An update of a rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced ovarian cancer

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CONFLICTS OF INTEREST

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The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme. Any errors are the responsibility of the authors.

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EXECUTIVE SUMMARY

1 RESEARCH QUESTION

The aim of this systematic review is to update the previous systematic review by bringing together the most recent reliable data to elucidate the following area of uncertainty: the use of paclitaxel (Taxol ®) as first-line treatment of ovarian cancer.

2 METHODS

This systematic review was conducted in accordance with the NHS Centre for Reviews and Dissemination's Guidelines for Conducting Systematic Reviews. All randomised controlled trials and full economic evaluations on the effectiveness of paclitaxel as first-line treatment for ovarian cancer were considered. The main outcomes were response rates, progression free survival, overall survival, quality of life and cost effectiveness.

3 THE BODY OF EVIDENCE

The original searches identified 2250 articles related to the taxanes. After independent assessment against the inclusion criteria by two reviewers, it was agreed that 213 references were to be obtained.

The update searches identified a further 1290 articles related to the taxanes. After independent assessment against the inclusion criteria by two reviewers, 80 additional references were obtained.

On examination of the obtained papers and reports, seven RCTs (including 4108 participants) and 15 economic evaluations were selected for review (includes both original and update searches).

4 RESULTS

There was considerable heterogeneity in the populations investigated, intervention and control regimens, and outcomes assessed. Some studies were available only as conference abstracts and overheads, limiting the amount of information that could be abstracted and the assessment of validity.

First-line treatment of ovarian cancer.

New data

Three new randomised controlled trials were identified: Simsek, Wolf and Gennatas, and three updates of trials reported in the original review: GOG111, OV10 and ICON3. A total of 3237 patients were included. ICON3 and Wolf evaluated the effectiveness of paclitaxel combined with carboplatin; the others evaluated a paclitaxel/cisplatin combination.

There were two new economic analyses, both based on OV10, and an update of a confidential economic analysis included in the original report.

Data from original report

Four randomised, controlled Phase III trials were identified: GOG 111, GOG 132, OV10 and ICON3. A total of 3770 patients were included. ICON3 evaluated the effectiveness of paclitaxel combined with carboplatin; the others evaluated a paclitaxel/cisplatin combination.

There were thirteen economic analyses.

Summary

Seven randomised controlled Phase III trials were included with 4108 participants: OV10, ICON3, GOG 111, GOG 132, Simsek, Wolf and Gennatas. ICON3 and Wolf evaluated the effectiveness of paclitaxel combined with carboplatin; the others evaluated a paclitaxel/cisplatin combination.
There were fifteen economic analyses.

Quality of studies
New data
The two larger studies (OV10 and ICON3) were deemed to be of good quality. A full report of GOG111 was included in the original report and the trial was deemed to be of good quality. The validity of the other three studies (Simsek, Wolf and Gennatas) was impossible to assess, due to a lack of details being reported. Simsek was published in Turkish language and Gennatas and Wolf were only available as conference abstracts, with many details missing. Gennatas was an interim report.

Data from original report
All the data from these studies were analysed on an intention to treat basis. The median length of follow-up ranged from 34 months (ICON3) to 6.5 years (GOG 111). The analysis of GOG 111 involved the censoring of patients who had started alternate treatment before progression was documented. In the economic analyses, estimation of benefits was based on a direct clinical comparison in only eight out of thirteen studies.

Median progression free survival
New data
Patients in the OV10 trial had a significantly greater median progression free survival than controls (15.3 months versus 11.5 months, p=0.0005, Hazard ratio 0.71 (95% CI: 0.58, 0.87)). ICON3 found no significant differences between groups (17.1 months versus 16.1 months, p=0.24, hazard ratio 0.94 (95% CI: 0.84, 1.05)).

Data from original report
The median progression free survival in the paclitaxel/platinum arm was 14.1 months in GOG 132 and 16.6 months in GOG 111. Patients in the GOG 111 trial had significantly greater median progression free survivals than controls (16.6 months versus 13 months, logrank p = 0.016). There was a difference in progression free survival in favour of the control arm in GOG 132 (14.1 months versus 16.4 months) but tests for statistical significance were not presented.

Summary
The median progression free survival in the paclitaxel/platinum arm was 14.1 months in GOG 132, 16.6 months in GOG 111, 15.3 months in OV10 and 17.1 months in ICON3. Patients in the GOG 111 and OV10 trials had significantly greater median progression free survivals than controls (16.6 months versus 13 months, logrank p = 0.016; 15.3 months versus 11.5 months, logrank p = 0.0005). ICON3 found no significant differences between groups (17.1 months versus 16.1 months, p=0.24).

