The University of Sydney

NHMRC Clinical Trials Centre

GYNECOLOGIC CANCER INTERGROUP

PoCoG Psycho-oncology Co-operative Research Group

ANZGOG

ANZGOG-0701

Does Palliative Chemotherapy Improve Symptoms in Women with Recurrent Ovarian Cancer?

Measuring subjective improvement as well as objective response to estimate the benefit of palliative chemotherapy in women with platinum resistant or refractory ovarian cancer

Version 3.0

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Does Palliative Chemotherapy Improve Symptoms in Women with Recurrent Ovarian Cancer?

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Note: Original and signed document held at the NHMRC Clinical Trials Centre

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ABBREVIATIONS

ANZGOG	Australian and New Zealand Gynaecological Oncology Group
CA125	Cancer Antigen
CRF	Case Report Form
CTC	Clinical Trial Centre
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FACT-O	Functional Assessment of Cancer Therapy - Ovarian
FOSI	FACT Ovarian Symptom Index
GCIG	Gynaecologic Cancer InterGroup
GCP	Good Clinical Practice
HADS	Hospital and Anxiety Depression Scale
HREC	Human Research Ethics Committee
HRQL	Health Related Quality of Life
ICF	Informed Consent Form
MOST	Measure of Ovarian Cancer Symptoms and Treatment Concerns
NCI CTC	National Cancer Institute Common Toxicity Criteria
NHMRC	National Health and Medical Research Council
DRSW	Disease Related Symptoms and Well-being
ATRC	Additional Treatment Related Concerns
PI	Principal Investigator
PIS	Patient Information Sheet
PoCoG	Psycho-Oncology Cooperative Research Group
PS	Performance Score
Pt DATA Form	Patient Disease and Treatment Assessment Form
QL/QoL	Quality of Life
QLQ-C30	EORTC Core QOL Questionnaire C30
QLQ-Ov28	EORCT Ovarian QOL Questionnaire Ov28
RECIST	Response Evaluation Criteria in Solid Tumours
SRQ	Symptom Representation Questionnaire
TMC	Trial Management Committee

PROTOCOL SYNOPSIS

Sponsor	University of Sydney
Study Design	Prospective observational cohort study conducted in 2 stages.
Aims	The purpose of this study is to develop a measure of symptom benefit that can be used as an endpoint in clinical trials of palliative chemotherapy. The aim of stage 1 is to determine the aspects of HRQL that are most troublesome pre-treatment, the changes in scores with treatment for each of these aspects, measures of hope, anxiety and depression and to identify optimal questionnaire(s) for assessing these aspects and changes in them. The aims of stage 2 are to develop criteria for defining symptom benefit, to determine how many women obtain this benefit, and to investigate prognostic models for benefit, time to progression and survival.
Primary Objectives	Stage 1: To determine the aspects of HRQL that are rated most severe and most noticed by patients, and the aspects that are most common Stage 2: To determine criteria for defining a clinically significant subjective improvement and the optimal instrument/s to measure benefit
Target Population	Stage 1: Women with recurrent platinum resistant or refractory ovarian cancer that are commencing 2nd or subsequent line chemotherapy as well as patients who are receiving > 3 lines of chemotherapy for recurrent ovarian cancer. Stage 2: Women from collaborating GCIG centers who have platinum resistant/refractory epithelial ovarian, fallopian tube or primary peritoneal cancers who are about to start 2nd or subsequent line chemotherapy.
Questionnaires	Stage 1 SRQ FACT-O EORTC QLQ C30 + Ov-28 Patient Data Form Expected and perceived benefit HADS Herth Hope Index Stage 2 MOST (recent and change) FACT-0 EORTC QLQ C30 + Ov-28 Expected and perceived benefit
Sample size	Stage 1: 50 - 100 pts. Stage 2: 800 pts (about 100 per country)

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1.0 BACKGROUND INFORMATION

Ovarian cancer is the leading cause of death in women with gynecological malignancies in the Western World and an important cause of cancer related deaths in women. The majority of women present with advanced disease and following debulking surgery receive platinum based chemotherapy, typically carboplatin and paclitaxel for 6 cycles. Most patients with advanced ovarian cancer initially respond to treatment but the majority, will relapse. The median time to progression is about 12-18 months and median overall survival of women with advanced ovarian cancer is 2-4 years (1). The median survival after recurrence is 2 years ,but this is variable and depends on multiple factors including initial response to treatment and time to progression.

The majority of women who relapse will be offered further chemotherapy with the likelihood of benefit related, in part to the initial response and the duration of response (2-6).The goals of treatment include controlling/palliating disease-related symptoms, maintaining or improving quality of life, delaying time to progression, and possibly prolonging survival. Many active agents (platinum, paclitaxel, topotecan, liposomal doxorubicin, docetaxel, gemcitabine, and etoposide) are available and more recently some patients are being treated with targeted therapies such as angiogenesis inhibitors.The choice of treatment is based on many factors including the individual clinician's perceived likelihood of benefit of chemotherapy for the patient, potential toxicity of treatment and patient convenience.Only a minority of patients are treated on clinical trials.

Women who relapse greater than 6 months after primary chemotherapy are classified as potentially "platinum sensitive" and usually receive further platinum based combination chemotherapy with response rates ranging from 27-65% and have a median survival of 12-18 months (2-6). Patients who relapse and progress within 6 months of completing first line chemotherapy are classified as "platinum resistant" and have a median survival of 6- 9 months and a 10-30% likelihood of responding to further chemotherapy (2-6). Patients who do not respond or progress while on treatment are classified as having "platinum refractory" disease. As a general rule objective response rates to chemotherapy in patients with platinum refractory ovarian cancer are low and less than 20% (2). "

Patients with platinum refractory and resistant ovarian cancer are commonly treated with chemotherapy and may have a number of lines of therapy depending on prior response, performance status, patient request and/doctor recommendations . Although response rates are low, there is a general perception that more patients have a subjective benefit, but this is poorly studied. It is increasingly appreciated that it is essential to measure and better quantitate the palliative benefit of therapy given that there are many potential side effects of treatment and the objective response rates are low and duration of response relatively short. The results of a recent study comparing topotecan with liposomal doxorubicin in women with recurrent ovarian cancer are a sobering reminder of the low response rates and poor prognosis particularly among women with platinum resistant ovarian cancer and underscore the importance of measuring symptom benefit in patients on chemotherapy. In a subset analysis of platinum-resistant patients, the median time to progression ranged from of 9.1 and 13.6 weeks for topotecan and liposomal doxorubicin respectively. The median survival (*P*=0.46) was 35.6 weeks for pegylated liposomal doxorubicin and 41.3 weeks for topotecan. Objective response rates of 6.5% for topotecan and 12.3% for pegylated liposomal doxorubicin were not significantly different (P=0.12) (7) which clearly demonstrates the limitations of chemotherapy in this patient population.

