. It is perhaps therefore not surprising that Elit questions the benefit of the routine use of investigations of any sort[39].

**Vulval Carcinoma**

There are no prospective studies, either observational or randomized.

Only two papers were identified that examined the role of routine follow-up after vulval carcinoma[18,19]. Oonk et al reviewed the cases of 238 women with all stages of vulval carcinoma, who were disease free three months after the end of treatment[19]. They were followed up three monthly for two years, six monthly for three years then annually for life. 65 women developed recurrence, of whom 21 (32%) were asymptomatic at the time of detection. The median time to recurrence was 21 months (range 3-76 months). The comparison made was between women whose recurrence was detected at routine review and at interval review. The tumours detected at routine review were smaller, but this did not confer any survival benefit over those whose recurrence was detected at interval appointments (log rank test, p=0.22). The authors conclude that, although their retrospective study was unable to detect any improvement in morbidity, it may be that detection of smaller volume tumour recurrences may reduce treatment morbidity in this group. Hence follow-up may be of benefit.

Nordin et al looked only at women who had node-negative squamous carcinoma of the vulva[18]. There were 138 cases who were followed up three monthly for the first year, six monthly for the second year and then annually for life. There were 18 recurrences (13%), all of whom were symptomatic at detection and 12 of whom recurred within the first year after diagnosis (median interval 8.7 months, range 1.0-85.4 months). The authors concluded that there was no evidence of benefit from routine follow-up in terms of early diagnosis of recurrence or improved survival. The issue of reduced morbidity from earlier intervention for recurrence is not addressed.

**Ovarian Cancer**

A recent review[6] suggested that it is uncertain whether the early detection of recurrence is beneficial in terms of survival and the clinical advantage of an intensive follow up program has not yet been demonstrated. The use of CA125 for early detection of recurrence is widespread[12,47], but the impact of this on the timing of chemotherapy has yet to be determined[48,49]. Only one, recently published, trial was identified[22] by this author in a Cochrane review[50].

***OVO5***[22]

One relevant prospective study was identified[22]. This is a randomised controlled, multi-centre trial in ovarian cancer of early treatment of disease relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/EORTC 55955 trials). The trial registered 1442 patients; all women had confirmation of remission with normal CA125 concentration and no radiological evidence of disease after surgery and first-line chemotherapy. 529 women were randomly assigned to treatment groups at relapse detected by a rise in CA125, and were included in the analysis. All 529 were assessed at the end of the trial (265 early, 264 delayed). The primary outcome measure was overall survival, calculated from date of randomisation to date of last follow-up or death from any cause.

Women assigned to early treatment after relapse started chemotherapy 4·8 months (95% CI: 3·6 to 5·3 months) earlier than those allocated delayed treatment. The median length of follow-up was 56·9 months (interquartile range (IQR) = 37·4 to 81·8 months from randomisation) and there were a total of 370 deaths (186 early, 184 delayed) in the trial. Median age at registration was 61 years (range: 53 to 68); 81% were FIGO stage III/IV. Second-line chemotherapy started a median of five months earlier in the immediate arm. Chemotherapy treatment was given according to local institutional protocols. Median follow-up from randomisation was 49 months.

Health related Quality of Life (QoL) was reported by calculating time to first deterioration in QoL score or death using the EORTC QLQ-C30 questionnaire.

Toxic outcomes were not included as a secondary outcome measure.

***Overall survival***

Median survival from randomisation was 25·7 months (95% CI: 23·0 to 27·9) for patients on early treatment and 27·1 months (22·8 to 30·9) for those on delayed treatment.

There was no statistically significant difference in the risk of death between women who received immediate treatment and those who received delayed treatment (unadjusted HR = 0·98, 95% CI 0·80 to1·20, p = 0·85). The unadjusted estimate was robust to estimates that were adjusted for stratification factors, prognostic factors and both stratification and prognostic factors (HR = 1·01, 95% CI: 0·82 to 1·25).

***Quality of life***

Time from randomisation to first deterioration in global health score or death was shorter (median 3·2 months, 95% CI: 2·4 to 4·3) in the early group compared with the delayed group (5·8 months, 95% CI: 4·4 to 8·5; HR 0·71, 95% CI: 0·58 to 0·88; p = 0·002). The trial authors claimed that subgroup

analyses of the QLQ-C30 sub-scales showed deterioration in score sooner in the early group than in the delayed group for almost all sub-scales. There was evidence of significant disadvantages for role, emotional, social, and fatigue sub-scales with early treatment. Furthermore the QLQ-C30 questionnaire asks about symptoms only in the previous week, and the forms were completed just before each course of chemotherapy. Hence this method could underestimate any reduction in quality of life due to chemotherapy.

Apart from OVO5[22] all other studies in ovarian cancer on follow up strategies use the detection of recurrence as the primary endpoint. This is problematic, as time to detection of recurrence is not an adequate surrogate marker for overall survival. The two may diverge depending on treatments available at relapse. Furthermore detection of recurrence without subsequent information on survival risks the introduction of lead-time bias.

**Clinicians' and Patients' Views**

Two studies in the gynaecological oncology field have addressed clinicians views and practice with regards to follow up[11,12]. Kerr-Wilson showed that, in the early 1990s, there appeared to be five rationales for following women up after treatment:

- detection of recurrence
- reassurance for patients
- audit, research or collect statistics
- assess side effects
- tradition

Barnhill showed that there was wide variation in the use of investigations to try to detect recurrence[12]. However, all investigations were analysed with a view

to whether or not they successfully detected recurrence, rather than whether or not this had any impact on the overall outcome.

A large recent quantitative survey of nearly 3000 service users[51], primary care physicians and specialists with experience of all types of cancer has shown that these groups regard the main reasons for follow up as being:

- to monitor for early complications
- to detect recurrences early
- to detect late effects of treatment.

Service users were significantly more likely to view detection of recurrence as highly important than were medical staff. Primary care physicians were more likely to view early detection of recurrence as important than were hospital specialist staff.

Kew et al also showed, in a sample of gynaecological oncology patients undergoing follow up, that patients regard detection of recurrence as the primary rationale for follow up, and that they rate this more highly than clinicians do[52].

Bradley et al showed, with a qualitative study of women with early stage gynaecological cancers, that women value follow up because it affords them ready access to specialist services[20]. The women described a feeling of increasing apprehension in the lead up to their appointments, but placed huge value on the reassurance derived from attending the appointment. She also demonstrated that women valued scans above all other investigations in determining their disease status.

A study using focus groups also showed that the patients viewed follow up visits as reassuring[53]. They were reluctant to consider follow up by General Practitioners or telephone follow up. This is in keeping with a quantitative study by Kew et al[54]. However a focus group of professionals working in medical oncology[53] felt that the main rationale for hospital-based follow up

clinics was to monitor the patients for symptoms of relapse. They also felt that the current system of routine follow up was unnecessarily labour intensive and needed reform, whilst recognising that patients may be reluctant to have shared care with their General Practitioners. However, improved communication may be required if such a change were introduced since less than half of General Practitioners were satisfied with aspects of communication regarding their patients who have been treated for cancer[55].

**Alternative Models**

Due to the lack of prospective work, alternative forms of follow up have not been investigated in women who have been treated for gynaecological malignancies. Follow up strategies using models other than the traditional secondary care model have been examined in patients following treatment for other malignancies. Follow-up by general practitioners has been shown to be effective and acceptable in breast cancer[56]. An equivalence trial in breast cancer comparing nurse delivered telephone follow up with traditional hospital follow up showed that there was no adverse outcomes in terms of physical or psychological outcomes, but did not assess survival[57]. A pilot study making use of open access after breast cancer was popular with the patients[58], but a full randomised trial was not funded. The use of specialist nurses has been reported to be safe and effective following lung cancer[59].

Work in women who have had a gynaecological malignancy has suggested that what they seek at follow up is reassurance from a cancer specialist[20]. This is further confirmed by Kew et al, who showed that women already undergoing follow up in secondary care prefer to continue to have review by a specialist, rather than being seen by a specialist nurse only or their General Practitioner[54]. It is difficult to determine whether or not this is due to pre-existing expectations in women who are already used to this sort of follow up, and there is evidence in a survey of service users in all fields of oncology that they rate most types of follow up highly if they have experienced it[51]. As such

it may be that introducing different sorts of follow up will require significant patient education for those who are already in a given follow up regimen.

## Conclusions

All papers assessing follow up after gynaecological cancer are retrospective and so are subject to significant bias. Whilst the better papers correct for lead-time bias and attempt to correct for length time bias, it is impossible to completely eliminate this from a retrospective non-randomised study. Many of the studies have small numbers of recurrences so it is impossible to be sure that significant differences in survival are being missed in these papers. It is also impossible to retrospectively assess the impact of different sorts of follow up on quality of life.

The majority of the papers found deal with patients who have been treated for early stage malignancy. The use of the term 'recurrence' implies that the women who were included were disease free at the end of treatment. There is virtually no data on patients with more advanced disease, whose needs may be very different. For these women, the primary rationale behind routine follow up – that of detecting and treating recurrent disease early – does not apply. Therefore it may be more appropriate to provide direct access than routine review. This may offer these women better support and quality of life, but further work is needed to determine any such benefits.

## Plan of work

As has been shown with this review, prospective studies are required to assess the impact of follow up in women who have been treated for gynaecological cancer. A large multi-centre randomised controlled trial should be initiated to compare the current routine follow-up schedule with an alternative system of follow up, such as patient self-referral based on their symptoms. The execution of such a trial has been shown to be acceptable to

General Practitioners[60]. This would allow the question of whether or not routine clinical review in secondary care improves survival, compared to presentation at the time of symptomatic relapse, to be answered. Such a trial would also allow determination of the impact that routine follow-up has on quality of life. There are examples of randomised trials in other, more common, malignancies such as breast and colon. These trials confirm that patients can be recruited into this type of trial[58,61,62].

In order to develop the protocol for a randomised trial, specific pieces of work were needed.

Work stream 1: Audit of practice

In order to determine the baseline for a trial, it was important to determine what was 'standard' practice regarding follow up. This was to be determined using a quantitative questionnaire developed specifically to collect the information considered necessary for the development of a 'standard care' arm in the full trial.

Work stream 2: Women's views

There is a lack of data on women's views of follow up after gynaecological cancer, especially in more advanced disease. In order to develop an intervention arm for a randomised trial it was necessary to understand how women view the current arrangements and the benefits and/or drawbacks they see with it. Given the lack of data in this area, a qualitative approach was planned in order to explore and understand the issues for women undergoing follow up, such as 'why?' and 'how?' rather than 'how much?'[63].

Work stream 3: Pilot Randomised Controlled Trial

A pilot randomised trial was planned to determine the feasibility of recruiting to and running a multi-centre randomised controlled trial. The null hypothesis for such a trial would be that there is no benefit from follow up.

## Tables

***Table 1.1: Summary of Papers in Endometrial Cancer that consider survival***

| Paper | Number of cases* | Limited/absent data | Follow-up length (years) | Follow-up visits** | Recurrences n (%) | Asymptomatic recurrences n (%) | Survival analysis (routine versus interval clinic or asymptomatic versus symptomatic) (NS = not significant) |
|---|---|---|---|---|---|---|---|
| Agboola[13] | 356 | 32 | Until death | 13 | 50 (14%) | 20 (40%) | NS; both comparisons performed |
| Allsop[23] | 142 | unknown | 10 | 8 | 12(8.5%) | 2 (17%) | 'No apparent benefit' |
| Berchuck[24] | 354 | unknown | 5 | 14 | 44 (12%) | 17 (39%) | 'Little impact on survival' |
| Gaducci[25] | 133 | 16 | Until death | 12 to 14 | 24 (18%) | 13 (54%) | 'survival similar'; asympto versus sympto |
| Gordon[26] | 127 | 3 | 5 | 9 | 17 (15%) | 4 (24%) | P=0.048; asympto versus sympto |
| Owen[27] | 90 | 4 | 10 | 8 or 9 | 17 (19%) | 6 (35%) | 'No apparent survival benefit from detection of asymptomatic recurrence' |
| Podczaski[28] | 300 | unknown | Until death | 14 | 47 (16%) | 24 (51%) | NS; asymptomatic versus sympto |
| Salveson[15] | 249 | 13 | 10 | 9 | 47 (19%) | 4 (8.5%) | NS; routine versus interval |
| Sartori[29] | Unk | Unk | Unk | Unk | 84 (unk) | 40 (48%) | P=0.02; asympto versus sympto |
| Shumsky[16] | 317 | 70 | 5 (minimum) | 12 | 53 (16%) | 13 (25%) | NS; routine versus interval |

* number of cases that were analysed who were disease free at the end of treatment

** standard number of visits recommended in the first five years

***Table 1.2: Timing of recurrences in endometrial cancer***

| Paper | Number of recurrences | Stage of disease included in study | Proportion of recurrences presenting by | | | | Disease free interval | |
|---|---|---|---|---|---|---|---|---|
| | | | Year 1 | Year 2 | Year 3 | Year 5 | Median (months) | Range (months) |
| Agboola[13] | 50 | I-III | | | 80% | | 18.5 | 3-194 |
| Allsop[23] | 12 | I-IV | | | | | 17 | 4-72 |
| Berchuck[24] | 44 | I-II | | | 82% | | unknown | unknown |
| Gaducci[25] | 24 | I | | | | | 17.5 | 6-64 |
| Gordon[26] | 17 | I-III | | 65% | | 100% | * | 4-53 |
| Owen[27] | 17 | I-III | | 82% | | | 20 (mean) | ?-72 |
| Podczaski[28] | 47 | 'early' | 47% | 70% | | | unknown | unknown |
| Salveson[15] | 47 | I-III | 34% | 68% | | | unknown | unknown |
| Shumsky[16] | 53 | I-III | | 58.5% | 70% | | unknown | unknown |

*21 months for symptomatic patients, 7.5 for asymptomatic patients; all asymptomatic patients detected within 2 years

***Table 1.3: Summary of papers on follow up after cervical carcinoma***

| Paper | Number of cases* | Limited/ absent data | Follow-up length (years) | Follow-up visits** | Recurrences n (%) | Asymptomatic recurrences n (% recurrences) | Survival analysis (NS = not significant) |
|---|---|---|---|---|---|---|---|
| Ansink[19] | 674 | 9 | 10 | 9 | 112 (17%) | 20(18%) [5 missing] | No calculation provided; routine versus interval follow-up |
| BBevers[20] | 993 | 55*** | until death | 14 | 133 (13%) | 19(14%) | P< 0.01 asympto vs sympto |
| Duyn[21] | 442 | 69 | until death | 13 | 47 (17%) | 6(13%) | NS; both analysed |
| Krebs[22] | 312 | unknown | until death | 24-28 | 40 (13%) | 10(25%) | NS; asymptomatic versus symptomatic |
| Larson[37] | 250 | 1 | >= 5 years | 13 | 27 (11%) | 10 (37%) | median survival 24 versus 23 months |
| Lim[23] | 291 | 27 | unknown | unknown | 53 (18%) | 2(4%) | 'not an independent prognostic factor' |
| Morice[14] | 583 | unknown | Until death | 11 | 45 (8%) | 7 (16%) | Median survival similar, asympto versus sympto |
| Samlal[24] | 271 | unknown | 10 | 11 | 27 (10%) | 9 (35%)[1 missing] | P=0.04 asymptomatic versus symptomatic |
| Sartori[29] | [29]unknown | unknown | unknown | unknown | 63 (unk) | 22 (35%) | NS; asymptomatic versus symptomatic |
| Zola[38] | Unknown | Unknown | Unknown | unknown | 327 (unk) | 163 (50%) | P=0.00001, no correction for prognostic features |

* number of cases that were analysed who were disease free at the end of treatment
** standard number of visits recommended in the first five years
*** followed up in a different unit

*Table 1.4: Timing of Recurrences after Cervical Carcinoma*

| Paper | Number of recurrences | Stage of disease included in study | Proportion of recurrences presenting by | | | | Disease free interval | |
|---|---|---|---|---|---|---|---|---|
| | | | Year 1 | Year 2 | Year 3 | Year 5 | Median (months) | Range (months) |
| Ansink[19] | 112 | IB | | 62% | 75% | 92% | 25 | 1-98 |
| Bodurka-Bevers[20] | 133 | IB | | | | | 16 | unknown |
| Duyn[21] | 47 | I-IV | 49% | 68% | | 100% | 18 | 3-50 |
| Krebs[22] | 40 | IB/IIA/IIB | 58% | 83% | | | 10 | unknown |
| Lim[23] | 53 | IB | | | 77% | | 18 | unknown |
| Morice[14] | 45 | I/II | 33% | 64% | 78% | 95% | 16 | 2-128 |
| Samlal[24] | 27 | IB/IIA | | | 77% | | 14 | 3-64 |

# Chapter 2 – Survey of Practice

## Introduction

Current practice with regards to follow up after gynaecological cancer in the United Kingdom is unknown. A previous survey of gynaecologists conducted in the United Kingdom in 1995 revealed 106 different schedules of follow up[11]. However, this was prior to the centralisation of all cancer services in the United Kingdom[64]. The Calman-Hine report introduced the concept of hub and spoke arrangements for cancer services, where rare cancers such as the gynaecological cancers were to be managed via a network with one cancer centre supported by several cancer units. Diagnostic work and some low-risk cancers can be managed in the units with all more complex cases referred on to the centre for management by subspecialists[65]. Centralisation resulted in profound changes to the way care for women who have gynaecological cancer was delivered. Care for all cancers is now delivered on the basis of a wheel and spoke arrangement, with care organized into networks with a cancer centre supported by cancer units[64]. Further guidance on commissioning care for women with gynaecological cancer included recommendations on follow up[65]. These stipulated that there should be guidelines on follow up in each cancer network, and that routine follow up should not be considered mandatory for women who are in complete remission after curative treatment for endometrial cancer. It also recommended that vault smears should not be used to detect recurrent endometrial cancer. However, beyond this there are no standard recommendations on the frequency or duration of follow up, nor on the use of routine investigations during follow up such as x-rays, Computerised Topogrophy (CT) scans, Magnetic Resonance Imaging (MRI) scans or tumour markers (specifically CA125 in ovarian cancer).