Median overall survival
New data
Patients in the OV10 trial had significantly greater median overall survival than controls (35.6 months versus 25.8 months, p=0.0016, Hazard ratio 0.73, 95% CI: 0.60, 0.89)). The

short update report of GOG 111 reported a hazard ratio at 3 years follow-up of 0.70 (95% CI: 0.57, 0.87) in favour of the paclitaxel containing regimen. ICON3 found no significant differences between groups (37.6 months versus 36.1 months, p=0.53).

Data from original report
The median length of overall survival in the paclitaxel/platinum arm was 26.6 months in GOG 132, 35.7 months in GOG 111 and 35 months in OV10. Patients in the GOG 111 and OV10 trials had significantly greater median overall survivals than controls (35.7 months versus 24.2 months, logrank p not stated; 35 months versus 25 months, logrank p = 0.001).

Summary
The median length of overall survival in the paclitaxel/platinum arm was 26.6 months in GOG 132, 35.6 months in OV10, 35.7 months in GOG 111 and 37.6 months in ICON3. Patients in the GOG 111 and OV10 trials had significantly greater median overall survivals than controls (35.7 months versus 24.2 months, logrank p not stated; 35.6 months versus 25.8 months, p=0.0016). At 3 year follow-up GOG 111 reported a hazard ratio of 0.70 (95% CI: 0.57, 0.87) in favour of the paclitaxel containing arm. ICON3 found no significant differences between groups (37.6 months versus 36.1 months, p=0.53).

Side effects and quality of life
New data
Only ICON3 reported on any aspects of quality of life. Anxiety and depression were measured and no significant differences were found between the paclitaxel and control arms.

Regarding side effects, ICON3 reported significantly less haematological toxicity in the paclitaxel than carboplatin arm. Paclitaxel/ cisplatin was associated with significantly more fever, alopecia, neurosensory and neuromotor events than single agent carboplatin, and significantly more flushing, myalgia, neurosensory and neuromotor events, alopecia and severe hypersensitivity reactions than combined cisplatin control treatment. Combined cisplatin control was associated with significantly more haematological toxicities and nausea and vomiting than paclitaxel/ cisplatin. Wolf reported more alopecia and neurotoxicity in the paclitaxel/ carboplatin arm and more haematological problems in the control arm.

Data from original report
Quality of life was not evaluated as such but performance status was assessed in GOG 111. There was no significant difference in the number of patients having lower performance status scores during the study compared with control. Also in GOG 111, a significantly greater incidence of neutropenia, cardiovascular adverse events, hypersensitivity and allergic reactions were seen in the paclitaxel than control arm despite premedications.

Summary
No significant differences were found between paclitaxel and control arms for any measures of quality of life reported in GOG 111 and ICON3, however ICON3 reported significantly less haematological toxicity in the paclitaxel than the control arm. Non-haematological toxicities were significantly increased in the paclitaxel arms compared to the control arms.

Economic analysis

New data

Both new economic evaluations were cost effectiveness analyses based on OV10. One study reported cost per life year gained as US$13,315 and cost per progression free life year gained as US$21,321. The other reported incremental cost effectiveness per life year gained as ranging from US$9103 to US$23,234. Both found paclitaxel/ cisplatin to be more costly and more effective than control treatment (matrix score 'A').

An update of a confidential economic evaluation from the original report was submitted by the manufacturer.

Data from original report
Nine were cost effectiveness and three were cost utility analyses. The range of incremental costs per life year gained (£7,173 to £12,417) found in three UK studies is within the range reported for all studies comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin (£3,960 to £13,360). The three UK studies used carboplatin rather than cisplatin in their analyses. In the cost utility analyses the range of cost per quality adjusted life years gained was £5273 to £11,269. All found paclitaxel / cisplatin to be more costly and more effective than control treatments (matrix score 'A').

Summary
Cost-effectiveness of paclitaxel was found to be acceptable in all included economic evaluations, however most based effectiveness data on the treatments given in OV10. None based effectiveness data on the results of GOG 132 or ICON3, which showed no difference in effectiveness between paclitaxel and control treatments. If the true effectiveness of paclitaxel is not significantly better than control treatments (as indicated by GOG 132 and ICON3 and as suggested in this review) these economic evaluations are invalid and in fact the confidence interval for cost per QALY would include infinity, making paclitaxel much less cost-effective than control treatments.