There is a paucity of information on the symptom benefits, either perceived or real, of "palliative chemotherapy" in women with platinum resistant or refractory recurrent ovarian cancer. Unfortunately, no large, randomized, controlled trials have yet demonstrated that systemic chemotherapy improves symptom palliation and quality of life in patients with relapsed ovarian cancer and this is the main reason for treatment.. It is not clear what proportion of women are symptomatic when they commence treatment and whether their symptoms improve as a result of treatment. The published literature on symptoms of women with recurrent ovarian cancer includes not only symptoms that can be attributed to recurrent disease ,but also those associated with prior chemotherapy such as neurotoxicity and fatigue as well as those associated with prior surgery such as menopausal symptoms and fertility issues in younger women. While these are all important and can impact on quality of life, they can not really be used to assess the benefit of palliative chemotherapy. It is essential and clinically important to determine whether symptoms that

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can be attributed to disease are improved with palliative chemotherapy and whether symptom benefit correlates with more objective measures of treatment effect such as CA125 response or RECIST response

There are only a relatively small number of studies that have addressed questions regarding patient perceptions and expectations of treatment for recurrent ovarian cancer. Doyle et al reported on a prospective study that included 27 patients with recurrent ovarian cancer prior to commencing either 2nd or 3rd line chemotherapy in Toronto (7). All were counseled about the aims and objectives of therapy and all agreed to participate in the study. Well validated questionnaires were used to assess palliative benefit and a questionnaire to evaluate patient expectations was also administered. Objective response to treatment was documented in 20% of patients and the median survival was 11 months. 65% of women expected that chemotherapy would make them live longer and 42% thought it would cure them despite the fact that they had been given verbal and written information that the treatment was palliative. Quality of life, particularly emotional function, was reported to be improved in 60% of patients raising questions as to whether it the treatment per se or the fact that the patient is having treatment that is important.

Donovan et al reported on a study of treatment preferences in recurrent ovarian cancer using a decision board in 81 patients receiving first line chemotherapy and 75 non cancer controls (8). The majority of women with ovarian cancer said they would have further chemotherapy if they relapsed but said they would switch from palliative chemotherapy to palliative care alone when the median survival was reduced to 5 months. How applicable this information is questionable as the women were all receiving first line therapy and none had recurrent ovarian cancer.

Penson et al reported a joint study from the USA and UK and addressed attitudes to chemotherapy in patients with ovarian cancer (9).122 patients were enrolled and 61% had recurrent ovarian cancer (9). Patients thought that second line chemotherapy was associated with remission in 50% of people treated and cure in 15%, which is reminiscent of the Toronto study. Patients were generally optimistic and would accept treatment for relatively little benefit and this is a common finding in studies of treatment for other cancers.

The common thread in these three studies was that treatment provides hope and this is an important need in patients with recurrent ovarian cancer. Although palliative chemotherapy is administered to improve symptom control and delay time to progression the provision of hope is possibly as important to individual patients. This is evident in a number of studies and is in keeping with clinical experience. Quality of life may possibly be of secondary importance to many women with recurrent ovarian cancer who are faced with a life threatening illness. It is clear that asking women who don't have cancer what they would do in a hypothetical situation provides information that is quite different to that obtained from women with recurrent ovarian cancer and this is not surprising. Donovan et al remarked that patients seemed to derive hope from clinical uncertainty and the fact that treatment might help while they perceived that palliative care meant no hope or death (8). All this needs to be considered when assessing the impact or benefit of palliative chemotherapy. Hope, anxiety and depression will be measured in stage 1 using relevant scales.

Response rates are a relatively crude way of defining benefit and clinical trials of palliative chemotherapy should also include subjective measures of benefit. The small study by Doyle suggested that quality of life and emotional well being improved in 50-60% of women receiving 2nd line therapy while only 7 of 27 had objective evidence of benefit (7). These observations should be confirmed, and clinical benefit measures that incorporate both objective response and subjective improvement should be used when evaluating the effect of palliative chemotherapy in women with recurrent ovarian cancer. Symptom relief without survival benefit is achievable in pancreatic cancer and lung cancers and it is important to determine if this is also the case in women with ovarian cancer.

The experience from gastrointestinal cancer and lung cancer in particular clearly demonstrates the utility of using symptom improvement as a primary endpoint of palliative chemotherapy and targeted therapies. The majority of patients with lung cancer die of disease and many experience debilitating symptoms such as pain, dyspnoea and fatigue. The three most common QOL instruments are the EORTC QLQ-C30 which includes the the lung cancer module LC13, the Lung Cancer Symptom Scale (LCSS) which includes a questionnaire based on lung cancer symptoms

reported by the patient and observer and the FACT-L. There is good evidence to show that chemotherapy provides improvement in cancer related symptoms and QOL over supportive care alone. Interestingly, the proportion of patients who have symptom relief is higher than objective response rates suggesting that patients who did not attain the threshold for objective response achieved clinical benefit. (10) There is also good evidence to show similar palliative benefits for targeted therapies such as erlotinib compared to placebo. Patients receiving erlotinib had a significantly longer time to deterioration of cough, dyspnoea and pain as well improvement in these symptoms in about 40% of patients which is accompanied by significant improvements in physical function.(11) These studies serve as a good example of how useful it can be to measure symptom benefit and it's likely that this approach can be extrapolated to patients with recurrent ovarian cancer.

This prospective study will also provide a valuable insight into the management of all women with platinum resistant /refractory ovarian cancer from many centers around the world and provide relevant information about the outcomes of patients treated in routine clinical practice rather than a selected group of women participating in clinical trials where the outcomes may be better due to selection bias. We will gain a better understanding of the reasons why treatment is given, what proportion of women have symptoms related to disease, what their expectations of benefit are and what price they pay in terms of toxicity. However, the major objective is to develop a more robust measure of benefit from chemotherapy that incorporates both subjective and objective response and we will then take this forward for use in prospective clinical trials in women with recurrent ovarian cancer.

We have a unique opportunity in this study to address issues that directly concern women with recurrent ovarian cancer and believe that a qualitative study in a selected subgroup of women in Australia may further help to refine the stage 2 study.

We recognize that we are asking patients to fill in a number of questionnaires and that there is some overlap between them. We will inform all women about the objective of the study and the need to develop better ways to measure benefit of treatment. Based on our previous experience we do not expect that patients will object to filling out all these questionnaires provided they are aware of why they are being asked to do so and how we will then modify the questionnaires for stage 2 based on their feedback and the findings of stage 1.