Following these changes there had been no data or assessment of practice with regards to follow up in the United Kingdom. However, the United

Kingdom has devolved health to its constituent states and so there are now four separate health services. It was therefore decided to assess follow up in by far the largest health service, the English National Health Service[66]. This project set out to determine current practice of follow up after gynaecological cancer in the 34 English Cancer Networks.

**Methods**

A two-page questionnaire (appendix 1) was developed in consultation with a consultant gynaecological oncologist and a statistician. It was piloted within the department of gynaecological oncology and James Cook University Hospital to ensure it was easy to understand and complete.

The aim was to send out one copy of the questionnaire to the lead clinician for gynaecological cancer in each cancer centre. However, at the time of the study, it was impossible to establish an accurate list of these individuals. Hence the survey was limited to English Gynaecological Cancer Centres only. No authoritative list was available, either on line or from the Department of Health. A list of the cancer networks and their gynaecological cancer centres was used which was obtained at a national meeting of the British Gynaecological Cancer Society. A contact point was established in each centre through a series of telephone calls and by indentifying individuals at national meetings.

In total 37 questionnaires were sent out to the 34 cancer centres. The duplication was due to the lack of a database of gynaecological cancer leads. Questionnaires were sent out by post, followed by another postal round to non-responders eight weeks later. This was followed up by distribution of the questionnaire at a face-to-face meeting of gynaecological cancer leads and it was then distributed by email to non-responders. Results were analysed using the Statistical Package for Social Sciences.

**Results**

Of the 37 questionnaires sent out, 25 replies were received from 24 different cancer networks. One response was excluded because it was from a cancer unit, where a response was received from that network's cancer centre. One reply was received from a cancer unit in a network where there was no response from the centre. Since networks are meant to have network guidelines including on follow up, this response was therefore included. The overall response rate was 24/34 networks (71%). 23/24 (96%) responses were from cancer centres.

All networks provide some routine follow up after gynaecological malignancy. Only one network reported curtailment of follow up at an early stage. They described reviewing patients twice in the first year after treatment and then no routine follow up in a clinic, but providing them with open access instead. In total 6/24 (25%) reported using open access as part of their follow up service. All routine follow up took place in secondary care, and was consultant based (table 2.1). In the majority of cases, there was also a specialist registrar in the clinic (15/23; 65%). 18/24 (75%) of networks had written guidelines on the frequency and timing of follow up.

The commonest follow up regimens are presented in table 2.2. 10/24 (42%) networks used the same follow up frequency and duration irrespective of the primary cancer site (ovary, endometrium, vulva or cervix), whereas the remainder varied according to the diagnosis. Overall results of frequency of visits are shown in table 2.3.

The stated duration of follow up is shown in table 2.4. Apart from the network mentioned above, that discharges patients from routine follow up after one year, three other networks (12.5%) described discharge from routine follow up within five years of completing treatment. One network discharged women who have been treated for cancer of the ovary, endometrium and cervix after three years of follow up. Another network discharged women who have been

treated for endometrial cancer after three years and a third discharges women who have been treated for cervical cancer after two years.

Very few routine investigations were undertaken to detect recurrence. The exception was Ca125 levels following treatment for ovarian cancer. 16/24 (67%) networks routinely performed this test at each routine review. One network used annual CT to check for recurrence after treatment for cervical cancer. No other routine investigations were recommended.

Overall it can clearly be seen that the most favoured follow up regimen was secondary care follow up by consultants with the patients attending 3 monthly for the first year, 3 or 4 monthly for the second year, 6 monthly for the third and fourth years and then an annual visit until discharge at 5 years. There is an inclination to follow up women who have been treated for ovarian cancer slightly more often than for the other cancer sites. For women being followed up after ovarian cancer, serum CA125 measurement was recommended at each follow up visit.

**Discussion**

This survey provides an up to date assessment of current practice in England with regards to follow up after gynaecological malignancy. It clearly demonstrates that the large majority of networks are continuing to follow up all women who have been treated for gynaecological cancer for at least five years, and in several cases for longer periods of time. In 1999 the Hayward report[65] stated that there was no evidence to support the routine follow-up of women in remission after a gynaecological cancer, and suggested that follow-up of women after endometrial cancer should not be considered mandatory.

Our survey demonstrates that 25% of networks are failing to follow recommendations that there should be a documented policy on the frequency and timing of follow up for each type of gynaecological cancer[65]. This may be because of a lack of good quality evidence on the best regimens for follow up.

There is no prospective data in the medical literature regarding the impact of routine follow up on survival after treatment for gynaecological malignancies[21].

It has been suggested that the use of routine review may in fact delay the detection of recurrence because some women delay presenting symptoms until their next routine appointment[17]. For some women, feelings of anxiety and apprehension may actually deter them from attending[20]. However qualitative work has shown that women find routine visits to the hospital reassuring, especially if they are experiencing unexpected symptoms, although the reassurance only lasts for short periods of time[20]. Whilst there have been moves with other cancer sites to use different forms of follow-up such as nurse led[59] or General Practitioner led[67], practice in gynaecological cancers has been shown to still follow the traditional secondary care model, with periodic review of decreasing frequency.

Van Voorhis wrote, in 1970, that 'the value and most desirable frequency and duration of follow-up examinations for patients with cervical cancer is not well established'[68]. The variability in regimens demonstrated in this paper seems to demonstrate that, 35 years later, clinicians remain uncertain as to how and when to follow women up after treatment for gynaecological cancer.

**Validity**

The aim of any survey is to gather valid, reliable, unbiased and discriminatory data from a representative sample of respondents, or in the case of a census from an entire population. However, the data collected are subject to error and bias from a range of sources. Our close attention to issues of questionnaire design and survey administration aimed to reduce these errors[69]. However research in to this methodology is limited and the heterogeneity of findings mean that there are no universal recommendations on best practice in terms of either questionnaire design or survey conduct[69].

Sampling

There are several alternative sampling options to the one that was utilised which may have influenced our results. Firstly, a survey could have been undertaken of all gynaecologists and their practice in relation to follow up, similar in nature to previous work in this area[11]. However the changes in provision of service mean that most gynaecologists no longer undertake care of women with gynaecological cancer, nor do they contribute to the provision of follow up. As such any results would not have been valid as the population sampled would have been inappropriate for the data collected.

A second option would have been to survey all gynaecological cancer centre leads and gynaecological cancer unit leads. This would have permitted evaluation of follow up procedures throughout the cancer networks, rather than determining the practice in the cancer centres. In theory practice should be standardised throughout each network with the use of guidelines [65], but, as this project showed, 25% of responding networks did not have written guidelines on follow up. There is also no evaluation of adherence to the protocols reported by the cancer centre leads. However assessment of compliance, whilst interesting, was not possible. In terms of surveying all cancer unit leads as well as cancer centre leads, practical considerations meant that a survey of that nature was unlikely to produce useful results. As described in the methods section of this chapter, the author found great difficulty in determining the whereabouts of the gynaecological cancer centres for each cancer network and then identifying a lead clinician within that service. Therefore to attempt to identify the gynaecological cancer units that feed in to the centres, and their lead clinicians, would have been unfeasible and unachievable.

Survey administration

There are essentially three options for survey administration: face-to-face interviews, telephone interviews and postal questionnaires (paper and/or electronic). The use of face-to-face interviews was impractical for this project as it would have required travelling to the 33 other gynaecological cancer centres.

Telephone interviews were a potential option. They are usually more effective than postal questionnaires at avoiding refusal, and they guarantee knowledge of which individual is completing the questionnaire. They also improve item non-response rates. However they may introduce bias from the views and characteristics of the interviewer and are more expensive to perform[69]. This study was not specifically interested in the views of individual clinicians, but rather the standardised practice of the department. As such one of the main benefits of telephone questionnaires does not apply to this survey. Strategies for enhancing response to a postal questionnaire are discussed below.

Questionnaire Design

The questionnaire was designed around standard recommendations[70]. Previous work by other researchers using open questions[11] were used to inform the development of this survey. Short questions requiring specific answers were used in order to standardise the data collected. Technical language was used, but only standardised terms were employed, such that any professional in this field would reasonably be expected to understand the question. Leading questions were avoided except where specific information was required (eg 'do you provide open access). 'Other' was included as an option so that unexpected responses would be captured. No opinions were sought so issues around response format were not relevant.

The questionnaire would have been enhanced had the questions stated 'the cancer centre in which you work' rather than 'you', since the term 'you' can be misinterpreted[70]. This may be particularly relevant for the 25% of centres where there are no guidelines in place and the follow up regimen may be specific to the consultant completing the form, rather than the department.

The questionnaire was designed to be only two pages of A4 paper in length, recognising that the people completing the forms are busy clinicians who may be put off completing a long survey. However length of survey has not been shown to affect response rates in studies outside of the health field [69]. Significant amounts of 'white space' were used so that the survey appeared

easy to fill in and the questions did not appear cramped [69], although the benefit of this strategy is not proven.

Response Rates

The response rate for this survey was 71%, which Mangione[71] would rate as 'very good'. Typically, response rates reported in the medical literature are low and surveys of physicians are lower still (on average 54%)[72].

Several approaches were adopted to maximise response rates. Firstly the questionnaire was kept brief. Secondly, reminders were sent to stimulate further responses, which has been shown to be effective at maximising response rates[69]. A return envelope was included in order to facilitate easy return of the questionnaire although, due to financial constraints, these were not stamped. The effect of providing a stamped envelope for return is equivocal[69]. Anonymity was not offered as it was necessary to identify non-responders so that reminders could be sent. Anonymity has not been shown to significantly improve response rates[69] and furthermore the information being collected was not personal in any way and in many cases is already in the public domain. Pre-notification has been shown to increase response rates, but was not used in this project, again because of cost limitations. Contacts were limited to reminders as they tend to be more effective in enhancing response rates than pre-notification.

**Implications for Research**

This survey was undertaken in order to provide information on current practice so as to determine the 'standard follow up arm' for a randomised controlled trial of follow up in women who have been treated for gynaecological malignancy. It can be clearly seen that such a regimen would consist of consultant review in secondary care. The most common schedule was three

monthly for the first year, three or four monthly for the second year, six monthly for the third year and then annual review until five years.

## Tables

***Table 2.1 grade of staff reviewing patients in the follow up clinic; n=22***

| **Grade of staff** | **N (%)** |
|---|---|
| Consultant only | 7 (30%) |
| Consultant and specialist registrar | 15 (62%) |
| Consultant and staff grade doctor* | 2 (8%) |
| General practitioner | 0 |
| Senior House Officer** | 1 (4%) |
| Clinical Nurse Specialist** | 5 (21%) |

* One clinic included consultant, specialist registrar and staff grade doctor

** Present in addition to the consultant

*Table 2.2 Commonest follow-up regimens; proportion of centres following the regimen in parenthesis*

| | Year 1 (%) | Year 2 (%) | Year 3 (%) | Year 4 (%) | Year 5 (%) |
|---|---|---|---|---|---|
| **Ovary** | 3 monthly (88%) | 3 monthly (46%) | 6 monthly (42%) | 6 monthly (50%) | 6 monthly (42%) |
| **Endometrium** | 3 monthly (74%) | 4 monthly (43%) | 6 monthly (57%) | Annual (48%) | Annual (57%) |
| **Vulva** | 3 monthly (73%) | 4 monthly (45%) | 6 monthly (59%) | 6 monthly (55%) | Annual (50%) |
| **Cervix** | 3 monthly (87%) | 4 monthly (52%) | 6 monthly (61%) | 6 monthly (43%); annual (43%) | Annual (57%) |

*Table 2.3 Recommended frequency of visit by cancer site*

| | Recommended visits per year | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|
| | | Number of survey respondents | | | | |
| **Ovary** | 0 | 0 | 1 | 1 | 2 | 2 |
| | 1 | 0 | 0 | 3 | 7 | 9 |
| | 2 | 1 | 2 | **10** | **12** | **10** |
| | 3 | 1 | 9 | 6 | 1 | 1 |
| | 4 | **21** | **11** | 3 | 2 | 2 |
| | 5 | 0 | 0 | 0 | 0 | 0 |
| | 6 | 1 | 1 | 1 | 0 | 0 |
| **Endometrium** | 0 | 0 | 1 | 1 | 3 | 3 |
| | 1 | 0 | 2 | 5 | **11** | **14** |
| | 2 | 2 | 6 | **13** | 9 | 6 |
| | 3 | 3 | **10** | 3 | 0 | 0 |
| | 4 | **17** | 4 | 1 | 0 | 0 |
| | 5 | 1 | 0 | 0 | 0 | 0 |
| **Vulva** | 0 | 0 | 1 | 1 | 1 | 1 |
| | 1 | 0 | 0 | 3 | 9 | **11** |
| | 2 | 2 | 5 | **13** | **12** | 10 |
| | 3 | 3 | **10** | 3 | 0 | 0 |
| | 4 | **16** | 6 | 2 | 0 | 0 |
| | 5 | 1 | 0 | 0 | 0 | 0 |
| **Cervix** | 0 | 0 | 1 | 2 | 3 | 3 |
| | 1 | 0 | 0 | 2 | **10** | **13** |
| | 2 | 1 | 3 | **14** | **10** | 7 |
| | 3 | 2 | **12** | 3 | 0 | 0 |
| | 4 | **20** | 7 | 2 | 0 | 0 |

Commonest responses are in bold type

*Table 2.4 Duration of follow up (n=24)*

| Cancer site | 5 years | 10 years | Lifelong |
|---|---|---|---|
| **Ovary*** | 15 | 7** | 1 |
| **Endometrium** | 22 | 2 | 0 |
| **Vulva*** | 17 | 4 | 2 |
| **Cervix** | 19 | 5 | 0 |

* data missing in one case

** two networks followed these women up six monthly; in all other cases the review beyond five years was annual

## Appendix 2.1 - Survey of Current Follow Up Practice

### Follow-up After Gynaecological Malignancy

### A survey of current practice

**Do you routinely follow up patients after treatment for gynaecological malignancy?**
***Yes/No***

*If no, do you provide open access?* Yes/No
Please give details:
.....
.....
.....
.....
.....

**If yes, where does this routine follow-up take place?**
Hospital clinic ☐
General Practice ☐
Other (please specify) .....

**Who sees the patient for follow-up (tick all that apply)?**
Consultant ☐
Consultant or SpR ☐
Consultant or Staff Grade ☐
General Practitioner ☐
Other medical staff (please specify) .....
Clinical Nurse Specialist ☐
Other (please specify) .....

**Do you have written guidelines on the recommended frequency of routine follow-up after treatment?** ***Yes/No***
If yes, please include a copy of these guidelines when you return the questionnaire.

*What is the recommended number of visits per year in each of the cancer groups (eg 3 monthly visits equates to 4 visits per year)?*

| | year 1 | year 2 | year 3 | year 4 | year 5 |
|---|---|---|---|---|---|
| **Ovary** | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Endometrium** | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Vulva** | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Cervix** | ☐ | ☐ | ☐ | ☐ | ☐ |

*Do you routinely carry out investigations in order to detect recurrence?*

In ovary yes/no

specify .....

.....

In endometrium yes/no

specify.....

.....

In vulva yes/no

specify.....

.....

In cervix yes/no

specify.....

.....

*Do you follow patients up for more than 5 years?*

Ovary Yes/No

If yes, for how long? .....

And how often? .....

Endometrium Yes/No

If yes, for how long? .....

And how often? .....

Vulva Yes/No

If yes, for how long? .....

And how often? .....

Cervix Yes/No

If yes, for how long? .....

And how often? .....

Name of person completing the form.....

Designation.....

Cancer Centre.....

Lead clinician for Gynae Cancers.....

**Thank you for your help**

# Chapter 3 – Women's Views of Follow up

## Introduction

It is increasingly recognised that the views of patients are vital to the establishment and design of healthcare services [65,73]. Despite this, very little has been published on women's views of follow up after treatment for gynaecological cancer. Only one piece of qualitative work has previously been undertaken in women who were having follow up after a gynaecological malignancy[20]. However this piece of work was carried out in women who had had early stage disease, and in all 4 main gynaecological cancers. It showed that the main element of follow up from the woman's point of view is the need to receive medical reassurance that there is no recurrence of the disease. This would not seem to fit with the high proportion of patients (75%) who were willing to accept nurse-led follow up in another study[59]. Furthermore, no qualitative work has been undertaken in patients receiving any model of follow up other than traditional, medically-based, routine clinic review. It is well established that qualitative studies offer an alternative when insight into the research is not well established or when conventional theories seem inadequate[74].

In terms of quantitative research, there is only a limited audit which showed that 32% of women preferred hospital follow up, 28% would prefer follow up

with a General Practitioner and 40% would prefer 'free access'[75]. However, the views of patients already in medical follow up on the role of specialist nurses in follow up has not been investigated, nor has their understanding of the reasons for follow up.