5 CONCLUSIONS

First-line treatment of advanced ovarian cancer
Paclitaxel is licensed and recommended for use as first-line treatment for ovarian cancer. The best available evidence casts doubt on use of paclitaxel in combination with platinum as first-line treatment of ovarian cancer: although two small trials show significant improvement in overall survival, a much larger trial and one other RCT show no significant differences between paclitaxel and control arms.
If the treatment were effective the cost-effectiveness ratios would be potentially acceptable, however if the treatment is no more effective than control the use of taxanes for first-line treatment of ovarian cancer is not cost-effective and should be discouraged.
Serious consideration should be given to the use of carboplatin as a first-line treatment for advanced ovarian cancer rather than a taxane, given the high cost and adverse effect profile of paclitaxel.
It has been suggested that paclitaxel may be more effective in people with bulky disease, although this is not supported by subgroup analysis in ICON3, however it may be worth conducting a further RCT of paclitaxel/ carboplatin versus single agent carboplatin in these people if this view is widely held.

This review is based on currently available evidence. The evidence does not appear to support the use of paclitaxel as first-line therapy for advanced ovarian cancer, and may provide a case for considering the use of carboplatin as first-line treatment for advanced ovarian cancer, rather than taxanes.

LIST OF ABBREVIATIONS

BNF	British National Formulary
CBA	Cost benefit analysis
CCA	Cost consequence analysis
CEA	Cost effectiveness analysis
CER	Cost-effectiveness Ratio
CI	Confidence interval
CMA	Cost minimisation analysis
CUA	Cost utility analysis
CMF	The combination of cyclophosphamide, methotrexate and 5-fluorouracil
CR	Complete response
CREC	Cardiac review and evaluation committee
DRG	Diagnosis Related Group
EORTC	European Organisation for Research and Treatment of Cancer
HRG	Health Related Group
HRQL	Health related quality of life
IHC	Immunohistochemistry
ITT	Intention to treat (analysis)
KPS	Karnofsky Performance Scale
LYG	Life years gained
MD	Mean difference
OR	Overall or objective response
PFLYG	Progression-free life years gained
PR	Partial response
QOL	Quality of life
QALY	Quality Adjusted Life Years
RCT	Randomised controlled trial
REC	Response evaluation committee
RR	Relative risk
UKCCCR	United Kingdom Co-ordinating Committee on Cancer Research. The national committee responsible for co-ordinating clinical trials for cancer treatment in the UK.
WHO	World Health Organisation

DEFINITIONS OF TERMS

Absolute risk reduction The decreased chance of having an outcome from the treatment compared to the comparator, or the increased chance of not having an outcome from the comparator compared to the treatment. In oncology, this can be considered as, for instance, the reduction of the risk of not responding to treatment.

Adjuvant treatment This usually refers to systemic chemotherapy or hormonal treatment or both, taken by patients after removal of a primary tumour (in this case, surgery for early breast cancer), with the aim of killing any remaining micrometastatic tumour cells and thus preventing recurrence.

Advanced disease Locally advanced (stage III) and metastatic (stage IV) disease.

Anthracycline refractory Never responded to anthracycline therapy.

Anthracycline resistant Patients, who, at some point in their therapy have stopped responding to anthracyclines.

Arthralgia Pain in the joints or in a single joint.

Ascites An accumulation of fluid in the abdominal (peritoneal) cavity.

Carcinoma A cancerous growth.

Chemotherapy The use of drugs that kill cancer cells, or prevent or slow their growth.

Clinical Oncologist A doctor who specialises in the treatment of cancer patients, particularly through the use of *radiotherapy*, but who may also use *chemotherapy*.

Combination chemotherapy regimens The use of more than one drug to kill cancer cells.
Classical CMF Cyclophosphamide (100mg/m^2 orally days 1-14), methotrexate (40mg/m^2 intravenously (iv) day 1 + 8), and 5-fluorouracil (600mg/m^2 iv day 1 + 8), every 4 weeks for up to six cycles of treatment given dependent on response.
CAF Cyclophosphamide (500mg/m^2 iv), doxorubicin (50mg/m^2iv), and 5-fluorouracil (500mg/m^2 iv), every 3 weeks for up to six cycles of treatment given dependent on response.
FEC 5-flurouracil, epirubicin, and cyclophosphamide every 3 weeks for up to six cycles of treatment given dependency on response.
FAC 5-flurouracil, doxorubicin, and cyclophosphamide every 3 weeks for up to six cycles of treatment given dependency on response.