Compliance with questionnaire completion was excellent with no major omissions or problems identified. There was little to differentiate the candidate instruments in terms of distributions of scores, therefore the choice of instruments for inclusion in Stage 2 was largely determined by coverage of the relevant symptoms. It was decided to retain the QLQ-C30, QLQ-Ov28 and FACT-O and the Patient DATA form was modified to become the MOST form. (see appendix 1 for full details)

Prognostic Score

It is well recognised and accepted that patients with platinum resistant/refractory ovarian cancer constitute a heterogeneous group with a variable response to treatment and a variable survival. Patients with recurrent ovarian cancer are characterised according to their treatment free interval or time to recurrence after 1st line platinum based chemotherapy and designated as having platinum sensitive, platinum resistant or platinum refractory disease based on treatment free interval and response to platinum based chemotherapy (12,13,14). However, it is pertinent to consider the findings of a multivariate analysis of predictors of response in 700 platinum pre-treated patients with recurrent ovarian cancer (15). The investigators found that only 3 factors were independent predictors of response and these included serous histology, number of disease sites and tumour size. Time from last treatment was not an independent prognostic factor, but was highly correlated with tumour size which raises questions of how we should define platinum sensitive and platinum resistance. It should be noted that the latter study included all patients with recurrent disease, not just those with "platinum resistant disease" based on currently used definitions. At present, most studies do not stratify patients with platinum resistant /refractory ovarian cancer into prognostic subsets and there is still inconsistency in the definitions of platinum resistant /refractory ovarian cancer. There are no accepted or widely used prognostic indices that

can be used to subcategorise these patients although clinically we recognise that there is significant variability among this group of patients (16, 17).

Traditional Factors	Potential Additional Factors
Performance status	HRQOL ECOG status
Response to prior therapy	Symptoms (large volume ascites, abdominal cramping)
Refractory vs. resistant CA125 only vs. measurable disease	weight loss
Volume of tumour	Measures of inflammation (CRP, Haemoglobin, WCC, platelets, LDH, alkaline phosphatase)
Number of metastatic sites	CA125 velocity
Histology Serous vs. Clear Cell vs. Mucinous	
Grade	

The traditional factors that predict response to treatment and prognosis in patient with recurrent ovarian cancer are outlined in the table above. There are however a number of other factors that could be potentially incorporated into a prognostic score including patient and tumour related factors. These include patient related factors such HRQOL at entry and we propose that we look at measures of HRQOLat study entry as well as ECOG performance status as it is likely that patients with a good performance status (16) and better HRQOL will have a better outcome. The presence of symptoms and the nature of the symptoms at the time of treatment may be important and we will document whether they have large volume ascites or symptoms of intermittent cramping abdominal pain that could herald a bowel obstruction. There are a number of other potentially important patient related factors and these include weight loss prior to treatment which may correlate with inflammation and the anorexia –cachexia syndrome (18). In addition, the number of sites of disease as well as the volume of tumour may also correlate with response to treatment and survival and all this is readily available and known at study entry but not typically used to predict response or prognosis. It is also clear that tumour related factors are important predictors of response and survival and these include histological subtype and grade (15, 19, 20). In addition, there is growing evidence in a number of tumour types including ovarian cancer to show that markers of inflammation and inflammatory response are of prognostic significance. These include CRP (C Reactive Protein), haemoglobin, white cell and platelet count as well as LDH alkaline phosphatase (18, 21, 22, 23, 24). Finally, it appears that the CA125 velocity may also be of prognostic significance and reflect the biological behaviour and is worthy of further study (25).The aim of designing this prognostic index/risk score is to develop a tool that better predicts patient outcome and this can then be validated in a different set of patients with platinum resistant/recurrent ovarian cancer.

2.0 AIMS

The purpose of this study is to develop a measure of symptom benefit that can be used as an endpoint in clinical trials of palliative chemotherapy.

The aim of stage 1 is to determine the aspects of HRQL that are most troublesome pre-treatment, the changes in scores with treatment for each of these aspects, measures of hope, anxiety and depression and to identify optimal questionnaire(s) for assessing these aspects and changes in them.

The aims of stage 2 are to develop criteria for defining symptom benefit, to determine how many women obtain this benefit, and to investigate prognostic models for benefit, time to progression and survival.

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3.0 OBJECTIVES

Stage 1

Primary Objective

To determine:

1. The aspects of HRQL that are rated most severe and most noticed by patients, and the aspects that are most common

Secondary Objectives

1. The changes in scores for these aspects that occur with treatment
2. The optimal items and questionnaires to measure changes in these aspects
3. Whether these aspects improve with chemotherapy
4. To classify these aspects according to their likelihood of being symptoms due to ovarian cancer or side-effects of its treatment
5. The associations between symptoms, side-effects and aspects of HRQL and anxiety, depression and hope at baseline and longitudinally

Stage 2

Primary Objective

To determine:

1. The criteria for defining a clinically significant subjective improvement and the optimal instrument/s for measuring this benefit

Secondary Objectives

2. The proportion of women benefiting from palliative chemotherapy as defined by the criteria developed above
3. The time to symptom deterioration
4. The proportion of women who receive treatment because they are (a) symptomatic, (b) have rising tumor markers alone, or (c) have imaging evidence of disease progression
5. The percentage of patients who complete 4 or more cycles of treatment
6. The duration of symptom benefit for those who improved
7. The most common, most severe and most noticed symptoms as perceived by patients.
8. To classify these according to their likelihood of being tumor related symptoms or side effects of prior or current therapy
9. How these symptoms change during the treatment period
10. The relationship between objective tumour response, CA 125 response and subjective responses (HRQOL, symptom scores, anxiety, depression)
11. To investigate and develop prognostic models for benefit, time to progression and survival.

4.0 STUDY DESIGN

This is a prospective, observational cohort study conducted in two stages. For the purposes of this study, the term “ovarian cancer” will include epithelial ovarian cancer, primary peritoneal and fallopian tube cancer.

5.0 SUBJECT POPULATION

Stage 1
Women with recurrent platinum resistant or refractory ovarian cancer that are commencing 2nd or subsequent line chemotherapy as well as patients who are receiving > 3 lines of chemotherapy for recurrent ovarian cancer.

Stage 2
Women from collaborating GCIG centers who have platinum resistant/refractory ovarian cancers, according to the definition below, who are about to start 2nd or subsequent line chemotherapy.

A specific definition of platinum resistant/refractory disease has been established for this study:

1. **Primary Platinum Resistant**
   Response to 1st line platinum based therapy with recurrence or disease progression within 6 months of completion of treatment
2. **Primary Platinum Refractory**
   Either a lack of response or disease progression during first line platinum based therapy
3. **Secondary Platinum Resistant**
   Response to 2nd line or more lines of platinum based therapy and disease progression within 6 months of treatment
4. **Secondary Platinum Refractory**
   Initial response to 1st line platinum based therapy but either a lack of response or disease progression whilst receiving 2nd or subsequent line of platinum based therapy

5.1 Inclusion criteria

- Age ≥ 18 years
- Clinical diagnosis of epithelial ovarian, peritoneal or fallopian tube cancers
- Recurrent or progressive disease (CA125, radiological or clinical)
- ECOG PS 0-3
- Life expectancy > 3 months
- Planning to start chemotherapy within 2 weeks of registration
- Able to complete questionnaires independently.

6.0 STUDY METHODS

6.1 Registration

Patients will commence treatment within 2 weeks of registration. Patients can be registered by faxing an enrolment form to the NHMRC Clinical Trials Centre at + 61 (0) 2 95625026

6.2 Treatment

This is not a treatment study. The type, duration and frequency of chemotherapy, biological therapy (targeted therapies) will be at the discretion of the treating physician. All supportive therapies and concomitant medications will be given as per usual local practice.