The aim of this study was to collect information on women's views of follow up. This was done in two ways. Firstly in-depth information was collected using qualitative methodology and this information was then triangulated[76] with quantitative data collected via a questionnaire. The information was then used to inform the design of follow up strategies suited to the expressed needs of women who have experienced follow up.

## Methods

### Qualitative Study

The qualitative study aimed to investigate the views, needs and experiences of women who had received three different models of follow up after treatment for ovarian cancer in a tertiary referral Gynaecological Cancer Centre.

The first model was standard follow up, as described in chapter 2. Patients typically attended for review 3 monthly in the first year, 4 monthly in the second year, 6 monthly in the third year and then annually until discharge at 5 years. At each appointment they would have a medically based history taken, an abdominal and vaginal examination and, more often than not, blood taken to determine the CA125 (tumour marker) level. The second group of women were participating in the MRC OVO5 study[22]. They were also included in order

to ascertain any impact from this trial on women's views. OVO5 was a blinded randomised controlled trial comparing early treatment of recurrent ovarian cancer based on tumour marker (CA125) relapse, compared with treatment at symptomatic relapse. Follow up within the trial protocol required two monthly clinic review with clinical examination and a blood test at each review. The third model was of nurse-led telephone follow up, which took place within the TRIFIDS trial (ethics reference 77/01) (trial never completed or published). The TRIFIDS trial compared intensive follow up (intensive by virtue of the use of CA125 and CT scans to detect recurrence early) with nurse-led telephone follow up (this trial was stopped early because of political problems and has never been published). Those who were allocated to nurse led follow up were telephoned by a specialist nurse every three months and asked a series of questions about their health. If there were symptoms suggestive of recurrent disease, they were invited to a clinic appointment to have an examination and investigations.

Qualitative methodology was used in order to investigate the detailed experiences and views of a broad cross section of women who were undergoing follow up after ovarian cancer. Specifically, grounded theory was used in order to develop a more in-depth understanding and explore the lived experience from a patient perspective and analyse the data through the iterative process of constant comparative analysis[77]. Interviews were semi-structured, based on themes previously identified by medical staff, nursing staff and patient groups (Appendix 3.1). Medical and nursing staff identified themes during informal discussions and formal research feedback sessions.

Patients' views were identified from previous research[20]. Interviews were tape recorded and then transcribed by a secretary in order to permit reference to the source data and allow the researcher to become immersed in the world of the sample being studied. Data collection continued until data saturation had been reached. It was estimated that this would require ten women to participate. Data saturation is described as being achieved simply when further interview data produces no new themes or perspectives[77].

Women were identified to take part in the study from clinic lists of attenders for routine follow up, from the list of participants from the TRIFID study, and from the list of women in the department who were participating in the OVO5 study. All women who had completed treatment for ovarian cancer and were undergoing follow up were potentially eligible for the study. The only exclusion criterium was women who did not speak fluent English.

Women were identified for potential recruitment using purposive sampling. This meant that a broad range of women with differing characteristics were recruited in order to maximise the information gleaned in relation to the follow up process. In addition to the different types of follow up, women with a wide age range, range of disease stage, length of time from diagnosis and different treatment modalities were invited to participate, since these factors were identified as potentially affecting their needs and views of follow up.

The study was undertaken using semi-structured interviews, with an interview schedule, which was amended as required during the course of the interviews. All interviews were conducted by the same researcher (not the

author). The interviewer was Dr Karen Roberts PhD, BSc (Hons), DPSN, RGN, who has extensive training and experience in qualitative methodology and the undertaking of interviews in qualitative research. She is nurse consultant in Gynaecological Oncology, Gateshead Health NHS Trust / Honorary Lecturer in the School of Health, Community & Education Studies at Northumbria University.

Consent to interview was sought from the respondent in an informal meeting prior to the interview. This appeared to set the scene for the interview and prepare and reassure the respondent of the general areas for discussion. The respondent also consented to the researcher contacting them following an interview if it was necessary to seek clarification of any part of the transcript. The consent to tape each interview was sought and the tapes that were used lasted for 90 minutes in a tape recorder with the facility for automatic tape reversal, therefore minimising the need to change tapes during the interview.

The interview could take place either in a clinic area at the hospital or at the woman's home, according to her preference. The presence of a friend or relative was permitted if the woman so wished. Interviews were taped and transcribed by clerical staff, who did not have access to information on the identity of the participant. Field notes were made immediately after each interview. The field notes contained reflections on the context and non-verbal behaviour that had taken place during the interviews. The transcript data was analysed following each interview by both researchers and this directed the researchers as to which research subject was most able to illuminate the categories and themes as they developed. This enabled constant comparison

of events, and this process was continuously shaped by subsequent data collection[78].

The data transcripts were then coded and analysed by the two main researchers (the interviewer and the author).

Ethical approval was granted by the local ethics committee.

## Quantitative Study

A questionnaire was developed and piloted in the gynae oncology outpatients' clinic. Questions were developed around themes and issues identified in previous qualitative[20] and quantitative[11] work in gynaecological oncology. 11 questions (3 pages) covered basic epidemiological data, reports of their existing follow up, views on follow up visits, views on the role of nurse practitioners and on the reasons for follow up (appendix 3.4). The questionnaire was reviewed by members of the gynaecological oncology team and the views of patient groups were sought. It was amended accordingly and distributed to 104 consecutive patients attending for a routine follow up visit after treatment for a gynaecological malignancy, over a six-week period. Questionnaires were given out by clerks on arrival to the department and collected in a box within the waiting area. All questionnaires were completed anonymously. Clinical staff had no direct contact with patients during the process of them filling in the questionnaire in order to minimise bias.

All women attending follow up after treatment for a gynaecological cancer were eligible to participate. Women with any or all treatment modalities (surgery, radiotherapy or chemotherapy) were included.

Data were analysed using the Statistical Package for the Social Sciences, version 12.0.

Both studies were undertaken on women attending for follow up at the Northern Gynaecological Oncology Centre at the Queen Elizabeth Hospital, Gateshead, which is a tertiary referral Gynae oncology centre providing care for a population of just over two million people in the North East and North West of England.

**Analysis of interviews**

The aim of data analysis of the interviews was to generate theory that is completely grounded in the reality of the social world. This is achieved by constant comparison of the data and refining theoretical constructs through comparison with new data derived from the ongoing interviews[79]. Data were treated as referring to and representing phenomena (e.g. feelings, perceptions, experiences) rather than. As such the researchers were concerned with capturing and interpreting common sense, substantive meaning in the data.

Women were selected for interview in order to derive data according to the grounded theory principles of theoretical sampling.

The interview transcript and the tape were stored together to facilitate open coding, and to enable subsequent revisits to the data for cross-referencing and comparison of data. The respondent number that had been allocated remained with the interview transcript, post-contact notes and tape. This assisted with the filing and comparative content analysis between the women and also between the different data sets relating to the same woman.

When reading and coding the interview transcripts line by line, the interview tape was listened to at the same time. This way, 'life' was returned to the transcript, and pauses, emotions and sarcasm was evident to the researchers. Therefore, although the words were transcribed 'verbatim', without any grammatical tidying, the transcripts were later refined with the non-verbal inferences included. The field notes were also reviewed at this time.

Data was initially coded independently, by both researchers, by hand. Computer analysis software was not used for two reasons. Firstly there were only a small number of interviews so the data was manageable by hand. Secondly there is a risk with the use of qualitative data software for analysis that the process of coding becomes automated and the meaning and sense of the data is lost. A cross-sectional analysis 'code and retrieve' method[80] was used. A common system of codes was developed that were then applied (manually) to the data. This then allowed chunks of related data from different interviews to be looked at together. The chunks of data were then organised and summarised on a white board display and sorted in diagrammatic form to spot connections and inter-relationships[81].

This enabled the codes to be drawn together in order to develop categories. Analysis of the data led to the development of ideas or concepts, which were then linked in order to develop the narrative. In this way, the results narrative were grounded in the data. The aim was to develop theoretical, albeit emergent, concepts from the data from an early stage of analysis[82] (Strauss and Corbin 1998). Outlying data, where discovered, were cross-checked with the themes developed in order to challenge the hypotheses that had been developed.

The analytic process involved data management (review, labelling, sorting and synthesising the raw data) descriptive accounts (making use of the sorted data to identify key phenomena and develop classifications) and explanatory accounts (building explanations and concepts to explain the data)[83].

## Results

### Qualitative Study

Seven interviews were carried out. Despite minor modifications to the interview schedule no additional concepts or themes were identified in interviews six and seven and therefore data saturation was regarded as having been achieved. Analysis was undertaken by both researchers. The audio tapes were listened to, field notes were reviewed and transcripts coded within a data management framework as described above. As major concepts and constructs were formed, the categories were collapsed together to form

meaning. Working hypotheses were developed and these were then checked against the data.

***Table 3.1 – interview participants' demographics***

| Respondent | Age | Stage | Type of follow up | Time from diagnosis (months) | Recurrence |
|---|---|---|---|---|---|
| 1 | 49 | 1C | routine | 44 | No |
| 2 | 55 | 1A | Routine | 19 | No |
| 3 | 60 | 1C | Routine | 6 | No |
| 4 | 76 | 2C | routine | 70 | No |
| 5 | 77 | 3C | OVO5 | 81 | No |
| 6 | 67 | 1C | Trifids/routine | 53 | Yes |
| 7 | 76 | 2C | OVO5 | 81 | No |

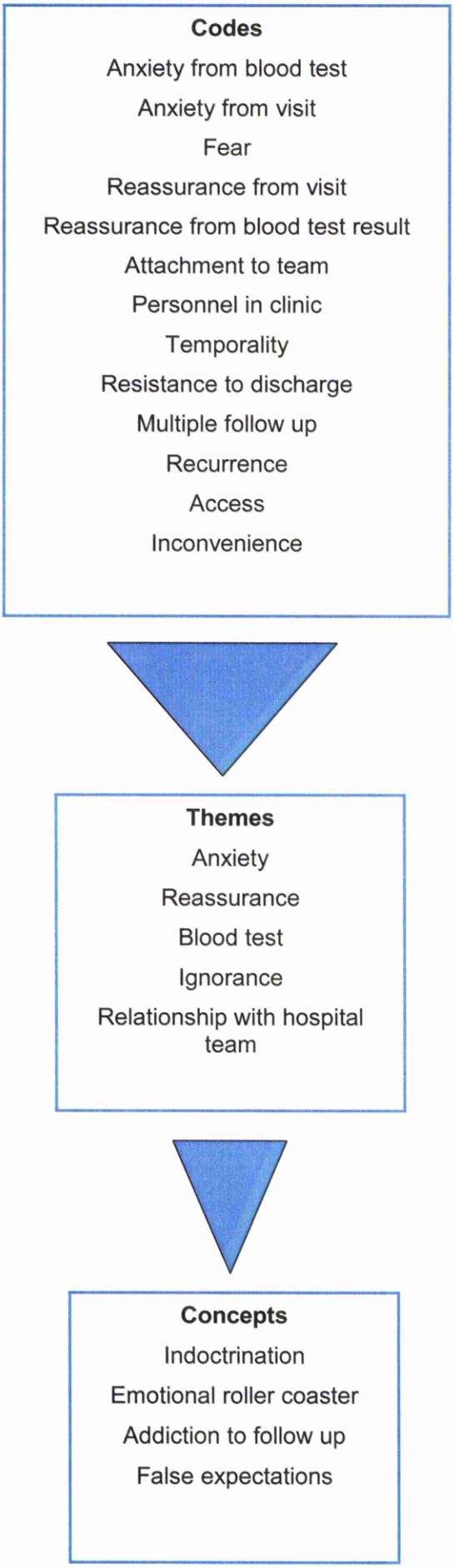
Only one patient was identified and participated who had previously participated in nurse-led telephone follow up, so it was not possible to corroborate responses in relation to this type of follow-up. This was due to the premature closure of the TRIFIDS trial (with small numbers of participants and

brief or no usage of nurse-based telephone follow up) and the subsequent demise of many of the participants.

One woman (respondent 6) chose to have her husband present and involved in the interview. All other women were interviewed on their own.

The participants had a range of disease stages, from stage 1A to stage 3C. They ranged from being six to 81 months after the completion of treatment.

***Figure 3.1 Codes, themes and concepts***



***Emotional experiences surrounding the follow up visit***

Faced with a diagnosis of cancer, most people react initially with numbed shock and disbelief followed by anxiety, anger and depression[84]. In the context of this study, the interviews clearly demonstrated that women experience powerful emotions in their survivorship with heightened affect in the run up to, and aftermath of follow up visits. Many of the women reported negative thoughts and feelings prior to attending follow up appointments.

*When it was time to come to the appointment I felt funny and scared.* (respondent 4)

*Going to the hospital makes me feel a little bit anxious.* (respondent 3)

These feelings seemed to be related to the fear of detection of recurrence.

*I wouldn't say I was anxious even (before the visit). It's like I think more about it; I think about what could happen.* (respondent 7)

*I just hope that everything is going to be alright.* (respondent 4)

The source of a patient's distress is often focused upon the reality of their diagnosis, what it means to them, and how they now appraise their future.

The women also reported gaining a lot of positive feelings afterwards from having attended the follow up visits. In particular many of them describe reassurance and a feeling of confidence that they derive from attending.

*I feel great when I go out...I just feel safe and it gives me confidence, that's the word really: confidence.* (respondent 7)

*It makes me feel confident that everything is alright and that I haven't got any cancer coming back.* (respondent 5)

*It gives me confidence that all is well or if anything is wrong they will spot it.* (respondent 5).

One woman who was interviewed had tried nurse-led telephone follow up, and did not get the same reassurance from it:

*There's always that thing deep down in your mind that you're not right and on the telephone they don't know. I'm the one to say 'oh yes, I'm all right' even if I'm not....I would rather have come to clinic.* (respondent 6)

For these women who are already in an established follow up scheme it would seem that they become psychologically reliant on the follow up for reassurance that they remain free of disease. They seem to experience powerful emotions around the time of their visits, with a sense of elation and relief afterwards due to the confirmation of their disease status. This may contribute to positive reinforcement of the benefits of follow up.

***Fear of recurrence***

The women interviewed all expressed concerns regarding recurrence of their disease.

*I suppose it's something that can come back* (respondent 3)

*I do think about it coming back; you can't say it would never come back.* (respondent 2)

*When you get your aches and pains and something different, you're thinking straight away 'Is the cancer back?'* (respondent 6)

Although there was some evidence of unrealistic expectations of what detection of recurrence at the clinic would deliver:

*They always say early detection is better, isn't it?* (respondent 3)

***Understanding of follow up and investigations***

For most women, the positive emotional experiences seemed to stem from what they regarded as being the primary reason for follow up: ensuring that there was no recurrence. Most of them were having regular CA125 blood tests (a tumour marker for ovarian cancer), and they rested a lot of importance on the blood test.

*Well I suppose they wouldn't do it if it wasn't important, and they can tell if there's any cancer cells there.* (respondent 4)

*The bloods, that to me is important. As soon as I know it's rising – I know there is something wrong.* (respondent 6 – previously had a recurrence)

*I think they rely on the blood test. So when I don't get a letter or a telephone call, I start to feel safe again and that everything is all right.* (respondent 7)

This may come from an iatrogenic introduction of reliance on CA125 measurements, especially for those women who undergo chemotherapy. These women have CA125 measurements after each cycle of chemotherapy to contribute to determining response to treatment. Many women therefore, for understandable reasons, become preoccupied with this measurement and its meaning with regards to their ongoing well being. The withdrawal of this at the end of treatment is in keeping with the withdrawal of all other forms of support, other than routine clinics at this point in time.

***Temporal Changes***

Perspectives on follow up seemed to change over time. Confidence was again a key theme, and the need to develop confidence after such a difficult diagnosis and treatment. Confidence for these women seemed to be bred by attendance at the cancer centre:

*I prefer to come here (cancer centre)* (respondent 7, 70 months from diagnosis)

*They offered to transfer me back to (the unit) but I didn't want that. I'd rather travel to (the centre); I'm happy there.* (respondent 2)

In some cases this may have been due to experiences earlier on in their care pathway, or possibly because of the requirement for referral to the centre to gain the type of care they needed:

*I am really glad that I am seen at (the centre) because I found the (unit) totally useless.* (respondent 5)

Confidence may also be bred by seeing a member of medical staff rather than nursing staff:

*I think I would rather see a doctor; nothing against nurses – I could not fault the care I have had here.* (respondent 7)

*I prefer to have a doctor, but I don't mind seeing the nurse.*

Although this view was not universal, and some women were happy to see either a doctor or a nurse. However this is a view that may alter with time, possibly as the women become more confident:

*Maybe at first, when you are more apprehensive (you want to see a doctor) but as time went on I didn't mind who I saw.* (respondent 4)

This may be linked with increased confidence that, as time progresses, the cancer is less likely to recur:

*The longer it gets, the better the chance I've got.* (respondent 7, 70 months from diagnosis)

***Quantity of follow up***

For many of the women interviewed, they would like to be seen as often as possible, and for as long as possible:

*She would come here every week, as long as we get good news every time!!* (husband of respondent 6)

*(I would come) as much as you like. I would come all of the time. I mean I wouldn't put a time on it, say ten years, or even fifteen years. I would come every six months, or at worst every year. I would hate (discharge). To me that's my safeguard* (respondent 7)

One woman was even having follow up at the centre and also at the unit:

*They do more or less the same (at the centre and unit). They just examine me ..and then sometimes do the blood test.* (respondent 4, who was still having follow up in the unit despite having been discharged by the centre)

Although for some, they came because they felt they had to and needed to, rather than because they found it personally beneficial:

*The least I have to go the better. It is necessary...I am happy to go every three months and let them see how I am. ...It could be away for a long time, but there is a chance it might come back. I've just got to keep getting followed up really.* (respondent 3)

## Quantitative Study

96 women replied to the questionnaire, and all questionnaires were used for analysis.