Complete response Total disappearance of all detectable malignant disease for at least 4 weeks (must state measurement device/ technology).

Cost-utility analysis Analysis in which the additional cost per Quality Adjusted Life Year (QALY) saved or gained is estimated.

Cycle Chemotherapy is usually administered at regular (normally monthly) intervals. A cycle is a course of chemotherapy followed by a period in which the patient's body recovers.

Cytology The trial of the appearance of individual cells under a microscope.

Cytotoxic Toxic to cells. This term is used to describe drugs which kill cancer cells or slow their growth.

Debulking Removal by surgery of a substantial proportion of cancer tissue. Optimal debulking refers to the removal of the largest possible amount of cancer while limiting damage to normal tissue; interval debulking refers to surgical removal of tumour after *chemotherapy* aimed at further reducing its bulk.

Differentiation The degree of morphological resemblance between cancer tissue and the tissue from which the cancer developed.

Disease free interval Time between surgery for early breast cancer and developing metastatic breast cancer. Clinical Evidence (Issue 3, June 2000)

Early breast cancer Operable disease (stage I or II), restricted to the breast and sometimes to local lymph nodes. Clinical Evidence (Issue 3, June 2000)

First-line treatment Initial treatment for a particular condition that has previously not been treated. For example, first-line treatment for metastatic breast cancer may include chemotherapy or hormonal therapy, or both. (Clinical Evidence (Issue 3, June 2000)). Used in advanced disease where the treatment intent may be curative (e.g. in some cases of locally advanced disease) but is usually palliative. The main treatment modality is systemic therapy.

Heterogeneous Of differing origins, or different types.

Histological grade Degree of malignancy of a tumour, usually judged from its histological features.

Histological type The type of tissue found in a tumour.

Histology An examination of the cellular characteristics of a tissue.

Incremental cost effectiveness analysis Estimates of the additional cost per specific clinical outcome.

Locally advanced disease (breast) Disease which has infiltrated the skin or chest wall or disease which has involved axillary nodes.

Localised disease Disease which is confined to a small part of an organ.

Lymph nodes Small organs which act as filters in the lymphatic system for white cells/ immune cells. Lymph nodes close to the primary tumour are often the first sites to which cancer spreads.

Marginal or minor response Less than 50% but greater than 25% tumour regression for all measurable tumours for at least 4 weeks with no new lesions appearing (measurement technique must be stated).

Measurable lesion Lesion which can be unidimensionally or bidimensionally measured by physical examination, echography, x-rays or CT scan.

Medical Oncologist Doctor who specialises in the treatment of cancer through the use of *chemotherapy*.

Meta-analysis The statistical analysis of the results of a collection of individual trials to synthesise their findings.

Metastatic or advanced breast cancer The presence of disease at distant sites such as the bone, liver, or lung. It is not treatable by primary surgery and is currently considered incurable. Symptoms may include pain from bone metastases, breathlessness from spread to the lung, and nausea or abdominal discomfort from liver involvement (Clinical Evidence (Issue 3, June 2000))

Myalgia Muscle pain.

Neo-adjuvant treatment Treatment given before the main treatment; usually *chemotherapy* or *radiotherapy* given before surgery.

Non-measurable lesion A lesion for which no exact measurements could be obtained e.g. pleural effusions, ascites.

Objective or Overall response A complete or *partial response*.

Oestrogen receptor (ER) A protein on breast cancer cells that binds oestrogens. It indicates that the tumour may respond to hormonal therapies. Patients with tumours rich in oestrogen receptors have a better prognosis than those with tumours which are not.

Palliative Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it. Hence palliative care, palliative *chemotherapy*.

Partial response At least 50% decrease in tumour size for >4 weeks without an increase in the size of any area of known malignant disease or the appearance of new lesions (definitions vary between trials – technique used for measurement must be stated).

Primary anthracycline resistance Failure to respond to a first or second-line anthracycline (disease progression) or relapse.

Progressive disease The tumour continues to grow or the patient develops more metastatic sites.

Prophylaxis An intervention used to prevent an unwanted outcome.

Protocol A policy or strategy which defines appropriate action.

Quality Adjusted Life Years Index of survival that is weighted or adjusted by the patient's quality of life during the survival period.

Quality of Life The individual's overall appraisal of her situation and subjective sense of well-being.