6.3 Duration of the study

Stage 1
Data will be collected at baseline, prior to every treatment cycle for 4 treatment cycles (12 – 16 weeks) and one month post completion of treatment or until disease progression, *whichever comes first*

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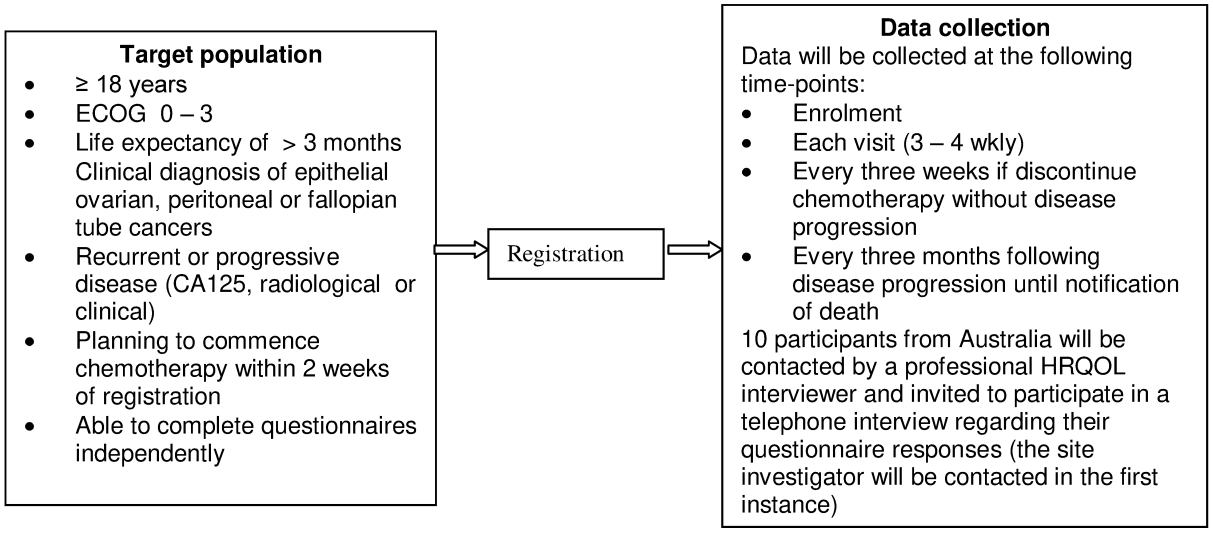
Stage 2
Data will be collected at baseline, prior to every treatment cycle, 3-4 weeks following completion of chemotherapy, and then 3-4 weekly until disease progression*; whichever comes last.*

6.4 Study Schema



7.0 OUTCOME ASSESSMENTS

7.1 Patient Reported Outcomes

Patients in stages 1 and 2 will fill out the following questionnaires at the intervals outlined below. It is estimated that it will take 20 - 30 minutes to complete these questionnaires. The measures selected cover the domains of perceived severity of symptoms, quality of life and hope. The measures are psychometrically sound and have been previously found to be sensitive to change and acceptable to ovarian cancer populations.

Stage 1

QoL Instrument	Baseline (within 2 weeks before first cycle)	Before every subsequent cycle of treatment q3 – 4 weekly	4 weeks after starting 4th cycle of treatment or after end of treatment
SRQ	X	X	X
FACT-O	X	X	X
QLQ-C30 + Ov-28	X	X	X
Pt DATA Form	X	X	X
Expected & perceived benefit	X	X	X
HADS	X		X
Herth Hope Index	X		X

Stage 2

QoL Instrument	Baseline (within 2 weeks before first cycle)	Before every subsequent cycle of treatment or until disease progression – whichever comes last* q 3 – 4 weekly	Before cycle 3 (3-4 weeks after day 1 of cycle 2)
MOST (recent status)	X	X	X
MOST (change)			**X**
FACT-O	X	X	X
EORTC QLQ C30 + Ov-28	X	X	X
Expected Benefit Scale	X	X	X
Perceived Benefit Scale		X	X

*includes those patients who cease study treatment but do not progress and continue with follow-up

MOST (change)

This data will only be collected at Cycle 3 and used to determine the minimal clinically important difference which is the primary aim of the study.

Questionnaires to be completed at each time point:

Baseline:
1. MOST – Recent
2. EORTC QLQC30/OV28
3. FACT-O
4. Expected Benefit Scale

Each Cycle or until progression
1. MOST – Recent
2. EORTC QLQC30/OV28
3. FACT-O
4. Expected & Perceived Benefit Scale

Additional Questions for Cycle 3 only – in addition to 'Each Cycle or until progression' booklet
1. MOST – Change

3 – 4 weeks post last cycle of study treatment
1. MOST – Recent
2. EORTC QLQC30/OV28
3. FACT-O
4. Expected & Perceived Benefit Scale

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Stage 1

Symptom Representation Questionnaire (SRQ) *(26)*
A wide variety of cancer symptom assessment instruments exist but there are limitations to the existing instruments particularly with respect to the study we have in mind. A group in Pittsburgh have recently developed and validated an instrument called the Symptom Representation Questionnaire (SRQ) (12). The SRQ is designed to provide a multi-dimensional assessment of multiple cancer-related symptoms. It was derived from information processing theory and assesses critical cognitive and emotional factors that are known to influence coping and outcomes. It has been validated in women with ovarian cancer. The SRQ is designed to assess the severity of 26 cancer-related symptoms followed by an assessment of five additional important dimensions of a person's three most bothersome symptoms. It appears to be a psychometrically sound and versatile instrument for assessing cognitive and emotional representations of a wide variety of cancer-related symptoms.

Functional Assessment of Cancer Therapy – Ovary (FACT-O) *(27)*
The (Functional Assessment of Cancer Therapy) FACT-G is a self reported measure that assesses four dimensions of well-being: physical, functional, social/family and emotional well-being. An ovarian cancer-specific subscale of the FACT has been developed and can be combined with the FACT-G subscales. Together, these scales are referred to as the FACT-O which consists of 38 items. It has been previously validated and found appropriate as a brief QoL assessment in clinical trials and descriptive studies.

EORTC QLQ-C30 + QLQ-Ov28 *(28)*
The QOL Core Questionnaire 30 (QLQ-C30) was designed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group in 1991. It initially comprised of 36 items, but has undergone multiple revisions with improvements in the scales which has resulted in the present 30 item measure (EORTC QLQ-C30 version 3), now the most widely used measure in oncology. The ovarian cancer module addresses additional important symptoms and concerns not included in QLQ-C30, and like all EORTC modules, is designed to be used in conjunction with the QLQ-C30.