***Table 3.2 Epidemiological Information***

| | N (n=96) | % |
|---|---|---|
| Cancer site: | | |
| Ovary | 31 | 32 |
| Corpus | 14 | 14 |
| Cervix | 23 | 24 |
| Vulva | 9 | 9 |
| Vagina | 1 | 1 |
| Missing | 18 | 19 |
| Treatment: | | |
| Surgery | 90 | 94 |
| Chemotherapy | 22 | 23 |
| Radiotherapy | 7 | 7 |
| Missing | 1 | 1 |
| Follow up frequency (months): | | |
| 3 | 37 | 39 |
| 4 | 1 | 1 |
| 6 | 29 | 30 |
| 12 | 26 | 27 |
| missing | 3 | 3 |

85/93 women (91%) thought that the current frequency of their follow up was just right. 2 women thought they were being seen too often. One was a 33

year old woman who was on three monthly follow up after surgery for carcinoma of cervix and who was 26 months since diagnosis. The other was a 59 year old woman on six monthly follow up who had had surgery and chemotherapy for carcinoma of the ovary and was 73 months post diagnosis. 5 women thought they were not being seen often enough (table 2).

***Table 3.3 Women who thought their follow up was not often enough***

| Case | Age (years) | Cancer site | Treatment(s) | Follow up frequency | Time since diagnosis |
|---|---|---|---|---|---|
| 11 | 59 | Ovary | Surgery, chemotherapy | 12 | 57 |
| 26 | 58 | Cervix | Chemoradiotherapy | 3 | Unknown |
| 32 | 64 | Corpus | Surgery | 12 | 61 |
| 33 | 37 | Cervix | Surgery | 6 | 150 |
| 34 | 36 | Cervix | Surgery | 6 | 44 |

82/92 (89%) of women thought that a hospital doctor should provide their follow up. Only 22/92 (24%) thought follow up should be by a specialist nurse and 6/92 (7%) thought it should be by a General Practitioner ($p<0.001$, multiple answers permitted). There was no difference between those who had

been in follow up for less than five years (n = 62) and those who had been in follow up for more than five years (n=30).

58/90 (64%) of women reported having a consultation and being examined during their clinic visit. A further 27/90 (30%) of women reported having a blood test in addition to the consultation and examination. 2/90 (2%) reported having a consultation and a blood test, but no examination. Women who had been treated for ovarian cancer were more likely to report having blood tests done (22/28) than those who had been treated for cancer in other sites (4/47) ($p<0.0001$). When asked to rank the components of the visit according to their importance (consultation, examination or blood test), women ranked examination as the most important, followed by the consultation then the blood test ($p<0.0001$). However, those women who reported having regular blood tests were much more likely to regard the blood test as being more important than the examination (16/29 (16%) versus 3/61 (84%), $p <0.0001$). The consultation was relatively less important to women who had been in follow up for more than five years ($p=0.01$). Women with ovarian cancer thought that the blood test was relatively more important, whereas women who were being followed up for other cancer sites thought the examination was more important ($p=0.001$).

6/86 (7%) reported always seeing the same doctor for follow up, 56/86 (65%) reported sometimes seeing the same doctor and 24/86 (25%) reported never seeing the same doctor. 21/85 (25%) of women reported seeing a specialist nurse when they attended for follow up. 7/20 women who reported seeing a specialist nurse in the follow up clinic thought they should be followed up by a

specialist nurse, whereas 13/49 women who did not see a specialist nurse thought that they should (p = not significant).

48/89 (54%) of women reported feeling more anxious than usual prior to attending for the routine follow up visit, whereas only 2/89 (2%) reported being less anxious. However after the follow up visit 9/90 (10%) still reported feeling more anxious than usual but 34/90 (38%) reported feeling less anxious than usual ($p<0.0001$, Wilcoxon signed rank test).

Women were asked to complete a five point Likert scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) on the role of the specialist nurse in the clinic. They ranked four statements: listen to concerns, answer questions, take blood and detect signs of disease recurring. Frequencies are presented in table 3. Women ranked listening to concerns and taking blood as the most important roles for the specialist nurse. They viewed detecting recurrence as significantly less important for nurses, when compared to their other functions within a follow up clinic (mean ranks compared, $p<0.0001$).

***Table 3.4. Responses to the question 'What do you think the nurse's role is?'***

(percentages in brackets)

| | Strongly agree | Agree | Neither agree/ disagree | Disagree | Strongly disagree | Mean rank (p<0.0001) |
|---|---|---|---|---|---|---|
| Listen to concerns | 31/80 (39) | 36/80 (45) | 11/80 (14) | 2/80 (3) | 0/80 (0) | 2.30 |
| Answer questions | 25/80 (31) | 39/80 (49) | 15/80 (19) | 1/80 (1) | 0/80 (0) | 2.47 |
| Take blood | 29/78 (37) | 34/78 (44) | 15/78 (19) | 0/78 (0) | 0/78 (0) | 2.36 |
| Detect signs of disease recurring | 27/80 (34) | 20/80 (25) | 22/80 (27) | 9/80 (11) | 2/80 (3) | 2.87 |

Finally women were asked to rank six statements about follow up in order of their importance (Table 4). They assigned numbers 1-6 to the statements, where 1 was the most important and 6 was the least important. The mean ranking for each statement was calculated and the rankings were compared using the Friedman test. Women ranked detection of recurrence as the most

important reason for attending for follow up ($p<0.0001$). They placed very little value on the collection of data as a rationale for follow up.

***Table 3.5 'Which of the following reasons for coming for follow up is most important to you?'***

(ranked 1 – 6, 1=most important, 6=least important).

| | Mean rank ($p<0.0001$) |
|---|---|
| To detect if disease is coming back | 1.40 |
| To check recovery from treatment | 3.01 |
| To treat and symptoms | 3.39 |
| To talk about concerns | 3.82 |
| To treat any side effects of treatment | 4.16 |
| So that the hospital can collect information about recovery from cancer | 5.22 |

***Views of Women in Follow up for More than Five Years***

Detection of recurrence remained the most important reason for follow up, even in those women who had been in follow up for more than five years, and they felt it should be by a hospital doctor. However, women who had been in

follow up for more than five years thought that checking recovery from treatment was more important than those with a shorter duration of follow up (chi squared, p=0.004). This group also placed a higher emphasis on the importance of the consultation than those women who had been in follow up for less than 5 years (chi squared, p=0.004). However, even after 5 years of attending, these women reported similar levels of anxiety around the follow up visit to those women who had been in follow up for a shorter period.

## Discussion

The qualitative interviews demonstrate, for the first time, the views of women undergoing follow up after both early stage and advanced ovarian cancer. Robust qualitative methodology has been used in order to produce valid data and analysis. However, qualitative research can only be generalised through the generation of theoretical statements which then need to be tested by application in other contexts[85]. That said, the degree of concordance across the interviews is quite striking. This resulted in data saturation after only seven interviews, compared to the expected ten interviews. The quantitative study presented provides triangulation[63] and confirms that these views of follow up are more widely held[54].

Grounded theory was developed as a means to enable qualitative researchers to respond to the belief held by many positivist (or quantitative) researchers that qualitative research was unscientific because it rejected controlled experiments and appeared to accept individual interpretation[86,87]. Therefore,

the development of grounded theory procedures, which include a set of rigidly systematic steps for sampling, data collection and analysis were developed by Glaser and Strauss[86]. This paper has used these methods to develop the narrative around women's expressed experiences of follow up.

One aspect of this is the collection of 'field notes' after the interview. In practice, field notes might fail to capture reflections upon the environment of data collection and that this may have an impact upon the subsequent analysis. Schatzman and Strauss[78] describe the need to develop different records of the same incident, which allows multiple recording of data that supports effective cross referencing, but also embeds within the field notes a foundation for data analysis. This ensures the movement of data beyond simple story telling.

The group that were interviewed were deliberately diverse in terms of their stage of disease and length of time in follow up (purposive sampling)[63]. Despite this they reported very similar experiences of the follow up process, which may indicate that such experiences are widespread. The group is biased by the fact that they are all women who, by definition, are complying with follow up and it would be interesting to be able to interview women who choose not to attend for follow up about their reasons for this. This, however, would be challenging to achieve as such women are no longer under the hospital's care and may be reluctant to consent to taking part. Furthermore this was outside the scope of this project.

Both parts of this chapter have shown that women think that detection of recurrence is the main reason for attending for follow up. This is coupled with some unrealistic expectations in terms of the likely impact on survival of the early detection of any recurrence. They derive both positive and negative emotional experiences from being reviewed. However the single biggest benefit identified is a feeling of reassurance and safety. This outweighs any negative views of the process.

The findings of this study are in keeping with a previous qualitative interview study conducted by Bradley et al, but that study was limited to women who had completed treatment for all gynaecological cancers, which had been found to be early stage[20]. Our paper supports the idea that the anxieties and reassurance achieved by attending for follow up is present in women with diverse stages of ovarian cancer and therefore with very variable prognoses. Even for those women with advanced stage disease, which is highly likely to prove terminal, the reassurance still seems to exist.

Some women would clearly like to be followed up as often as possible and for as long as possible, despite a lack of evidence to show any benefit from such a practice. This is at odds with moves to shift from a clinically led approach to follow up care to supported self-management [88].

## Conclusions

Women report positive experiences from routine follow up. Despite some feelings of anxiety prior to the visit, confidence is gained from the reassurance that their disease has not returned. Therefore any move to reduce the length and frequency of routine follow up care, or to introduce nurse-based follow up, may meet with resistance from women, especially those already established in a follow up programme. This study has demonstrated that it would be important for any randomised trial comparing different sorts of follow up to address issues around reassurance and confidence for women who have completed treatment for gynaecological cancer. Failure to do so could potentially prevent women from consenting to randomisation in a trial since they would otherwise receive current standard practice of routine follow up.

## Appendix 3.1 Interview Schedule for Follow up Interviews

- Introduction to research project
- Get consent form

1. Why do you think you are being followed up?
    - How does that feel?
    - What is the benefit of early detection of recurrence?
    - What do you think is the risk of the disease recurring?
    - How would you feel if that happened?
2. What are the benefits and drawbacks of being followed up?
    - For different types of follow up (previous trial patients)
3. How do you find the appointment itself?
    - How do you feel before you come?
    - Who, where and when would you wish to be followed up?
    - What is the most important part of the follow up visit for you?
    - How do you feel about the blood test and its results?
    - Any practical problems with follow up appointments?
    - How do you feel afterwards?
4. Do you worry about recurrence between visits?
    - If worried, what would you do?

## Appendix 3.2 – Consent Form

**Qualitative Study of Follow up after Ovarian Cancer**

Name of Researchers: Miss FM Kew, Sr JA Guest

**Please read carefully and tick box as appropriate:**

- ☐ I confirm that I have read and understood the information sheet for the above study and have had sufficient time to consider my participation.
- ☐ I understand that my participation is voluntary and that I am free to withdraw at any time without giving reason or affecting my medical care.
- ☐ I understand that staff involved in the research may examine my medical records for the purpose of checking the information recorded.
- ☐ I understand that any documentation relating to me will not identify me by name and will be kept confidential.
- ☐ I agree that my General Practitioner may be told that I am taking part in this study.

***Patient's Name*****.....**

***Signature*****.....*****Date*****.....**

I (the Investigator/Doctor in charge), confirm that I have explained to and fully discussed with the patient the nature, purpose and likely effects of this study.

***Doctor's Name*****.....**

**Signature.....Date.....**

## Appendix 3.3 – Patient Information Text

The Northern Gynaecological Oncology Centre at the Queen Elizabeth Hospital in Gateshead is currently looking at the experiences women have in relation to their follow up care following treatment for ovarian cancer.

At present there are many different kinds of follow up and we need to understand what is important to women in their follow up care.

**What does the study entail?**

If you agree to take part in the study, your name will be passed on to our Researchers, Fiona Kew and Alison Guest. Fiona is a Senior Registrar and Alison is a Macmillan Clinical Nurse Specialist based at Queen Elizabeth Hospital, Gateshead. They will organise a trained interviewer to talk to you for about one hour about your experiences of follow up. This can be done at the hospital or at home, which ever you prefer. The discussion will be recorded so that we can refer back to it. Anything you say will be anonymous and will not have any effect on your care.

**Anticipated benefits of the study:**

Participation in this study may not benefit you directly. However, we have often found that being offered the opportunity to talk about your experience can be helpful. We are hoping that any issues or problem areas that are discussed will help the medical and nursing teams to develop interventions in these areas. It will also serve us well in developing our future research programmes, and help us to ensure that we are asking the right questions that are relevant to patient care.

If any issues are raised that you as an individual wish to discuss further then we will arrange for you to see and speak to someone who can help you.

Thank you for taking time to read this information sheet.

For Further information, please contact:

Miss FM Kew—Senior Registrar

(0191) 482 0000

Alison Guest—Modern Matron

(0191) 482 0000 Bleep 2344

Secretary: (0191) 445 6148

## Appendix 3.4 Questionnaire

Gateshead Health NHS
NHS Foundation Trust

Northern Gynaecological Oncology Centre
Queen Elizabeth Hospital, Gateshead

PATIENT QUESTIONNAIRE

Age: .....
Marital Status: .....
Type of Cancer .....
Date of Diagnosis: Month: ..... Year: .....

Type of treatment: (tick all that apply)
❑ Surgery ❑ Chemotherapy (drug treatment) ❑ Radiotherapy (x-ray treatment)
❑Other:.....

---

PLEASE TICK ✓ ALL THAT APPLY TO YOU

| | | Yes | No |
|---|---|---|---|
| 1. | Has your cancer returned since your original treatment? | ❑ | ❑ |
| | If yes, have you had further treatment? | ❑ | ❑ |

2. How often do you come for follow-up at the hospital?
❑ Every 3 months ❑ Every 6 months
❑ Every year ❑Other / state: .....
Do you think this is:
❑ Just right ❑ Too often ❑ Not enough
If not right, how often would you like to be seen? .....
Please turn the page ↳

3a. Who do you think should do your follow-up? (please tick all that apply)

❑ Hospital doctor

❑ Specialist nurse

❑ General practitioner

❑Other, please specify .....

4a. When you visit the doctor at the hospital what happens? (please tick ONE)

❑ Chat and examination (internal and tummy)

❑ Chat, examination and blood test

❑ Chat and blood test

❑Other(Pleasestate):.....

5. When you visit the hospital, do you see the same doctor?

❑ Always ❑ Sometimes ❑ Never

6. Before you come to the hospital do you feel:

❑ More anxious than usual

❑ Same as usual

❑ Less anxious than usual

6a. After you have been to the hospital do you feel:

❑ More anxious than usual

❑ Same as usual

❑ Less anxious than usual

7. Which part of your appointment do you feel is most important?

❑ Chat ❑ Blood test ❑ Examination ❑ Other: .....

Why? .....

.....

.....

8. When you come for your appointment do you usually see a specialist nurse?

❑ Yes ❑ No

9. When you visit the hospital, do you see the same nurse?

❑ Always ❑ Sometimes ❑ Never

What do you think the nurse's role is? (Please ✓ one for each statement)

Listen to concerns:

❑Strongly agree ❑Agree ❑Neither agree/disagree ❑Disagree ❑Strongly disagree

Answer questions:

❑Strongly agree ❑Agree ❑Neither agree/disagree ❑Disagree ❑Strongly disagree

Take blood:

❑Strongly agree ❑Agree ❑Neither agree/disagree ❑Disagree ❑Strongly disagree

Detect signs of disease recurring

❑Strongly agree ❑Agree ❑Neither agree/disagree ❑Disagree ❑Strongly disagree

Which of the following reasons for coming for follow up is most important to you? (Please put in order of importance, where 1 is most important and 6 is least important).

..... To check recovery from treatment
..... To treat any side effects of treatment
..... To talk about concerns
..... To detect if disease is coming back
..... To treat any symptoms
..... So that the hospital can collect information about recovery from cancer

Other: .....

.....

.....

We would welcome any comments your hospital appointments.
Please return the questionnaire in the box provided in the waiting room.
Thank you for taking time to complete this questionnaire.

# Chapter 4 – Feasibility Study

## Introduction

As discussed, the routine follow up of patients after treatment for cancer is standard practice. It is done on the assumption that picking up recurrent cancer before symptoms develop will permit earlier treatment and therefore better survival rates rather than waiting for a patient to develop symptoms. It is also assumed that these visits are reassuring for the patients. However, there is a lack of evidence to support this practice in gynaecological cancers, and no randomised trials have been performed.

In order to determine the feasibility of a randomised controlled trial, and to assist with power calculations for the trial, a pilot randomised controlled trial was designed. Trial information and consent forms were developed (appendices 4.1 and 4.2) and ethical approval was granted by the South Tees Local Ethics Committee. No funding was secured so the study was run within existing resources.

## Method

The study was designed to assess feasibility for a pragmatic randomised-controlled trial comparing routine hospital follow-up appointments with a system of patient-initiated follow up. Blinding of participants or clinicians was clearly not feasible. The primary outcome of the main trial was to be survival.