Patient DATA Form *(29)*
This is a validated 47 item instrument rating a range of symptoms, concerns and functions important to people with advanced cancer. The troublesomeness of each symptom is rated on a uniform scale from 0 = "none at all" to 10 = "worst I can imagine"

Expected and Perceived Benefit
At baseline and before starting chemotherapy patients will answer 'How much do you expect your symptoms to improve with chemotherapy?' using a numeric rating scale from 0 = "none at all" to 10 = "completely". At each of their follow up visits, after starting chemotherapy and **prior** to objective assessment of response, patients will answer: "How much have your symptoms improved with chemotherapy?" using the same scale. Finally, if patients indicate an improvement in symptom control, they will be asked to complete one item on a 5 point Likert scale (ranging from not at all to very much so) asking whether their symptom improvement was enough to affect their overall quality of life.

HADS *(30)*
The Hospital and Anxiety Depression Scale is comprised of 14 items in 2 subscales independently measuring anxiety and depression.

Herth Hope Index *(31)*
The Herth Hope Index measures the degree to which a patient feels they feel help and a sense of meaning in their lives. The scale has three subscales: temporality and future, positive readiness and expectancy, and interconnectedness.

Stage 2

The rationale for the measures included in Stage 2 is presented in Appendix 1, which provides a brief report of Stage 1 analyses. In summary, there was little to differentiate the candidate instruments in terms of distributions of baseline or change scores, so the choice of instruments for inclusion in Stage 2 was largely determined by coverage of the symptoms and aspects of QOL as those most noticed by Stage 1 patients.

MOST – Measure of Ovarian Cancer Symptoms and Treatment Concerns

The MOST is an ovarian cancer symptom benefit instrument, devised specifically for this study. It comprises 35 individual items which provide comprehensive coverage of all the symptoms and aspects of QOL identified as those most noticed by Stage 1 patients in this study and corroborated in a cohort of 421 women dying of ovarian cancer. (32). Each item is on a discrete scale of 0-10, where major symptomatic distress is represented by 10. It is an adaptation of the Pt-DATA form based on the results of the Stage 1 analysis. The changes include additions (two additional items: abdominal bloating and abdominal pain) and deletions (items which were deemed irrelevant to this clinical context, and clinical opinion of the investigators).

There are two forms:

1. Recent status
2. Change in status

The recent status form asks patients to report their perceived levels of symptoms and concerns 'on average during the last 3-4 weeks'. It is divided into sections. The first section addresses disease related symptoms and concerns (18 items). The first 15 of these items refer to disease symptoms and have an objective interpretation by patients. Items 16 and 17 refer to physical and emotional well-being whilst item 18 is a question referring to overall well-being. The second section addresses additional treatment related concerns (17 items). This is an adaptation of the Pt-DATA form based on the results of the Stage 1 analysis. The changes include additions (two additional items: abdominal bloating and abdominal pain) and deletions (items which were deemed irrelevant to this clinical context, and clinical opinion of the investigators).

The change form includes the same items as the recent status form, but asks patients to report their perceived change in levels of symptoms and concerns since 'before you started this course of chemotherapy 6-8 weeks ago'. The recent status form will be administered prior to each cycle of chemotherapy, while the change form will be administered only prior to the third cycle of chemotherapy. The change form will be used to help determine the minimum clinically important difference in the status form scores, as has been done previously (33, 34)

Functional Assessment of Cancer Therapy – Ovary (FACT-O)
EORTC QLQ-C30 + QLQ-Ov28

The decision to include both QLQ-C30/OV28 and FACT-O was based on the need to be able to conduct a robust validation of the MOST against the two current leading candidates for measuring ovarian-specific HRQOL.

Expected and Perceived Benefit

At baseline and before starting chemotherapy patients will be asked to answer 'How much do you expect your symptoms to improve with chemotherapy?' using a numeric rating scale from 0 = "none at all" to 10 = "completely". After their 2nd cycle, and after their final cycle of chemotherapy, patients will be asked: "How much have your symptoms improved with chemotherapy?" using the same scale. If patients indicate an improvement in symptom control, they will be asked to answer the question "How much better is your overall quality of life as a result of your symptoms improving?" on a 4-point, ordinal scale (No better, a little better, moderately better, much better). Patients will also be asked to answer "On balance, how worthwhile has this course of chemotherapy been for you" on a 4-point, ordinal scale (not at all, somewhat, moderately, extremely).

7.2 Qualitative Component

A subset of approximately 20 patients from Australia in stage 1 will undertake a telephone interview to ascertain patient opinion about the candidate questionnaires in Stage 1, and to explore how much improvement in QoL is required by patients to make treatment worthwhile. The first 11 interviews were conducted during 2009, and informed the choice of measures for Stage 2 (see Appendix 4). The findings of this qualitative sub-study will also augment other more quantitative approaches to determining the minimum clinically meaningful difference in Stage 2. Further interviews will be conducted, with a slightly modified interview schedule to provide greater insights for the purpose of Stage 2.

7.3 Tumor response assessment

The method of assessing tumor response will be at the discretion of the treating physician and reflects what happens in routine clinical practice. The same method of assessment should be used throughout the study and response must be assessed at a minimum of 6 – 8 week intervals. Tumor response may be assessed clinically, by GCIG criteria for CA125 response or by RECIST criteria as deemed clinically appropriate for the patient.

8.0 END-POINTS

Stage 1

1. Symptoms identified as most noticed
2. HRQOL scores and change in HRQOL as measured by various QOL questionnaires

Stage 2

Primary Endpoint

1. A clinically significant difference as determined by changes in subjective symptoms, objective responses and QoL scores from baseline to post treatment assessment

Secondary Endpoints

1. The proportion of patients experiencing a clinically significant improvement in symptoms
2. Reason for treatment: (a) symptomatic, (b) rising tumor markers alone, or (c) have imaging evidence of disease progression
3. Symptoms rated most severe by patients
4. HRQL scores at baseline, during and after post treatment
5. Causes of major symptoms: ie, predominantly treatment-related, predominantly disease related, or potentially caused by both treatment and disease)
6. Objective tumor response as measured by RECIST or GCIG criteria for CA 125 response
7. Time to symptom deterioration
8. Duration of symptom improvement
9. Time to disease progression
10. Time to death

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size

The sample sizes are 50 - 100 for stage 1 and about 800 for stage 2.

This study is a prospective cohort study thus sample size calculations are based on ensuring estimates of those with clinically significant symptom improvement are within an acceptable margin of error. For this study, the acceptable margin of error has ben arbitrarily set at ± 5% and for a 50% proportion, a sample size of 600 patients with evaluable data after 2 cycles of chemotherapy will produce the 95% confidence interval (46%, 54%), within the acceptable bounds. As the variance of a proportion is largest at 50%, proportions different from 50% will yield 95% confidence intervals narrower than +/- 5%. We expect a total of about 800 patients will need to be recruited to provide 600 patients with evaluable data after 2 cycles of chemotherapy based on the experience of stage 1. Patients will be recruited from several countries and cooperative groups. We aim to recruit approximately 100 patients per country or cooperative group and welcome the participation of countries or groups able recruit 50 patients over 12 months.

The sample size of 600 with complete data for stage 2 will provide over 80% power to detect differences of 10% in the proportions of women benefiting from palliative chemotherapy in dichotomised subgroups (based on a 2:1 ratio of patients in subgroups with improvement rates of 15% vs 25%).

9.2 Statistical analysis

Stage 1

The aim is to determine which are the most common and most noticed symptoms in this population of patients. At each assessment period descriptive statistics will be used to rank the symptoms as in order of severity, 'most noticed' and most common.

Correlation and regression analysis will be used to determine the associations between symptoms, side-effects and aspects of HRQL and anxiety, depression and hope at baseline and longitudinally.

Qualitative analysis: The audio-recorded interviews will be transcribed and coded by two investigators for discrete themes using standard qualitative methods. Differences in coding will be resolved after discussion between coders. A final coding frame will be applied to the data to identify themes and characteristic quotes.

Stage 2

Primary objectives:

Cross-sectional validity of the PRO questionnaires at baseline will be assessed by examining baseline distributions, convergent validity, divergent validity, discriminative validity and predictive validity. A detailed analysis plan including a priori hypotheses will be specified before examining the data.

The individual quality of life and symptom benefit scores will be summarized by standard descriptive statistical measures. The QLQ-C30/OV28 and FACT-O will be scored according to standard scoring algorithms for those instruments. The 35 items of the MOST will be scored as 35 single-item scales. For each symptom and domain covered by the MOST and the QLQ-C30/OV28 and/or FACT-O, comparisons across instruments will provide a robust validation of the MOST against the two current leading candidates for measuring ovarian-specific HRQOL.

The study will develop a global measure of clinically significant symptom improvement by examining changes in symptom items from baseline at each time point and the duration of such changes in an exploratory fashion. Patient views on minimum benefit required in individual items as well as global QoL measures will be used to determine the number of items and the change in those items which constitutes improved symptom benefit. Patient views will be derived from both the qualitative interviews and the MOST Change forms administered pre-cycle 3. The latter

methodology has been used previously to determine the minimum clinically important difference in similar contexts (30, 31). The general approach for assessing improvements will be to calculate absolute changes from baseline. Various criterion levels (e.g. 1, 1.5 and 2 points on a 10 point scale) and durations (e.g. 3 and 6 weeks) or improvement will be assessed to determine a criterioun that is both sensitive (avoids false negatives – missing true benefit) and robust (avoids false positives). Relative changes from baseline will also be examined (e.g. 50% reduction from the baseline score). This approach will be applied primarily to individual symptoms, but also to domain subscales (e.g. physical wellbeing, emotional wellbeing) and total scores (e.g. FACT-G overall wellbeing). It is anticipated that benefits will be much more evident in individual symptoms than in domain subscales or total scores.

Since the MOST has been constructed as a comprehensive measure of all the relevant symptoms for this patient population, a *global symptom benefit* measure will also be examined which combines the first 17 items of MOST and constructs a weighted average of these and item 18 (details of this methodology are provided in Lumley et al (Statistics in Medicine 2000)).

Secondary objectives:

To evaluate the proportion of women benefiting from palliative chemotherapy as defined by a clinically significant improvement in HRQL scores, the relationship between changes in perceived symptoms, HRQOL, anxiety and depression and objective tumour response.

Each patient's subjective responses will be categorized as having improved, worsened or remained stable in comparison to baseline according to the criteria defined above.

Best objective tumor response will be categorized as complete or partial response, stable disease, or progressive disease using RECIST and GCIG definitions of response. 3x3 tables of subjective response versus tumour response will be presented.

Subjective response will be further categorised dichotomously as improved or not by combining the stable and worsened groups. To assess the relationship between improvement in subjective responses and improvements in tumour response, 3x2 tables of subjective response versus tumour response will be analysed using a test for trend.

Time to event endpoints will be analysed using the Kaplan-Meier method.

Multivariable prognostic risk models of time-to-event endpoints will be developed using proportional hazards regression, and patients will be classified as low, medium or high risk.

For all other endpoints, summary statistics will be presented (counts and percentages for categorical outcomes and descriptive statistics for continuous outcomes)

A statistical analysis plan with further details of the analyses will be completed and agreed upon prior to the final data analysis.

10.0 SUBJECT FOLLOW-UP

Participation in this study is voluntary; subjects may withdraw at any time. Patients will provide written informed consent to permit access to their health information.

10.1 Maintaining Follow Up and Withdrawal of Patients

In consenting to participate in the study, patients agree to register and attend for all study assessments and data collection. If a patient wishes to withdraw from the study, site staff should explain the importance of maintaining follow-up information on other outcomes. In this case, sites should ask patients permission to have their medical records reviewed for the purposes of following up their progress.

If the patient explicitly states their wish not to contribute further data to the study (i.e. withdraw their consent to all aspects of the study), the ANZGOG Coordinating Centre should be informed.

11.0 STUDY STRUCTURE

The study is co-ordinated by the NHMRC Clinical Trials Centre, University of Sydney in collaboration with the Australian New Zealand Gynaecological Oncology Group (ANZGOG) and Psycho-Oncology Cooperative Research Group (PoCoG) as well as with collaborating investigators from other GCIG groups. A Trial Management Committee (TMC) will be set up. A Trial Executive Committee may be selected from the TMC in order to expedite decision-making and will be led by the Study Chair.

The TMC will meet regularly during start-up phase, quarterly to 6-monthly thereafter. Face-to-face meetings will occur as permitted by the study budget, preferably at least annually for the TMC.

The TMC responsibilities include protocol development, study planning, monitoring and progress, review of information from related research and implementation of recommendations from other study committees and external bodies (e.g. HRECs).

In addition, the TMC has responsibilities to hospital sites in taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the Study Chair is to help the investigators maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

12.0 ETHICS AND REGULATORY COMPLIANCE

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Therapeutic Goods Administration DSEB July 2000), the interim New Zealand GCR Guidelines and in compliance with applicable laws and regulations within countries. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004. The investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the CTC, principal investigator and HREC must be advised immediately.

12.1 Institutional Human Research Ethics Committees (HRECs)

The protocol, patient information sheet (PIS) and informed consent form (ICF) must be approved by a Human Research Ethics Committee in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

A copy of the written approval/advice must be sent to the ANZGOG Coordinating Centre, which should outline the documents approved (protocol, patient information sheet and informed consent form) and the date of approval. A copy of the approved patient information sheet and informed consent should also be sent to the ANZGOG Coordinating Centre.

If there are any version changes to the patient information sheet or informed consent forms, these must be submitted to the ANZGOG Coordinating Centre for review PRIOR to use.

12.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC Clinical Trials Centre, University of Sydney and will only be available to staff directly involved with the study.

Personal data identifying trial subjects will be held securely at the sites according to local institutional requirements for the purpose of follow up after the conclusion of the protocol-specified period. Sites may be asked to submit copies of source documents to CTC e.g. radiology reports,

however, all reports must be de-identified prior to sending, with only patient trial number and initials detailed. The sites will be asked to provide follow up status of the subject (alive or dead).