The feasibility study was run in the Gynaecological Oncology Cancer Centre in the James Cook University Hospital in Middlesbrough. This cancer centre provided care for the Teesside Cancer Care Alliance, which was responsible for the provision of care for a population of just over 1,000,000 people. Ethical approval was granted by the South Tees Ethics Committee.

Inclusion Criteria

All patients who had completed first-line treatment for a histologically confirmed gynaecological cancer, regardless of stage or site, were potentially eligible for recruitment.

Exclusion Criteria

- Women who needed ongoing review for problematic symptoms or side effects
- Women who were under follow-up for a previous malignancy
- Women who were enrolled in another trial that required follow up.

Randomisation and Stratification

Randomisation was performed by the University of York Telephone Randomisation service based in the Department of Health Sciences. This service provided locations across the United Kingdom with immediate and unbiased allocation of patients to treatments through the use of a freephone telephone number and appropriate bespoke computer software. Randomisation was stratified into two groups based on the natural histories of

the different cancer sites. For the feasibility study, there was a 2:1 ratio randomisation for patient initiated follow up versus standard follow up. This was in order to provide maximum information on any issues relating to the feasibility of administering patient-initiated follow up. All consenting eligible patients were randomised to either 'patient-initiated follow-up' or 'standard follow-up'. Randomisation was stratified by cancer type (ovary, fallopian tube, primary peritoneal versus endometrium, cervix, vagina, vulva) and disease status (disease free versus residual disease) to ensure that these variables were evenly distributed across the two groups of patients. The stratification is based on the premise that that there are no curative salvage treatments for the first group, whereas there are (in some cases) for the second group.

Outcome Measures

Disease specific and overall survival were planned to be the primary outcome measures in the main trial. Rates of recurrence were not collected as it was thought to be an unreliable surrogate marker for survival, in view of potential length time bias in the detection of recurrence in the routine follow up arm. Planned secondary outcome measures for the main trial were quality of life, anxiety and depression scores, cost effectiveness, rates of surgical and medical intervention in primary and secondary care and patient acceptability. However cost effectiveness calculations and attempts to collect information on rates of intervention, patient acceptability and clinic use in the routine follow up were not undertaken in the feasibility study due to lack of funding. In order to assess feasibility, within this study data was collected on recruitment rates amongst eligible patients, ability to complete quality of life, anxiety and

depression scores at baseline, 6 and 12 months, use of clinic appointments and use of the telephone line in the patient initiated group. Data collection of quality of life, anxiety and depression scores was not feasible beyond twelve months due to the lack of funding.

Quality of life and patient acceptability data was collected using standardised questionnaires using EQ-5D, SF-36 and condition-specific measures (EORTOC QLQ C30 and OV24). Anxiety and depression was measured using the Hospital Anxiety and Depression scale. Questionnaires were administered at randomisation, after six months and after twelve months.

A sample size calculation was not performed since the outcome measures were based around feasibility.

Feasibility Study Protocol

Standard follow up was determined as being the model of care recommended in the Teesside Cancer Care Alliance Gynaecological Oncology guidelines at the time. An intervention arm of patient initiated follow up was developed based on previous work in women who had completed treatment for breast cancer[58,89]. All potentially eligible women were seen in out patients' clinic eight weeks after completion of treatment. All women who agreed to participate in the trial completed baseline quality of life questionnaires (SF36, EQ5D, EORTOC QLQ-C30 and OV24, Hospital Anxiety and Depression scales).

Standard Follow-up Arm Protocol

Women randomised to standard follow up were given appointments for outpatient clinics according to the following schedule:

- Year 1 3 monthly visits
- Year 2 4 monthly visits
- Year 3 6 monthly visits
- Year 4 annual visit
- Year 5 annual visit, then discharge

At each visit the woman were seen by medical staff (consultant or specialist registrar), with or without the presence of specialist nursing staff, according to standard local practice. A relevant history was taken and a clinical examination undertaken. Investigations were not performed routinely (as was standard practice), and were only performed when clinically indicated.

Interval visits could be arranged according to clinical need, as determined by hospital medical staff, nurse specialist or the General Practitioner.

Patient-initiated Follow up Arm

Women randomised to patient-initiated follow up participated in a semi-structured interview with a gynaecological oncology specialist nurse. This was undertaken shortly after randomisation. They were given advice about how to contact the service and then no further routine appointments were arranged.

*Semi-structured interview*

The interview was structured around the following areas:

- what is patient initiated follow up
- when to contact the hospital
- when to contact the General Practitioner rather than the hospital
- how to contact the hospital
- what will happen when the woman telephones the help line
- any other issues the woman wishes to discuss

Each patient was given a patient-information leaflet (an example is given in appendix 4.3), which gives details of symptoms that may cause concern, when they should contact the hospital and how to access the service. Four different leaflets were developed, each of which was specific to one cancer type. All leaflets were reviewed and approved by the trust's 'Patient Information Group'.

*Telephone Help Line*

The telephone help line was a confidential service, which participants were encouraged to use if they develop worrying symptoms. The telephone line was manned at defined times by Nurse Specialists (specified in the patient information leaflet), and a confidential answer phone was available at all other times. Women were guaranteed a return call within two working days of any

message and a clinic appointment, if appropriate, within five working days. General Practitioners were also able to access the system through this route if they wished, or through the traditional route via the consultants' secretaries.

Arrangement of Clinic Appointments

Clinic appointments were arranged if the woman complained of the following symptoms:

- Any new lumps or masses in her abdomen
- Bleeding from the vagina
- Bleeding after sexual intercourse
- Weight loss, without being on a diet or exercising
- Haematuria
- Lump in her neck

Clinic appointments were arranged if the patient complained of the following symptoms, lasting for more than 3 days:

- Pain in the abdomen or pelvis, that was not present previously
- Bloating or abdominal swelling
- Feeling generally unwell
- Nausea and vomiting

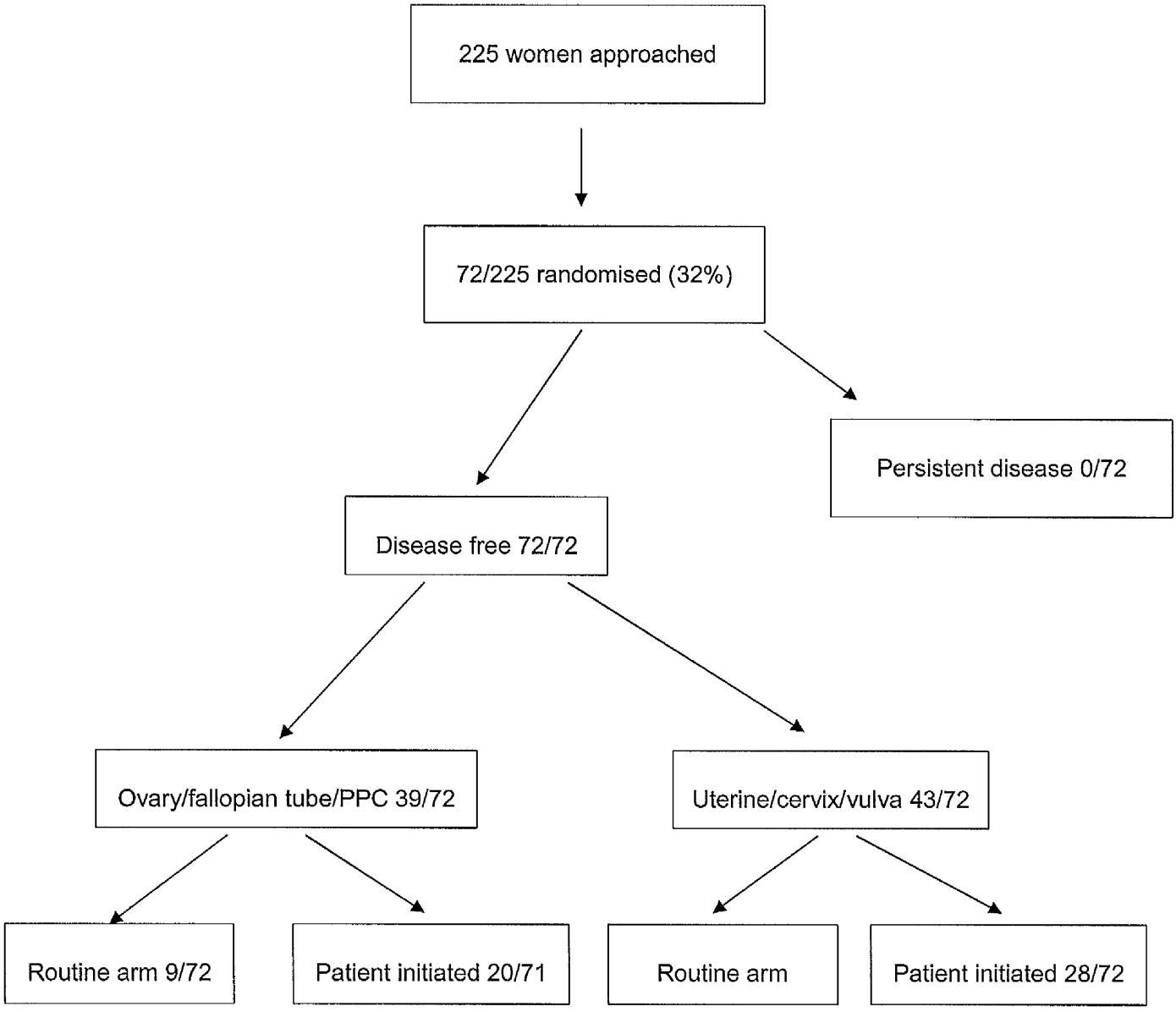
- Diarrhoea (new – no obvious cause)
- Bleeding from the rectum
- Constipation (new – no obvious cause)
- Urinary frequency

For other symptoms the patient was advised to contact their General Practitioner. Appointments could be made out with these recommendations at the discretion of the clinical team.

**Results**

72/225 (32%) of eligible women were recruited between September 2001 and July 2003. Recruitment was halted after 23 months because sufficient information had been gleaned to support a grant application. 48/72 (67%) of women were randomised to patient initiated follow up and 24/72 (33%) were randomised to routine follow up. 29/72 women had completed treatment for ovarian/fallopian tube/primary peritoneal cancer, of whom 9 were randomised to routine follow up and 20 were randomised to patient initiated follow up. 43/72 women had been treated for uterine/cervical/vulval cancer, 15 were randomised to routine follow up and 28 to patient initiated follow up. All women were disease free at randomisation.

***Recruitment Flow Diagram***




At September 2006, 6/24 (25%) women in the routine follow up arm and 11/48 (23%) women in the patient initiated arm had died. 3 women were alive with disease in each arm. Disease status was not available for one woman in the

patient initiated arm. 2/72 (3%) had withdrawn from the trial. As such the overall recurrence rate was 23/72 (32%).

Baseline quality of life and anxiety/depression questionnaires were completed by 71/72 (99%) women. 32/71 (45%) completed 6 month questionnaires and 26/67 (39%) completed 12 month questionnaires. No significant differences were seen in quality of life or anxiety and depression at randomisation or at six months. However, this was a feasibility study and as such was not powered to detect a difference.

Over a four year period from the start of randomisation (01/09/2001 to 01/09/2005), there were 37 telephone calls from 24 women within the patient initiated arm. 21/37 (57%) calls were made within 6 months of randomisation. 5 women had clinic appointments made after consulting with their general practitioner, without contacting the help line. There were 82 clinic visits for women in the patient initiated follow up arm. The median length of follow up for this group was 35 months (range 26 – 46 months). Had they received routine follow up, they would have been expected to have a minimum of 392 visits based on the routine follow up schedule.

## Discussion

This feasibility study demonstrates that recruitment to a randomised controlled trial comparing patient initiated follow up with routine follow up in secondary or tertiary care clinics in women who have completed treatment for a gynaecological cancer is feasible. The recruitment rates, however, are lower

than those demonstrated by Gulliford et al[58]. They reported recruitment rates of 93% in women who had completed treatment for breast cancer, in a trial that compared standard follow-up with reduced-frequency follow-up. A lower rate of 66.5% is seen in Grunfeld's paper, also in women who had completed treatment for breast cancer[15]. The intervention arm of this particular trial considers follow-up in General Practice rather than patient-initiated follow-up. However most of these patients were already in a scheme of hospital-based follow-up when approached which may explain the lower recruitment rates. In both of these studies women were still offered scheduled consultations, unlike in this study, and it is possible that this is one of the reasons that a higher proportion of women in our study declined randomisation. Lack of funding for the study may also have contributed to a failure to identify and approach all potentially eligible women. Ohlsson recruited 107 patients[62], and Kjeldsen recruited 597 patients[61] in people who had been treated for colorectal cancer but rates of recruitment are not available for these studies.

Data on the planned primary outcome measure for the main trial (survival) was readily available for all patients recruited to the feasibility study through the local gynaecological oncology database, which was populated through the multi-disciplinary meetings. There were no women for whom mortality data was not available. In a larger trial it is likely that some women would be lost to their local cancer centre, but mortality data should be available for all women via the cancer data registries using their NHS number.

All but one woman completed the quality of life and anxiety and depression measures at baseline. This suggests that completion of this large array of

measures is practicable for women who are motivated to be in the trial. The dramatic drop off in the numbers of questionnaires completed at 6 and 12 months mostly reflects a failure to send out many of the questionnaires and a failure to send out the planned reminders due to lack of funding. It also highlights the need to address collection of this data, particularly from women in the patient-initiated arm, in the main trial.

The use of the telephone line did not result in an excessive workload. It also resulted in a notable decrease in the number of clinic reviews compared to that which would have been expected if the same group of women had been receiving routine follow up.

Brown et al carried out a trial of patient initiated follow up of breast cancer[89]. 50 women were randomised between routine follow up and patient initiated follow up. Over the course of one year, only three telephone calls were made: one from the standard arm and two from the patient-initiated arm.

Gulliford et al similarly found that using patient initiated review between routine mammography visits did not result in an excessive use of the telephone line, when compared to women who were having standard follow up after treatment for breast cancer[58].

This study clearly demonstrates that a randomised controlled trial of follow up after gynaecological malignancy is feasible. The feasibility study showed acceptable rates of recruitment and follow up. Rates of recruitment and research follow up are likely to be enhanced by having dedicated funding and staff time. Research follow up can be further enhanced by repeated postal

and telephone reminders to women who have not returned their questionnaires and also with the use of web based questionnaires and data collection.

**Appendix 4.1 - trial information**

South Tees Hospitals NHS
NHS Trust

# The Role of Follow-up after Gynaecological Cancer

Patient Information Leaflet

## Introduction

You are being asked to take part in a research study. Before you decide, you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk about it with friends, relatives and your GP (General Practitioner), if you wish. Ask us if there is anything that is not clear or if you would like to know more. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) have a leaflet called 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Thank you for reading this leaflet.

## What is the purpose of this study?

It is normal for patients to have follow up appointments in hospital clinics after treatment for cancer. It has always been thought that finding people whose cancer has returned ('recurred') at these visits would allow earlier treatment, and this would mean that they would, on average, live longer. However, research has shown that most people discover that their cancer has returned for themselves, in between their hospital visits, because they get symptoms. Research in breast and bowel cancers tell us that those people whose cancer is found again by a doctor in the clinic do not live longer, on average, than those people who find the cancer has returned for themselves.

The reason for doing this study is to compare routine follow-up appointments in hospital clinics with appointments that are given when you, the patient, asks for it (patient-initiated follow-up).

## Why have I been chosen?

We are asking all our patients that have just finished treatment for cancer to take part in this trial. The only people that will not be asked are those that still have problems and so need to keep seeing us.

## Do I have to take part?

It is up to you whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to pull out of the trial at any time, and without giving a reason. This will not affect the standard of care you will receive.

## What will happen to me if I take part?

Sometimes, because we do not know which way of treating patients is best, we need to compare two different ways of doing things. People will be put into groups and then compared. A computer, which has no information about the people involved, selects the groups – i.e. by chance or 'randomly'. Patients in each group then have a different type of follow-up and the two groups are compared.

You have a 2/3 chance of being allocated to patient initiated follow up, and a 1/3 chance of being allocated to standard follow up. The research project will last for five years in total.

If you are chosen to have routine follow-up, you will see us in the clinic for five years. You will be seen every three months for the first year, every four months for the second year, every six months for the third year and then once a year until the end of the five years (two visits). After this you will be discharged. If you have any problems in between these visits you can get in touch with us, either through your General Practitioner (GP) or by telephoning the department, and we can bring the appointment forward if needed.

If you are chosen to have patient-initiated follow-up then it will be up to you when, or if, you are seen. We will give you information about your disease so that you know which symptoms to look for and when to call us. There is a special telephone line that is just for patients in this part of the trial. If you telephone us and we need to see you, we will see you within five working days of the call. You will also be asked to answer some questions about your health and general well-being after six months, then at 12 months and then once each year, until five years have passed.

## What are the possible risks and benefits of taking part?

We hope that both ways of looking after you will be of benefit. However there may be some differences in the benefits from the two different types of follow-up. The information we collect from this trial will help us to know in future the best way of following patients after they have been treated for cancer.

## What happens when the research stops?

When the trial has finished, everybody will have the same type of follow-up. The trial will tell us which type of follow-up is best and therefore which type of follow up everybody will have.

## What if something goes wrong?

If you are harmed by taking part in this trial, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints processes are available to you.

## Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital/surgery will have your name and address removed, so that you cannot be recognised from it.

Your General Practitioner (GP) will be told if you choose to take part in this trial.

## What will happen to the results of the research study?

When the study is finished, the results will be published in one of the medical journals. The results will also be presented at medical meetings. You will not be identified in any way in any such article or at any such meeting.

## Who is organising and funding the research?

This study is a pilot study and is being funded by the Gynae Oncology Unit. We hope to get further funding from the NHS Regional Office. We aim to get funding from the Medical Research Council for the main part of the trial. This is the organisation through which the government funds medical research.

## Who has reviewed the study?

The South Tees Ethics Committee has approved this study.

**Contact for Further Information.**

Miss Jane McNeil
Lead Nurse, Gynae Oncology
Ward 19
James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

01642 282418

**Appendix 4.2 – consent form**

South Tees Hospitals NHS
NHS Trust

Follow-up In Gynaecological Oncology

**Name of Researchers:** Miss Fiona M Kew, Specialist Registrar, Gynae Oncology

Mr Derek J Cruickshank, Consultant Gynae Oncologist

Mr James Nevin, Consultant Gynae Oncologist

Dr Adrian J Rathmell, Consultant Clinical Oncologist

Please initial box

1. I confirm that I have read and understand the information sheet dated June 2001 for the above study and have had the opportunity to ask questions ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐
3. I agree to take part in the above study. ☐

| | / / | |
|---|---|---|
| ---------- | ---------- | ---------- |
| **name of patient** | **date** | **signature** |
| | / / | |
| ---------- | ---------- | ---------- |
| **name of person taking consent (if not researcher)** | **date** | **signature** |
| | / / | |
| ---------- | ---------- | ---------- |
| **researcher** | **date** | **signature** |

**Appendix 4.3 – patient information leaflet**


# Patient Information Leaflet

## Patient Information Leaflet – After Cancer of the Endometrium

### Introduction

You have now completed treatment for the cancer that you had. Hopefully you will not have any further problems in the future, but sometimes people do. The role of follow-up after treatment is to deal with problems when they arise and arrange any further treatment, if necessary. As part of the trial that you agreed to help us with, you have been selected to have patient-initiated follow-up. This is instead of the traditional practice of routine appointments, which do not always arrive when you actually need help.

### What is Patient-Initiated Follow-up?

This means that we will see you as and when you think it is necessary, rather than bringing you back to the hospital on a routine basis. Problems may be caused by the treatment itself, or by the return of the cancer or, very commonly, have nothing to do with the cancer. In order to help you decide when (or if) you need seeing we have written this leaflet, which gives details of how to get hold of us. It also gives you some guidance on when you may need to contact us

### Phone Line

There is a new telephone line especially for ladies that are participating in this trial. The telephone number is xxxxxxxxxx. A trained nurse will be available to answer

your call between xxxxxxxxxxxxxxxxxxxxxxxxxxxx. At all other times there is a confidential answer phone, where you can leave a message. We will return your call within two working days.

## When to use the phone line

You should phone us if you have symptoms that may indicate that the cancer has returned, or if you have ongoing problems from your treatment that you need help with.

We have listed below some of the more common symptoms people get if their cancer returns. However, it is important to remember that most people will not experience any one of these symptoms, and that even if you have all of them it does not necessarily mean that the cancer has come back.

If you get any of the following symptoms for no apparent reason, and they last for more than a few days, we recommend that you phone us for further advice:

- Bleeding from the vagina ('front passage')
- Bleeding from the rectum ('back passage')
- Bleeding after sexual intercourse, if this is new
- New aches and pains in the abdomen ('stomach') or pelvis
- Vaginal discharge
- Weight loss without dieting or exercise
- Feeling generally unwell
- Any new lumps or masses in the abdomen ('stomach')

Some people have problems with their bowels, water works or with sexual intercourse after treatment. If you have these problems and need help, then feel free to call us (or your GP if you prefer).

## When should I see my General Practitioner (GP)?

It is important to remember that you will still get coughs, colds, aches and pains just like anybody else. Your General Practitioner (GP) will be happy to treat any such problems. If they are concerned about your symptoms when they see you, they can also contact us and arrange for you to be seen.

Remember, if you are uncertain about the importance of any of the symptoms you are having, you should contact us or your GP.

## What information will we need when you phone?

Your name

Your date of birth

A daytime telephone number (we will need this even if you phone when the phone line is manned in case we need to contact you further).

Details of your symptoms – you may find it helpful to make a list.

## What will happen after you have phoned us?

Any problems you are having may be caused by the treatment itself, or by the return of the cancer or, very commonly, have nothing to do with the cancer. Often, we need to see you in order to decide which of these is the case. When you phone, we will suggest one of the following:

1. A clinic appointment

*We may wish to see you at the hospital to assess you further. Should we feel this is necessary, we will give you an appointment to come to the clinic, or possibly the ward, within five working days.*

2. A visit to the GP

*In some cases it may be more appropriate for you to see your GP for you problems. If your GP has any concerns he/she can always contact us for further help.*

3. Reassure you that nothing further is needed

*If we, and you, are happy that no further action is needed, we may suggest that you just keep an eye on things.*

We will keep a record of your phone call, for future reference.

PHONE LINE NUMBER: xxxxxxxxxxxx

This number will be staffed during the following times:

**A confidential answer phone is available at all other times.**

# Chapter 5 – Conclusions

It is estimated that in the UK approximately 1.2 million people are currently living with and beyond a cancer diagnosis[90], and the evidence suggests that many people suffer adverse physical and psychological consequences in the time following treatment that generally go unrecognised. People following cancer treatment will universally feel distressed at some point in their illness trajectory. As increasing numbers of medical therapies develop in treating cancer, more people are cured but also many more are living longer with disease. Therefore, cancer is increasingly being viewed as a chronic illness[91]. This has important consequences when considering the role and function of follow up in cancer services.

The government has recently promised to 'reshape the health services around the needs and aspirations of patients'.[92] A commitment has been made to seek and listen to the views of patients and act on them in order to provide care that is tailored to the needs of the individual[93]. In order to provide individualised care it is vital to understand the views and needs of individual patients. This in turn will allow the assessment of existing follow up regimens and the planning of alternative strategies for the ongoing care of these women. What qualitative work has been done has shown that women find routine visits to the hospital reassuring, especially if they are experiencing unexpected symptoms, although the reassurance only lasts for short periods[20]. The qualitative work in chapter 3 would seem to indicate that the women become emotionally reliant on these bursts of reassurance and that they value highly the process of attending clinic visits at the hospital. This was confirmed by the wider survey reported in Chapter 3.

Whilst there have been moves with other cancer sites to use different forms of follow-up such as nurse led[94] or General Practitioner led[95], practice in gynaecological cancers still follows the traditional secondary/tertiary care model. Although treatment has been individualized, follow up has remained standardised. There continues to be a one-size fits all approach to follow up

after gynaecological cancers. In 1999 the Haward report[65] stated that there was no evidence to support the routine follow-up of women in remission after a gynaecological cancer, and suggested that follow-up of women after endometrial cancer should not be considered mandatory. However, as demonstrated by the survey of practice in chapter 2, there is very little variation between different Gynaecological cancer centres in their follow up regimens, and no suggestion that such care is individualised. This may be because of a lack of good quality evidence on the effectiveness of follow up to improve any type of outcome and no assessment of the best regimens for follow up, as has been shown in the literature review in chapter 1. Therefore clinicians stick to what they are used to.

Given this paucity of evidence demonstrating any benefit from follow up of any description, further research is strongly indicated. This should be in the form of a prospective randomised trial, since this is the only way to eliminate the possibility of length time bias inherent in all the retrospective studies reported in gynaecological cancers. Furthermore the trial must be adequately powered to ensure that a clinically significant difference in outcome between different types of follow up is not missed.

**Proposed Trial**

The null hypothesis for a trial should be that there is no benefit from follow up of any kind. As such it should compare no follow up with one or more different types of follow up.

In spite of this, given the information from chapter 3 on women's views, it seems unlikely that a trial comparing no follow up to standard follow up would be acceptable to the target population. Additionally, the survey of practice in chapter 2 has demonstrated that routine clinic follow up for five years after treatment remains standard practice for women who have had a gynaecological cancer. As such, the feasibility of recruitment to a trial that has no follow up as one arm has to be questioned.

The pragmatic approach is, therefore, to design a trial that compares minimal acceptable follow up with current standard practice (as defined from the data collected in chapter 2). Blinding of participants and clinicians is not feasible given the nature of the study.

The control arm would be that of patient initiated follow up as described in chapter 4. Women would have open access to the Gynaecological Oncology team via the use of a telephone line or by accessing appointments through their General Practitioner. No routine appointments will be made after randomisation. Women will be given advice regarding symptoms that may indicate recurrence and when to contact the hospital. The use of open access via a telephone line seems to give women sufficient reassurance that they can access the system if they have a problem, rather than leaving them with no follow up or support what so ever. This is in keeping with information from Bradley et al[20] that shows that one of the things that women value the most from follow up is the access to specialist services if they develop problems. However, it should be noted that this reduced level of follow up in the patient-initiated arm may have contributed to the low level of recruitment in the feasibility study.

The intervention arm would be that of standard follow up as determined by the survey of practice. Women would be given routine clinic appointments at three monthly intervals in the first year, four monthly intervals in the second year, six monthly intervals in the third and fourth years and then an annual visit in year five.

Further trials should be designed to compare follow up for women who have been treated for cervical and vulval cancer. This is appropriate for these three cancers because there are potentially curative salvage treatments, so an intervention (follow up) that detects recurrence earlier and therefore enables treatment to be given earlier has the potential to improve survival.

This proposal differs from the feasibility study in two crucial ways. Firstly these three different cancer sites have been separated. Following consideration of

the feasibility study it is obvious that the women who suffer from these three cancers have differing epidemiological and aetiological factors that may have a differential influence on outcome and as such it is not appropriate to pool results across the different cancer sites.

Secondly ovarian/fallopian tube/primary peritoneal carcinomas have been excluded. Data published after the completion of the feasibility study[22] have shown that there is no survival benefit from treatment of recurrent ovarian cancer with chemotherapy at biochemical relapse, as opposed to at symptomatic relapse. As such it is difficult to justify a further randomised trial in this group at this point, where survival and detection of recurrence are the main endpoints. Further work in women who have been treated for ovarian cancer would be better geared at looking at the forms of support and follow up they would wish for in order to deal with the physical and psychological after effects of their disease and treatment. This would lend itself to trialing of different types of follow up with the outcomes geared around patient satisfaction, quality of life and psychological well-being. This study has not been considered further within the remit of this thesis.

**Inclusion and Exclusion Criteria**

The trial should compare the two different types of follow up in women who have completed treatment for endometrial cancer and do not require follow up for any reason. All stages and histological subtypes will be included. Women who require further follow up for any reason (ongoing symptoms, side effects of treatment) will be excluded. Women without access to a telephone will also be excluded. Women who cannot read and write English will be excluded because they will not be able to complete the quality of life assessments.

Women who have been treated previously for another cancer will also be excluded because they may have ongoing follow up and will have experienced other regimens and approaches to follow up which may affect their views.

**Outcome Measures**

Primary Outcome Measure

The primary outcome measure should be survival – both absolute and quality adjusted using the EQ5D[96]. About 85% of women treated for endometrial cancer survive for three years. An expert group of gynaecological oncologists regarded an absolute change of 5% or greater in three-year survival as clinically important.

To detect a 5% absolute change in three-year survival (to more than 90% or less than 80%) with 80% power when using a 5% significance level needs 1800 patients. A two-tailed test has been used since it is possible that a clinically important difference could be seen in either direction. Allowing for 10% complete loss to follow-up recruitment would need to be a total of 2000. Patients' time in the trial will range between 1.5 and 4.5 years. Follow up research questionnaires will be completed after 6 and 12 months, and two, three and four years. Allowing for death and other loss to follow-up, it is estimated that at least 1000 (50%) will respond to their planned final questionnaire. This will yield 90% power when using a 5% significance level to detect a standardised difference of 0.2 (regarded as the boundary between small and trivial change)[97] in the secondary outcome measures. Because the 1000 patients who respond, and the 300 patients who die, all contribute to the estimation of quality-adjusted survival (QALYs), this power will increase to 95% when comparing QALYs. (Calculation performed by Professor I T Russell, see appendix 1).

Data on survival will be collected within the trial and checked against data in the cancer registry.

Two studies of breast cancer have tested the feasibility of recruiting patients into trials comparing different follow-up packages. Gulliford et al[58] recruited 93% of women treated for breast cancer to a trial comparing reduced follow-

up with standard follow-up. Grunfeld et al[95,98] recruited 66% of such women to a trial comparing follow-up in general practice with standard follow-up. Even the unfunded feasibility study randomised 31% of eligible patients treated for gynaecological cancer between routine and patient-initiated follow-up. These three studies suggest that an adequately resourced trial can recruit at least 50% of eligible patients. Thus to recruit 2000 patients over 3 years will require cancer centres which together treat 1350 eligible patients a year. This we equates to at least 27 centres who treat an annual average of 50 eligible patients with endometrial cancer.

Secondary Outcome Measures

1. Disease Free Survival. The full project should, as an interim outcome, assess the rate of detection of recurrence between the two arms. If a difference in time to detection of recurrence is shown, then the trial should be continued to test for differences in survival. If there is no difference in time to detection of recurrence it is unlikely that any difference would be found in survival.

2. State Trait Anxiety Inventory[99]. It clearly differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety" which is useful in a setting where there are potential stress points (follow up visits) as opposed to an ongoing problem (living beyond a cancer diagnosis).

3. Beck Depression Inventory[100]. This should be used in preference to the hospital anxiety and depression scale because it has been shown to work in non-psychiatric patients and discriminates subtypes of depression and differentiates depression from anxiety[101].

4. Quality of Life Measures. As shown in the feasibility study, women are willing to complete several quality of life tools. The EQ5D is mentioned above. It is best to use disease-specific tools as well as a more general quality of life tool. Therefore the EORTOC QLQ-C30 (a generic cancer quality of life measure) should be used (as in the feasibility study)[102]. A

specific module for use in women with endometrial cancer has now been developed (EORTOC QLQ-EN24)[103] and should also be used.

5. Patient satisfaction. There are multiple methods by which to measure patient satisfaction. However, in the first place a study using qualitative interview methodology is appropriate since this will allow collection of in depth information on the feelings of the women about the different types of follow up. A small purposive sample will be identified from both arms of the trial and data compared. This data should then be triangulated by using a specifically designed and validated questionnaire survey of all women participating in the study. Further information will also be collected by way of exit interviews for women who choose to leave the trial in order to determine if withdrawal is linked to dissatisfaction with the mode of follow up they have experienced.

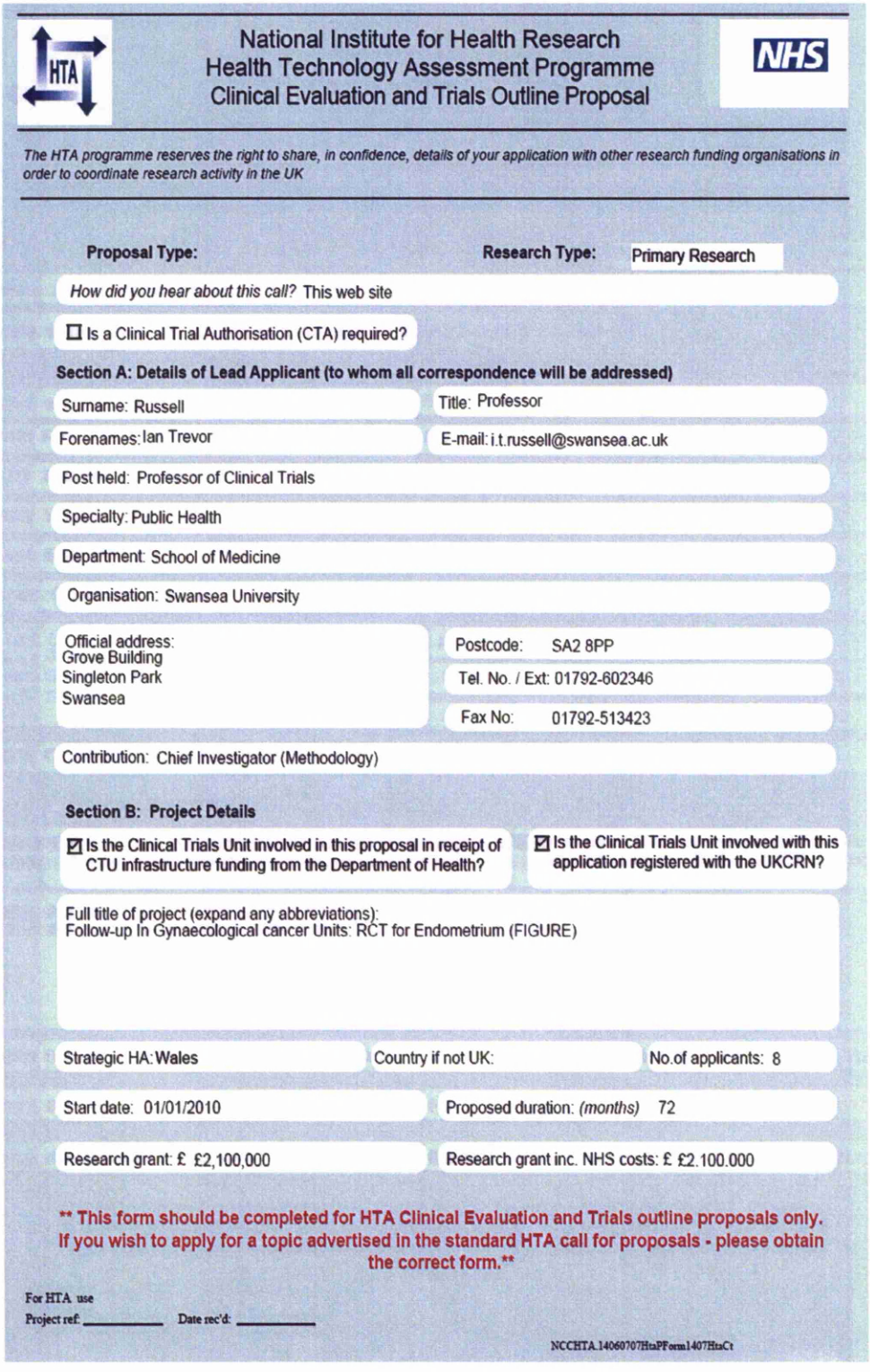
6. Economic. Full economic evaluation of quality adjusted life years will be required in the event of a difference in survival being demonstrated. A costs analysis for each mode of follow up will be produced. This will need to include number of clinic appointments, cost of the telephone line, length of appointments, along with medical and surgical interventions. It will also need to collect information on the use of primary care, since there is a risk that provision of less secondary care may simply mean that women attend to see their General Practitioner more often.