12.3 Protocol amendments

Changes and amendments to the protocol can only be made by the TMC. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the CRFs, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

12.4 Data handling and record keeping

Trial data will be recorded on the CRFs provided. All required data entry fields will be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

a. Subject's name, contact information and protocol identification.
b. The date that the subject entered the study, and subject number.
c. A statement that informed consent was obtained (including the date).
d. Relevant medical history
e. Dates of all subject visits and results of key trial parameters.
f. The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.

The data management of all case report forms will be managed centrally at the Clinical Trials Centre. Submission rates and timing of assessment as stipulated in the protocol will be monitored by the CTC. On a regular basis hospital sites will receive feedback on their submission rates and other specific problems pertaining to that hospital site.

All study-related documentation will be maintained for 15 years following completion of the study.

12.5 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (CTC). Monitoring will include centralized review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during for source data verification, review of the investigator's site file and drug handling records. The CTC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorized CTC staff direct access to their medical records and the study data.

13.0 PUBLICATION POLICY

The TMC will appoint a Writing Committee to draft manuscripts based on the trial data. Manuscripts will be submitted to peer-reviewed journal(s). The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. This plan will be consistent with ANZGOG and GCIG guidelines.

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15.0 LIST OF APPENDICES

Appendix 1 Patient Assessment Schedule

Appendix 2 QoL Questionnaires

Measure of Ovarian Cancer Symptoms and Treatment (MOST) – Recent
Measure of Ovarian Cancer Symptoms and Treatment (MOST) – Change
EORTC QLQ – C30
EORTC OV28
FACT-O
Expected Benefit Scale
Perceived Benefit Scale

Appendix 3 Brief report on Stage 1 analysis

Aims, methods, results and rationale for choice of patient reported outcome measures (PRO) for Stage 2

The University of Sydney

NHMRC Clinical Trials Centre

Appendix 1 Patient Assessment Schedule

Tests & Observations	Registration Baseline	Pre-each cycle of treatment until progression	Pre-cycle 3[1]	Every 6-8 weeks until progression/off study	3 – 4 weeks post last cycle of study treatment	3 monthly following progression[2]
Informed Consent	X					
History	X					
Physical Exam	X	X				
Performance Status (ECOG)	X					X
FIGO stage at initial diagnosis	X					
Life expectancy > 3 months	X					
Type of resistance: (see NOTES) 1. Primary Platinum Resistant 2. Primary Platinum Refractory 3. Secondary Platinum Resistant 4.Secondary Platinum Refractory	X					
Height and weight	X					
Estimated weight 3/12 ago	X					
Date cancer 1st diagnosed	X					
Debulking at initial diagnosis? If yes, status[3]	X					
Secondry debulking surgery for recurrence?	X					
No. of lines of previous treatment for OC	X					
Response to most recent line of therapy[4]	X					
Date of completion of last line of therapy	X					
Date chemotherapy planned to commence	X					
Regimen – drug name, dose, frequency	X					
Reasons for proposed treatment[5]	X					
Investigator Questions: Predicted likelihood of objective response, symptom improvement, how many cycles of treatment do you expect to administer, life expectancy in months **(this information must be obtained from the investigator)**	X					
Symptoms						
Cancer related symptoms	X					
Symptomatic ascites	X					
Symptoms of cramping abdominal pain or intermittent/incomplete bowel obstruction?	X					

Tests & Observations	Registration Baseline	Pre-each cycle of treatment	Pre-cycle 3	Every 6-8 weeks until progression/off study	3 – 4 weeks post last cycle of study treatment	3 monthly following progression[2]
Tumour Related						
Pathology[6]	X					
Grade at initial diagnosis[7]	X					
Extent of disease[8]	X					
Sites of disease[9]	X					
Pre-Treatment Blood Tests **please note these may not all be *routine* for your site**						
Absolute Neutrophil Count (ANC)	X					
Platelets	X					
Lymphocytes	X					
Haemoglobin	X					
Serum Albumin	X					
Alkaline Phosphotase	X					
C Reactive Protein	X					
LDH (lactate dehydrogenase)	X					
CA-125	X			X[10]		
CA-125 Velocity[11]	X					
Toxicities						
Toxicity Data[12]	X					
Adverse Events[13]		X				
Tumour Response						
Tumour Response Assessment[14]				X		
Response[15]				X		
Method of Assessment[16]				X		
Response[17]				X		
Symptom benefit or deterioration[18]				X		
Follow-up						
Patient status[19]						X
Has the patient progressed?[20]						X
Reason for ceasing treatment[21]						X
Current treatment[22]						X
Death notification[23]	*Please complete at notification of patient death*					
QoL Questionnaires						
Baseline Booklet[24]	X					
Each cycle of treatment booklet[25]		X				
Cycle 3 additional questions booklet[26]			X			
Post last cycle of study treatment booklet[27]					X	

NOTES:

[1] Additional questions at Cycle 3. To be completed by the patient in addition to the "Each cycle of treatment" booklet
[2] **OR:** every three weeks until progression for those who have ceased study treatment but not progressed, and then three monthly after progression
[3] Status = No residual disease, Residual disease <1cm, Residual disease >1cm, Not applicable, Unknown
[4] Response = CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease), NE (not evaluable)
[5] Reasons = Symptom control/palliation, if asymptomatic, to delay the development of symptoms, Rising CA125, Radiological evidence of progression
[6] Serous, endometrioid, clear cell, mucinous, transitional, undifferentiated, mixed – please specify, other – please specify
[7] Low Grade or Hi Grade (includes 2 and 3)
[8] Elevated CA125 or measurable disease. If measurable disease, please indicate maximum diameter of largest tumour
[9] Intra-peritoneal tumour, Nodal, Liver/spleen, Lung, Other
[10] CA125 at 6 – 8 weekly only if using CA125 as the Method of Assessment – actual value is not required
[11] Include 3 most recent CA-125 levels in the three months prior to commencing chemotherapy with dates
[12] Symptoms/pre-existing toxicities present at study enrolment
[13] Adverse Events from treatment
[14] Complete the Tumour Response Assessment at 6 – 8 weekly intervals ie. after every second cycle of chemotherapy using CA125, clinical or radiological assessment criteria
[15] Has there been a response since the last assessment?
[16] What was the method of assessment? CA125, clinical assessment, radiological assessment (RECIST). The method of assessment is at the physician's discretion
[17] What was the response? CA125, Clinical response, Radiological response (according to RECIST criteria)
[18] Has there been any symptom benefit or symptom deterioration?
[19] Is the patient alive or dead?
[20] If the patient is alive, has she progressed?
[21] Please list the reason for ceasing treatment ie. completed planned no. of cycles, AE, Tumour progression, clinician preference, patient preference, death, other
[22] Is the patient currently receiving treatment? If yes, please select type of treatment and indicate what line this treatment will be
[23] Please complete the Death Form at notification of death
[24] Baseline is equivalent to pre-Cycle 1
[25] From pre-Cycle 2 onwards. Baseline is equivalent to pre-Cycle 1
[26] Additional questions at Cycle 3 only. Please ensure the patient completes the each cycle of treatment booklet in addition to these additional questions
[27] QoL questionnaires to be completed 3 – 4 weeks post last cycle of study treatment. This is the same booklet as each cycle of treatment booklet

The University of Sydney

NHMRC Clinical Trials Centre

Appendix 2 QoL Questionnaires

Appendix 3 Stage 1 analysis

Brief report on Stage 1 Analysis. (prepared by Madeleine King and Martin Stockler. December 2009)

Rationale for choice of patient reported outcome measures (PRO) for Stage 2

Background: Four questionnaires relating to symptoms and health-related quality of life (QOL) were used in Stage 1: Symptom Representation Questionnaire (SRQ, 66 items), Patient Disease & Treatment Assessment (Pt-DATA Form, 48 items) Functional Assessment of Cancer Therapy Ovarian (FACT-O, 39 items including 8 items of which comprise the FACT Ovarian Symptom Index), EORTC's Quality of Life Questionnaire Core plus ovarian module (QLQ-C30 and QLQ-Ov28, 58 items).