All questionnaires will be administered at randomisation and then at six, 12, 24, 36 and 48 months after recruitment. Postal reminders will be sent after two and six weeks to non-responders and then they will be contacted by telephone if they still have not responded.

If a significant difference in survival is demonstrated, this will allow healthcare providers to provide the most effective form of follow-up to its patients. If there

is no significant difference in survival, then it will allow the service to decide the most effective type of follow-up based on cost, use of resources in primary and secondary care and the views and experiences of the patients themselves. Furthermore, a different model of follow up has the potential to improve capacity, by reserving the use of resources for those who need it, and to improve patient access, through the use of the telephone line. Overall such a trial would provide vital evidence to make significant changes in the way healthcare is delivered.

## Appendix 5.1 – grant application



National Institute for Health Research
Health Technology Assessment Programme
Clinical Evaluation and Trials Outline Proposal

*The HTA programme reserves the right to share, in confidence, details of your application with other research funding organisations in order to coordinate research activity in the UK*

**Proposal Type:** **Research Type:** Primary Research

*How did you hear about this call?* This web site

☐ Is a Clinical Trial Authorisation (CTA) required?

**Section A: Details of Lead Applicant (to whom all correspondence will be addressed)**

Surname: Russell
Title: Professor
Forenames: Ian Trevor
E-mail: i.t.russell@swansea.ac.uk
Post held: Professor of Clinical Trials
Specialty: Public Health
Department: School of Medicine
Organisation: Swansea University
Official address:
Grove Building
Singleton Park
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Postcode: SA2 8PP
Tel. No. / Ext: 01792-602346
Fax No: 01792-513423
Contribution: Chief Investigator (Methodology)

**Section B: Project Details**

☑ Is the Clinical Trials Unit involved in this proposal in receipt of CTU infrastructure funding from the Department of Health?

☑ Is the Clinical Trials Unit involved with this application registered with the UKCRN?

Full title of project (expand any abbreviations):
Follow-up In Gynaecological cancer Units: RCT for Endometrium (FIGURE)

Strategic HA: Wales
Country if not UK:
No.of applicants: 8
Start date: 01/01/2010
Proposed duration: *(months)* 72
Research grant: £ £2,100,000
Research grant inc. NHS costs: £ £2.100.000

**** This form should be completed for HTA Clinical Evaluation and Trials outline proposals only. If you wish to apply for a topic advertised in the standard HTA call for proposals - please obtain the correct form.****

For HTA use
Project ref: _____ Date rec'd: _____

NCCHTA.14060707HtaPForm1407HtaCt

**Please note: The first stage of HTA Clinical Trials assessment will only use this section (Section C) of the form. You must complete this section of the form in anonymised format - you must not include any information that enables any individual or team associated with your application to be identified.**

**Section C: Justification of Project Proposed**

**1. Specification of research question:**
Please state in one sentence the research question to be addressed.

In patients who have completed treatment for endometrial cancer, which of self-initiated or routine follow-up is the more effective and the more cost-effective?

**2. Importance of the health problem to the NHS:**
Please describe the frequency of the health problem in the population and its impact on patients and the NHS.

Across the UK there are about 7000 newly diagnosed cancers of the endometrium each year. Five-year survival rate for Stage I tumours is about 85%. Routine follow-up of these patients after treatment of their cancers remains standard. This assumes that detecting recurrent cancer before symptoms develop will permit earlier treatment and improve survival rates. However there is no randomised controlled trial (RCT) that tests whether routine follow-up affects survival rates in gynaecological oncology. Furthermore 4 RCTs in breast cancer show no significant survival benefit from intensive follow-up compared with little or no follow-up. In contrast meta-analysis has shown that intensive follow-up after curative resection for colorectal cancer improves survival relative to routine follow-up. In lung cancer nurse-led follow-up was acceptable to patients and generated better functional outcomes. Given the absence of evidence for routine visits, and pressure from NHS priorities, there is a strong case for an RCT to evaluate whether health technology comprising training and full support for self-initiated follow-up in endometrial cancer is effective or cost-effective or both. This case has the full support of the NCRI Gynaecological Cancer Studies Group, who also endorse this application.

**3. A description of the technology and its possible effect on health status:**
You should also discuss current and projected use in the NHS, with approximate costs.

We have developed, & tested the feasibility of, a protocol for training patients to initiate their own follow-up, and leaflets for patients & GPs about the symptoms of recurrence, all suitable for use across the NHS. So experimental patients will receive a structured briefing from a Nurse Specialist & the number of a telephone help line staffed by their local centre. Calls to the help line, by patients or their GPs, generate clinic appointments whenever appropriate and without limit. Participating gynaecological oncology centres will also offer GPs continuing education on the post-treatment care of endometrial cancer. Our survey of current practice showed consensus around follow-up intervals of 3 months for the 1st year, 4 months for the 2nd year, and 6 months for the third year and then annually until discharge at 5 years. Building on this survey we have also developed guidelines for routine follow-up in secondary care (notably a minimum of 6 visits over 3 years), thus ensuring general consistency without undermining local autonomy. Feasibility studies in two distinct centres suggest that the new technology is at least as effective as usual treatment & may save costs.

**Please note: The first stage of HTA Clinical Trials assessment will use this section (Section C) of the form only. You must complete this section of the form in an anonymised format - there must not be any information that enables any individual or team associated with your application to be identified.**

**4. Summary of the current evidence:**

Please describe the current knowledge and outline other research taking place in this area. You should discuss how the proposed research will add to the existing evidence base. You must also consider any relevant published or ongoing HTA programme projects.

We conducted a systematic review of follow-up for gynaecological cancer and searched MeSH terms for [genital neoplasms] & [female] & [aftercare/ambulatory care/follow-up studies/population surveillance/primary health care] and text for a wide range of synonyms of these terms. Of the 13000 resulting references, only 18 retrospective studies of women treated for cancer rigorously reported on survival. Of 9 that studied endometrial cancer, only 1 reported a survival benefit from routine follow-up; however it did not control for the bias inherent in retrospective studies. Repeating the same search strategy recently identified no useful extra references or current RCTs. In these circumstances we expect the proposed RCT to dominate the literature & either to change or to confirm current practice, for which there is little rigorous evidence.

**5. What outcomes will be measured?:**

Primary: Survival over mean of 3 years – both absolute & adjusted by EQ5D to yield quality-adjusted life-years. 2ndary after 6, 12, 24, 36 & 48 months: Quality of life – generic (EORTC-QLQ-C30, which assesses emotional, functional, physical & social well-being in cancer) & site-specific [EORTC-QLQ-EN34, recently developed by Quality Of Life Group of European Organisation for Research & Treatment in Cancer (EORTC) specifically for endometrial cancer]; anxiety & depression – State-Trait Anxiety Inventory & Beck Depression Inventory; progression-free survival; cancer-specific symptoms; patient attitudes to follow-up especially acceptability & preferences. Costs from perspective of NHS & patients: patients will use Client Service Receipt Inventory to report NHS resource use in secondary & primary care, focusing especially on use of primary care to advise on, & initiate, contact with secondary care; they will also report personal costs.

**Please note: The first stage of HTA Clinical Trials assessment will use this section (Section C) of the form only. You must complete this section of the form in an anonymised format - there must not be any information that enables any individual or team associated with your application to be identified.**

**6. Summary for the Non-Expert**

Please provide a summary of sections 1 to 5. This summary should enable the non-expert reviewer to understand how the proposal addresses a question important to the NHS, how and where the research will be carried out, what outcomes will be used to assess the success of the research, what if any, are the ethical issues involved in this study and arrangements for handling these, why this team is well placed to carry out the research and provide justification for the costs requested (including any NHS costs).

Aim: To compare the effectiveness & cost-effectiveness of patient-initiated follow-up after completed treatment for endometrial cancer with routine follow-up in secondary care.
Objective: To evaluate whether these regimes differ in survival & cost per quality-adjusted life year.
Design: Pragmatic RCT collecting patient preferences as potential prognostic variable.
Health technologies being assessed: Experimental patients receive training, written information especially about symptoms of recurrence, phone number giving direct access to outpatient clinic, & possibly access to patient-initiated decision support software; control patients receive current best practice, that is guideline-based routine follow-up.
Setting: 30 gynaecological oncology centres with 1500 eligible new patients / year.
Patients: 2000 women treated for endometrial cancer over 3 years.
Outcomes: Survival over mean of 3 years; quality-adjusted life-years; generic & cancer-site-specific quality of life after 6, 12, 24, 36 & 48 months.
Ethical issues: Though there could be concern that there is political motivation to cut costs, our feasibility studies suggest that patient-initiated follow-up is as effective as usual care.
Team: National collaboration of gynaecological & medical oncologists, GP, cancer nurse & trialists.
Research costs: £1000 per recruited patient represents good value for money (no net NHS costs).

**Please note: The following sections (D onwards) of the form are used (along with those earlier) in the second stage of the assessment process where the study design and scientific merit are also scrutinised. You should provide a clear explanation of your intended study.**

**Section D: Objectives**

Please provide a clear summary of your research objectives.

We aim to evaluate whether patients who have completed treatment for endometrial cancer fare better or worse if, rather than routine follow-up in secondary care, they receive training in initiating their own follow-up together with the number of a telephone help-line .

Thus our research objectives are:

1 to estimate whether these two regimes differ in effectiveness as measured by survival, quality of life (both generic and cancer-site-specific) and quality-adjusted survival over an average of 3 years from completing treatment;

2 to evaluate whether these two regimes differ in cost-effectiveness as measured by cost per quality-adjusted life-year when the EQ5D ('EuroQol') is the criterion for quality of life;

3 to test for differences in long-term survival and resource use if the trial shows that patient-initiated follow-up generates benefits over an average of 3 years from completing treatment – by designing the trial to permit an extension focusing on routine data.

4 to study the process of patient-initiated follow-up, both quantitatively & qualitatively, with a view to refining it for future implementation.

**Section E: Summary of Project**

Please provide a summary of your proposed research using the headings listed in the Guidance Notes.

Background – routine follow-up in hospital of patients treated for endometrial cancer is standard. This assumes that detecting recurrent cancer before symptoms develop will permit earlier treatment & improve survival rates. While some argue that hospital follow-up is reassuring for patients, routine appointments can be source of stress & delay. However there is no randomised controlled trial (RCT) testing whether routine follow-up affects survival rates in gynaecological cancer.

Design: Pragmatic RCT – traditional rather than 'patient preference', but collecting patient preference as potential prognostic variable.

Health technologies being assessed: Patient-initiated follow-up – patients receive training, info especially about symptoms of recurrence, phone number for immediate access to outpatient clinic, & possibly access to patient-initiated decision support software; care as usual – patients receive routine follow-up in secondary care, based on consensual guidelines.

Target population: Women completing curative treatment for endometrial cancer.

Setting: 30 gynaecological oncology centres with 1500 eligible new patients / year.

Sample size: 2000 randomised equally between technologies. About 85% of women treated for endometrial cancer survive for 3 years. To detect 5% change in 3-year survival (to more than 90% or less than 80%) with 80% power when using 5% significance level needs 1800 patients. Allowing for 10% complete loss to follow-up, we aim to recruit total of 2000. Patients' time in the trial will range between 1.5 and 4.5 years, depending on whether they join late or early. We shall ask them to complete questionnaires after 6 & 12 months, and 2, 3 & 4 years. Allowing for death & other loss to follow-up, we estimate that at least 1000 (50%) will respond to their planned final questionnaire. This will yield 90% power when using a 5% significance level to detect standardised difference of 0.2 (usually taken as boundary between small & trivial change) in secondary outcome measures – EORTC-QLQ-C30 & EN34. Because the 1000 patients who respond, & the 300 patients who die, all contribute to the estimation of quality-adjusted survival (QALYs), this power will increase to 95% when comparing quality-adjusted life-years (QALYs).

Measurement of outcomes.

Primary: survival over mean of 3 years– absolute & adjusted by EQ5D to give QALYs.

Secondary: Quality of life at 6, 12, 24, 36 & 48 months – generic (EORTC-QLQ-C30, which assesses emotional, functional, physical & social well-being in cancer) & site-specific (EORTC-QLQ-EN34); anxiety & depression – State-Trait Anxiety Inventory & Beck Depression Inventory; progression-free survival; cancer-specific symptoms; patient attitudes to follow-up especially acceptability & preferences.

Measurement of costs from perspective of NHS & patients: patients will use Client Service Receipt Inventory to report NHS resource use in 2ndary & primary care, focusing especially on time in primary care to advise on, & initiate, contact with 2ndary care; they will also report personal costs.

Project timetable: set-up – 12 months; recruitment – 36 months; follow-up ranging from 18 months for final recruits to 42 months for initial recruits; definitive analysis & report – 6 months.

**Section F: Team Expertise**

Please provide a clear account of the team assembled and the skills and expertise each member will provide.

The FIGURE trial development group (TDG) represents a strong collaboration between gynae oncology, led by FMK, & clinical trials expertise, led by ITR. The TDG comprises a research-active team of 15 including 7 who will become applicants on any full application – Richard Edmondson, John Kirwan & John Murdoch (gynae oncologists) Rhiannon Tudor Edwards (health economist) David Ingledew (health psychometrician) Richard Neal (GP cancer specialist) & Adrian Rathmell (medical oncologist). Of 8 current applicants DJC, FMK & AJN are gynae oncologists who have published extensively on follow-up in gynae cancer. JAG is an academic medical oncologist who has published extensively on translational issues. HCK is an eminent academic gynae oncologist who chairs the NCRI Gynaecological Cancer Studies Group. AL is a well-published cancer nurse leading research into follow-up in ovarian cancer. AJN led, & AL was a member of, the EORTC Quality Of Life Subgroup who developed the EORTC-QLQ-EN34, the new HRQOL module specific to endometrial cancer & due for use in FIGURE. ITR & RhW are experienced trialists: ITR was previously Director & currently Non-Executive Director of the North Wales Organisation for Randomisation Trials in Health (NWORTH – Registered Clinical Trials Unit in receipt of CTU infrastructure funding from Welsh Assembly Governmentl) & Director of WWORTH, the West Wales equivalent (currently applying for registration as CTU in collaboration with NWORTH); & RhW is executive manager of NWORTH. Thus the proposed trial has access to a full range of Standard Operating Procedures & trials expertise.

Please provide details about any related (planned or active) grants held by any member of your research team in this or similar research areas. You should include a clear explanation of how the research being proposed in this application will fit.

ITR has finished academic administration to focus on his portfolio of 7 large trial grants – 4 funded by NIHR HTA Programme (COGNATE, COnStRUCT, FolATED & RemCare) & 3 programme grants, 2 from NIHR (DemCare & SHIELD) & 1 from Wellcome Trust (Staying Well After Depression). This portfolio spans the collaboration between the North (NWORTH) & West Wales Organisations for Randomised Trials in Health (WWORTH). RhW manages NWORTH and its core grant from the Welsh Office for R&D in health & social care. Together all these grants provide evidence of effective collaboration in clinical trials between Bangor & Swansea. AJN & AL hold a grant from the European Commission for the continuing validation of the EORTC-QLQ-EN34.

**Section G: Network Collaboration**

Please say with which of the UK Clinical Research Networks (http://www.ukcrn.org.uk) you intend to link for this research

National Cancer Research Institute (including Gynae Cancer Studies Group), Comprehensive Local Research Networks, Clinical Research Collaboration Cymru (including North & West Wales Organisations for Randomised Trials in Health)

Please list any benefits you may have identified from working with the network(s).

In their different ways these 3 types of network have all contributed, & are continuing to contribute, to the unprecedented growth in clinical research across the United Kingdom. Benefits include major improvements in resources, professionalism, morale & esteem. The only real threat lies in the danger that, when the recent growth stabilises, consolidation will take time & effort. That would be a small price to pay for the spectacular advances over the past 20 years.

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# References


1. CRUK. 2011. CancerStats Incidence UK. <http://info.cancerresearchuk.org/cancerstats/reports/ >. Accessed

2. CRUK. 2011. Ovarian cancer survival statistics. <http://info.cancerresearchuk.org/cancerstats/types/ovary/survival/ >. Accessed

3. CRUK. 2011 16/03/2011. Uterine Cancer Survival Statistics. <http://info.cancerresearchuk.org/cancerstats/types/uterus/survival/>. Accessed 16/03/2011.