The SRQ and the Pt-DATA Form are both designed to measure clinically important symptoms and other aspects of quality of life (QOL), they have similar layouts, both have item response scales that range from 0 to 10, and both are based on single-item scoring rather than multi-item or domain-based scoring. The QLQ-C30/Ov28 and FACT-O are both designed to measure QOL in cancer clinical trials. They have a similar format and layout, similar response scale, and multi-item domains & scoring, although the QLQ-C30 includes some single items.

There is considerable overlap in terms of the type of symptoms and aspects of QOL covered between these candidate questionnaires, and therefore there is arguably some substitutability. The booklet was deliberately long and repetitive to corroborate findings and help determine the best subset of questionnaires and items for Stage 2.

Aim: to determine which PRO questionnaires to retain for Stage 2

Sample: The 31 patients who were recruited and had completed QOL questionnaires at baseline (before cycle 1) and before cycles 2 and/or 3 by July 2009. Qualitative interviews were conducted with 11 of these patients.

Methods: The prevalence at baseline (pre-cycle 1) of each symptom nominated by women as one of the 'three most noticed symptoms in the last week' (as asked by SRQ) was determined. Summary statistics and frequency distributions were calculated for items and domain scores for each symptom at baseline, and changes in item and domain scores from baseline (before cycle 1) to before cycle 2 and before cycle 3. For each symptom and aspect of QOL, similar items were identified across the candidate questionnaires, and the distributions and summary statistics for both baseline and change scores were compared.

Results: The symptoms most commonly reported as among the 'three most noticed symptoms in the last week' at baseline are listed in rank order in Table 1, and the coverage of these by the questionnaires is given in Table 2. There were no major ceiling or floor effects on any items. The distributions for similar items were similar, both in terms of location and spread. Mean change scores were typically close to zero, with large standard deviations reflecting, improvements in some women and deteriorations in others. For similar items and domains, results were comparable across candidate questionnaires. Interviews with 11 patients indicated that they neither preferred nor disliked any particular questionnaires.

Table 1: The symptoms most commonly reported as among the 'three most noticed symptoms in the last week' at baseline (number and proportion of patients, n=31)

Symptom	**Number**	**Proportion**
Fatigue	17	0.55
Pain – General	11	0.35
Abdominal bloating	10	0.32
Sleep Disturbance	9	0.29
Nausea and vomiting	8	0.26
Appetite	7	0.23
Shortness of breath	6	0.19
Bowel disturbances (including constipation)	6	0.19
Pain – abdominal	5	0.16
Numbness/tingling/ discomfort	3	0.10
Hot flashes	3	0.10
Urinary problems	3	0.10
Emotional problems (including depression)	3	0.10

Table 2: Coverage of the most prevalent symptoms by candidate questionnaires

Symptom	**SRQ**	**Pt-DATA**	**FACT-O**	**FOSI**	**QLQ-C30**	**QLQ-OV28**
Fatigue	2	2	1	1	3	-
Pain - General	1	1	1	1	2	-
Abdominal bloating	1	-	1	1	-	1
Sleep disturbance	1	1	1	-	1	-
Nausea & vomiting	2	2	2	2	2	-
Appetite	1	2	1	-	1	1
Shortness of breath	1	1	-	-	1	-
Bowel disturbances	1	2	1	-	2	3
Pain - abdominal	-	-	1	1	-	1
Numbness/tingling/ discomfort	1	1	-	-	-	2
Urinary problems	1	1	-	-	-	1
Emotional problems	1	4	1	1	4	1
Global QOL	-	1	1	1	2	-

Outcome of Stage 1: finalizing questionnaires for Stage 2

Since there was little to differentiate the candidate instruments in terms of distributions of scores, the choice of instruments for inclusion in Stage 2 was largely determined by coverage of the relevant symptoms. It was decided to retain the Pt-DATA form, the QLQ-C30, QLQ-Ov28 and FACT-O. The deciding factor in favour of the Pt-DATA form over the SRQ was that the Pt-DATA form was developed by one of the investigators, A/Prof Martin Stockler and colleagues at the NHMRC Clinical Trials Centre, and it was therefore feasible to adapt it to maximise coverage of the relevant symptoms in one questionnaire for use in future studies beyond Stage 2.. To achieve this, it was decided to add an item on abdominal bloating and another on abdominal pain to the Pt-DATA form to ensure complete coverage of all of the symptoms commonly reported as among the 'three most noticed symptoms in the last week', and to include both 'current status' and 'change' versions to capture both of these aspects of symptoms. The decision to retain both QLQ-C30/OV28 and FACT-O was to allow validation of the modified Pt-DATA forms again the two current standards for assessment of QOL in ovarian cancer, to provide a definitive comparison of the measurement properties of these two QOL measures and the FOSI in this patient population.

The final version of the adapted Pt-DATA form to be used in Stage 2 has been named the **Measure of Ovarian Cancer Symptoms and Treatment Concerns (MOST).**

It contains 35 individual items on a discrete scale of 0-10, where major symptomatic distress is represented by 10. It is an adaptation of the Pt-DATA form based on the results of the Stage 1 analysis. The changes include additions (two additional items: abdominal bloating and abdominal pain) and deletions (items which were deemed irrelevant to this clinical context and clinical opinion of the investigators).

It contains two forms:

1) The recent status form asks patients to report their perceived levels of symptoms and concerns 'on average during the last 3-4 weeks'. It is divided into sections. The first section addresses disease related symptoms and concerns (18 items). The first 15 items refer to disease symptoms and have an objective interpretation by patients. Items 16 and 17 refer to physical and emotional well-being whilst item 18 is a question referring to overall well-being. The second section addresses additional treatment related concerns (17 items).

2) The change form contains the same items as the recent status form, but asks patients to report their perceived change in levels of symptoms and concerns since 'before you started this course of chemotherapy 6-8 weeks ago'. The recent status form will be administered prior to each cycle of chemotherapy, while the change form will be administered only prior to the third cycle of chemotherapy. The change form will be used to help determine the minimum clinically important difference in the status form scores, as has been done previously (33, 34)