4. CRUK. 2011 16/03/2011. Cervical Cancer Survival Statistics. <http://info.cancerresearchuk.org/cancerstats/types/cervix/survival/>. Accessed 16/03/2011.

5. CRUK. Vulval Cancer Survival Statistics. 2011.

6. Gadducci A, Cosio S, Zola P, Landoni F, Maggino T, Sartori E. Surveillance procedures for patients treated for epithelial ovarian cancer: a review of the literature. Int J Gynecol Cancer 2007;17(1):21-31.

7. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. Gynecol Oncol 2009;112(1):265-74.

8. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol 2006;101(3):520-9.

9. Petignat P, Jolicoeur M, Alobaid A, Drouin P, Gauthier P, Provencher D, Donath D, Van Nguyen T. Salvage treatment with high-dose-rate brachytherapy for isolated vaginal endometrial cancer recurrence. Gynecol Oncol 2006;101(3):445-9.

10. Kunkler IH, Kerr GR, Ludgate SM. The value of follow-up in stage II carcinoma of the cervix. Clin Oncol (R Coll Radiol) 1991;3(1):28-31.

11. Kerr-Wilson RH, McCrum A. Follow-up of patients with gynaecological cancer. Aust N Z J Obstet Gynaecol 1995;35(3):298-9.

12. Barnhill D, O'Connor D, Farley J, Teneriello M, Armstrong D, Park R. Clinical surveillance of gynecologic cancer patients. Gynecol Oncol 1992;46(3):275-80.

13. Agboola OO, Grunfeld E, Coyle D, Perry GA. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. Cmaj 1997;157(7):879-86.

14. Morice P, Deyrolle C, Rey A, Atallah D, Pautier P, Camatte S, Thoury A, Lhomme C, Haie-Meder C, Castaigne D. Value of routine follow-up

procedures for patients with stage I/II cervical cancer treated with combined surgery-radiation therapy. Ann Oncol 2004;15(2):218-23.

15. Salvesen HB, Akslen LA, Iversen T, Iversen OE. Recurrence of endometrial carcinoma and the value of routine follow up. Br J Obstet Gynaecol 1997;104(11):1302-7.

16. Shumsky AG, Stuart GC, Brasher PM, Nation JG, Robertson DI, Sangkarat S. An evaluation of routine follow-up of patients treated for endometrial carcinoma. Gynecol Oncol 1994;55(2):229-33.

17. Olaitan A, Murdoch J, Anderson R, James J, Graham J, Barley V. A critical evaluation of current protocols for the follow-up of women treated for gynecological malignancies: a pilot study. Int J Gynecol Cancer 2001;11(5):349-53.

18. Nordin A, Mohammed KA, Naik R, de Barros Lopes A, Monaghan J. Does long-term follow-up have a role for node negative squamous carcinoma of the vulva? The Gateshead experience. Eur J Gynaecol Oncol 2001;22(1):36-9.

19. Oonk MH, de Hullu JA, Hollema H, Mourits MJ, Pras E, Wymenga AN, van der Zee AG. The value of routine follow-up in patients treated for carcinoma of the vulva. Cancer 2003;98(12):2624-9.

20. Bradley E, Pitts M, Redman C, Calvert E, Howells R, Wafai C. What are the factors associated with the follow-up preferences of women in long-term remission from gynaecological cancer? J Obstet Gynaecol 2000;20(4):408-11.

21. Kew FM, Roberts AP, Cruickshank DJ. The role of routine follow-up after gynecological malignancy. Int J Gynecol Cancer 2005;15(3):413-9.

22. Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, Kristensen G, Mediola C, Coens C, Qian W and others. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet 2010;376(9747):1155-63.

23. Allsop JR, Preston J, Crocker S. Is there any value in the long-term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol 1997;104(1):122.

24. Berchuck A, Anspach C, Evans AC, Soper JT, Rodriguez GC, Dodge R, Robboy S, Clarke-Pearson DL. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol 1995;59(1):20-4.

25. Gadducci A, Cosio S, Fanucchi A, Cristofani R, Genazzani AR. An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. Anticancer Res 2000;20(3B):1977-84.

26. Gordon AF, Owen P, Chien PF, Duncan ID. A critical evaluation of follow-up of women treated for endometrial adenocarcinoma. J Obstet Gynaecol 1997;17(4):386-9.

27. Owen P, Duncan ID. Is there any value in the long term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol 1996;103(7):710-3.

28. Podczaski E, Kaminski P, Gurski K, MacNeill C, Stryker JA, Singapuri K, Hackett TE, Sorosky J, Zaino R. Detection and patterns of treatment failure in 300 consecutive cases of "early" endometrial cancer after primary surgery. Gynecol Oncol 1992;47(3):323-7.

29. Sartori E, Pasinetti B, Carrara L, Gambino A, Odicino F, Pecorelli S. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. Gynecol Oncol 2007;107(1 Suppl 1):S241-7.

30. MacDonald JH, Kidd GM. An audit of endometrial carcinoma: the value of routine follow up. J Obstet Gynaecol 1990;10:548-50.

31. Ansink A, de Barros Lopes A, Naik R, Monaghan JM. Recurrent stage IB cervical carcinoma: evaluation of the effectiveness of routine follow up surveillance. Br J Obstet Gynaecol 1996;103(11):1156-8.

32. Bodurka-Bevers D, Morris M, Eifel PJ, Levenback C, Bevers MW, Lucas KR, Wharton JT. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. Gynecol Oncol 2000;78(2):187-93.

33. Duyn A, Van Eijkeren M, Kenter G, Zwinderman K, Ansink A. Recurrent cervical cancer: detection and prognosis. Acta Obstet Gynecol Scand 2002;81(8):759-63.

34. Krebs HB, Helmkamp BF, Sevin BU, Poliakoff SR, Nadji M, Averette HE. Recurrent cancer of the cervix following radical hysterectomy and pelvic node dissection. Obstet Gynecol 1982;59(4):422-7.

35. Lim KCK, Howells REJ, Evans AS. The role of clinical follow up in early stage cervical cancer in South Wales. BJOG: An International Journal of Obstetrics & Gynaecology 2004;111(12):1444-8.

36. Samlal RA, Van Der Velden J, Van Eerden T, Schilthuis MS, Gonzalez Gonzalez D, Lammes FB. Recurrent cervical carcinoma after radical hysterectomy: an analysis of clinical aspects and prognosis. Int J Gynecol Cancer 1998;8(1):78-84.

37. Larson DM, Copeland LJ, Malone JM, Jr., Stringer CA, Gershenson DM, Edwards CL. Diagnosis of recurrent cervical carcinoma after radical hysterectomy. Obstet Gynecol 1988;71(1):6-9.

38. Zola P, Fuso L, Mazzola S, Piovano E, Perotto S, Gadducci A, Galletto L, Landoni F, Maggino T, Raspagliesi F and others. Could follow-up different modalities play a role in asymptomatic cervical cancer relapses diagnosis? An Italian multicenter retrospective analysis. Gynecol Oncol 2007;107(1 Suppl 1):S150-4.

39. Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009;114(3):528-35.

40. Esajas MD, Duk JM, de Bruijn HW, Aalders JG, Willemse PH, Sluiter W, Pras B, ten Hoor K, Hollema H, van der Zee AG. Clinical value of routine serum squamous cell carcinoma antigen in follow-up of patients with early-stage cervical cancer. J Clin Oncol 2001;19(19):3960-6.

41. Rintala MA, Rantanen VT, Salmi TA, Klemi PJ, Grenman SE. PAP smear after radiation therapy for cervical carcinoma. Anticancer Res 1997;17(5B):3747-50.

42. Gerdin E, Cnattingius S, Johnson P, Pettersson B. Prognostic factors and relapse patterns in early-stage cervical carcinoma after brachytherapy and radical hysterectomy. Gynecol Oncol 1994;53(3):314-9.

43. Tinga DJ, Bouma J, Boonstra H, Aalders JG. Symptomatology, localization and treatment of recurrent cervical carcinoma. Int J Gynecol Cancer 1992;2(4):179-188.

44. Soisson AP, Geszler G, Soper JT, Berchuck A, Clarke-Pearson DL. A comparison of symptomatology, physical examination, and vaginal cytology in the detection of recurrent cervical carcinoma after radical hysterectomy. Obstet Gynecol 1990;76(1):106-9.

45. Look KY, Rocereto TF. Relapse patterns in FIGO stage IB carcinoma of the cervix. Gynecol Oncol 1990;38(1):114-20.

46. Muram D, Curry RH, Drouin P. Cytologic follow-up of patients with invasive cervical carcinoma treated by radiotherapy. Am J Obstet Gynecol 1982;142(3):350-4.

47. Kew FM, Cruickshank DJ. Routine follow-up after treatment for a gynecological cancer: a survey of practice. Int J Gynecol Cancer 2006;16(1):380-4.

48. Goonewardene TI, Hall MR, Rustin GJ. Management of asymptomatic patients on follow-up for ovarian cancer with rising CA-125 concentrations. Lancet Oncol 2007;8(9):813-21.

49. Vaidya AP, Curtin JP. The follow-up of ovarian cancer. Semin Oncol 2003;30(3):401-12.

50. Kew FM, Galaal K, Naik R, Bryant A, Dickinson H. The role of routine follow up after treatment for epithelial ovarian cancer. Cochrane Database Syst Rev 2011;in press.

51. Frew G, Smith A, Zutshi B, Young N, Aggarwal A, Jones P, Kockelbergh R, Richards M, Maher EJ. 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(10):874-84.

52. Kew FM, Galaal K, Manderville H, Verleye L. Professionals' and patients' views of routine follow-up: a questionnaire survey. Int J Gynecol Cancer 2007;17(3):557-60.

53. Lydon A, Beaver K, Newbery C, Wray J. Routine follow-up after treatment for ovarian cancer in the United Kingdom (UK): patient and health professional views. Eur J Oncol Nurs 2009;13(5):336-43.

54. Kew FM, Galaal K, Manderville H. Patients' views of follow-up after treatment for gynaecological cancer. J Obstet Gynaecol 2009;29(2):135-42.

55. Watson EK, Sugden EM, Rose PW. Views of primary care physicians and oncologists on cancer follow-up initiatives in primary care: an online survey. Journal of Cancer Survivorship 2009;4:159-166.

56. Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, Fitzpatrick R, Vessey M. Routine follow up of breast cancer in primary care: randomised trial.[see comment]. BMJ 1996;313(7058):665-9.

57. Beaver K, Tysver-Robinson D, Campbell M, Twomey M, Williamson S, Hindley A, Susnerwala S, Dunn G, Luker K. Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. BMJ 2009;338:a3147.

58. Gulliford T, Opomu M, Wilson E, Hanham I, Epstein R. Popularity of less frequent follow up for breast cancer in randomised study: initial findings from the hotline study. BMJ 1997;314(7075):174-7.

59. Moore S, Corner J, Haviland J, Wells M, Salmon E, Normand C, Brada M, O'Brien M, Smith I. Nurse led follow up and conventional medical follow up in management of patients with lung cancer: randomised trial. Bmj 2002;325(7373):1145.

60. Moses SH, Olaitan A, Murdoch JB, Goodwin A. A pilot randomised controlled study of three models of follow-up of patients treated for gynaecological cancer: attitudes in general practice and feasibility of randomisation. J Obstet Gynaecol 2004;24(2):165-6.

61. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. The pattern of recurrent colorectal cancer in a prospective randomised study and the characteristics of diagnostic tests. Int J Colorectal Dis 1997;12(6):329-34.

62. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg KG. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. Dis Colon Rectum 1995;38(6):619-26.

63. Kuper A, Reeves S, Levinson W. An introduction to reading and appraising qualitative research. BMJ 2008;337:a288.

64. Calman K, Hine D. A policy framework for commissioning cancer services. London: Department of Health; 1995.

65. Haward RA. Improving Outcomes in Gynaecological Cancers: The Manual. London: Department of Health; 1999.

66. NHS Choices. 2011. About the NHS. <http://www.nhs.uk/NHSEngland/thenhs/about/Pages/overview.aspx>. Accessed 2011

67. Grunfeld E, Levine MN, Julian JA, Coyle D, Szechtman B, Mirsky D, Verma S, Dent S, Sawka C, Pritchard KI and others. Randomized trial of long-term follow-up for early-stage breast cancer: a comparison of family physician versus specialist care.[see comment]. Journal of Clinical Oncology 2006;24(6):848-55.

68. Van Voorhis LW. Carcinoma of the cervix. II. A critical evaluation of patient follow-up. Am J Obstet Gynecol 1970;108(1):115-21.

69. McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, Thomas R, Harvey E, Garratt A, Bond J. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients. Health Technol Assess 2001;5(31):1-256.

70. Oppenheim A. Questionnaire Design, Interviewing and Attitude Management. London: Continuum; 1992. 303 p.

71. Mangione T. Mail surveys - improving the quality. Thousand Oaks, CA: Sage; 1995.

72. Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. J Clin Epidemiol 1997;50(10):1129-36.

73. Kizer KW. Patient centred care: essential but probably not sufficient. Quality & Safety in Health Care 2002;11(2):117-8.

74. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. JAMA 2000;284(4):478-82.

75. Howells REJ. Audit of the views of gynaecological cancer patients regarding follow-up. Journal of Obstetrics and Gynaecology 1999;19(2):167 - 168.

76. Campbell DTF, D.W. . Convergent and discriminant validation by the multitraitmutimethod matrix. Psychological Bulletin 1959;56:81-105.

77. Strauss A, Corbin J. Basics of qualitative research. London: Sage; 1990.

78. Schatzman L, Strauss A. Field Research. Englewood Cliffs, N.J: Prentice-Hall, Inc; 1973.

79. Lingard L, Albert M, Levinson W. Grounded theory, mixed methods, and action research. BMJ 2008;337:a567.

80. Mason J. Qualitative Researching. London: Sage; 2002.

81. Miles MB, Huberman AM. Qualitative Data Analysis: an expanded source book. London: Sage; 1994.

82. Strauss A, Corbin J. Basics of Qualitative Research: Grounded THeory Procedures and Techniques. Thousand Oaks, CA: Sage; 1998.

83. Spencer L, Ritchie J, O'connor W. Qualitative Research Practice. Ritchie J, Lewis J, editors. London: Sage Publications; 2003.

84. Sellick SM, Edwardson AD. Screening new cancer patients for psychological distress using the hospital anxiety and depression scale. Psychooncology 2007;16(6):534-42.

85. Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P. Qualitative research methods in health technology assessment: a review of the literature. Health Technol Assess 1998;2(16):iii-ix, 1-274.

86. Glaser B, Strauss A. The discovery of grounded theory: strategies for qualitative research. Chicage: Aldine; 1967.

87. Smith K, Biley F. Understanding grounded theory: principles and evaluation. Nurse Researcher 1997;4:17-30.

88. NHSImprovement. National Cancer Survivorship Initiative Vision. Department of Health; 2010.

89. Brown L, Payne S, Royle G. Patient initiated follow up of breast cancer. Psycho-Oncology 2002;11(4):346-55.

90. Macmillan Cancer Support. Tackling the financial impact of cancer. A briefing paper for the cancer reform strategy patient experiences working group. London; 2007.

91. White CA. Cognitive Behaviour Therapy for Chronic Medical Problems – A guide to assessment and treatment in practice. West Sussex, UK: John Wiley & Sons. Ltd. ; 2001.

92. Richards M. The NHS cancer plan and the new NHS: Providing a patient-centred service. Department of Health; 2004 27/10/2004.

93. DoH. High Quality Care For All – NHS Next Stage Review Final Report. London: Department of Health; 2008.

94. Cox K, Wilson E. Follow-up for people with cancer: nurse-led services and telephone interventions. J Adv Nurs 2003;43(1):51-61.

95. Grunfeld E, Fitzpatrick R, Mant D, Yudkin P, Adewuyi-Dalton R, Stewart J, Cole D, Vessey M. Comparison of breast cancer patient satisfaction with follow-up in primary care versus specialist care: results from a randomized controlled trial. British Journal of General Practice 1999;49(446):705-10.

96. Kind P. In: Spilker B, editor. Quality of Life in Trials. Philadelphia: Lippincott; 1996.

97. Cohen J. Statistical power analysis for the behavioral sciences. New Jersey: Lawrence Erlbaum Associates; 1988.

98. Grunfeld E, Levine MN, Julian JA, Coyle D, Szechtman B, Mirsky D, Verma S, Dent S, Sawka C, Pritchard KI and others. Randomized trial of long-term

follow-up for early-stage breast cancer: a comparison of family physician versus specialist care. J Clin Oncol 2006;24(6):848-55.

99. Spielberger CD. State-Trait Anxiety Inventory. The Corsini Encyclopedia of Psychology. John Wiley & Sons, Inc.; 2010.

100. Beck AT, Steer RA, Brown GK, Psychological C. 1996. Beck Depression Inventory (2nd ed.). Accessed

101. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clinical Psychology Review 1988;8(1):77-100.

102. European Organisation for Research and Treatment of Cancer. 15/09/2011. EORTC QLQ-C30. <http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_c30.pdf>. Accessed 15/09/2011.

103. European Organisation for Research and Treatment of Cancer. 15/09/2011. EORTC QLQ-EN24

<http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_en24.pdf>. Accessed 15/09/2011.