Radiotherapy The use of radiation, usually X-rays or gamma rays, to kill tumour cells.

Recurrence/disease free survival Time from the primary treatment of the breast cancer to the first evidence of cancer recurrence.

Remission A period when cancer has responded to treatment and there are no signs of tumour or tumour-related symptoms.

Secondary anthracycline resistance Disease progression after initial objective response to first or second-line therapy or disease progression during treatment with an anthracycline.

Second-line or salvage chemotherapy Used in advanced (usually metastatic disease) following relapse or failure following first-line chemotherapy. The main intervention is systemic treatment with the intent to palliate.

Stable disease No change or less than 25% change in measurable lesions for at least 4 to 8 weeks with no new lesions appearing.

Staging The allocation of categories (stage I to IV) to tumours defined by internationally agreed criteria. Stage I tumours are localised, whilst stage II to IV refer to increasing degrees of spread through the body from the primary site. Tumour stage is an important determinant of treatment and prognosis.

Time to progression The length of time from the start of treatment (or time from randomisation within the context of a clinical trial) until tumour progression.

Utility approach Assigns numerical values on a scale from 0 (death) to 1 (optimal health). It provides a single number that summarises all of health related quality of life – a global measure of health related life quality.

Utility scores Strength of a patient's preference for a given health state or outcome.

Utilities Preference with risk.

Values Preferences without risk or uncertainty.

1. AIM OF THE REVIEW

The aim was to update the previous rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes in ovarian cancer, which was completed in December 1999.[1] The questions which the updated version of the review aimed to answer were the same as the original review, namely:

1. How effective is **paclitaxel**, compared with other standard chemotherapeutic regimens, as **a first-line** treatment of **ovarian** cancer in terms of response, progression free survival, overall survival, adverse effects and quality of life?

2. What are the cost implications of the use of paclitaxel as above?

2. BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

Ovarian cancer is the fourth most common cause of cancer deaths in women in England and Wales.[2] See Table 1.

Table 1 Incidence and deaths from Ovarian Cancer in the UK [3]

	Number of registrations, 1993	Incidence rate, 1995	Deaths, 1996
Ovarian Cancer	5,337	5%	4,580

Ovarian Cancer

The natural history of ovarian cancer is inconsistent.[4] Hormonal factors may play a part in the aetiology of this cancer, with reduced ovulation, the use of oral contraceptives,[5, 6] pregnancy and early menopause associated with reduced risk.[2] There appears to be an inherited pre-disposition to develop ovarian cancer in about 5 to 10% of cases[4] and more than 80% of these are linked to the BRCA1 gene.[4]

The biology of the tumour has a strong influence on survival.[7] Ovarian cancer is not easily identified because the most common symptoms of ovarian cancer: persistent abdominal distension, pain, pressure in the pelvis can be attributed to a number of causes. In the majority of cases, the disease has progressed to a late stage before it is diagnosed. The FIGO system is used to stage ovarian cancer (See Appendix 1).

The two most important prognostic factors for epithelial ovarian cancer are the FIGO stage at diagnosis and the size of residual disease after surgery.[8] When ovarian cancer is diagnosed early (Stage I), surgery alone can lead to survival rates of over 80% at 5 years.[2] Unfortunately, about three-quarters of patients are at stage II to IV at time of diagnosis.[2] Five year survival in European countries which report to FIGO has increased from 27% in 1958-

62 to 42% in 1990-1992.[2] However, an overall survival of only 30% has been cited for the UK.[4, 8]

Surgery is currently the first intervention used to treat ovarian cancer, but in most women the disease is too far advanced by the time of diagnosis for complete removal of the tumour to be possible.[9] Consequently, survival time is likely to be improved by appropriate chemotherapy following expert surgery.[2]

A previous consensus statement on standard practice recommended that standard chemotherapy for patients with ovarian cancer should include a platinum compound, and in general the preferred analogue is carboplatin[10] and for the majority of women with ovarian cancer, the recommended chemotherapy should comprise a combination of paclitaxel with a platinum compound (either cisplatin or carboplatin).[10]

The results of a systematic meta-analysis[11] in which cisplatin and carboplatin were compared demonstrated no obvious advantage of one compound over the other in terms survival.

The Taxanes

The taxanes are a class of anticancer drugs, originally derived from the bark of the Pacific yew, *taxus brevifolia*. Paclitaxel (Taxol ® Bristol-Myers Squibb) was identified as the active constituent in 1971. Docetaxel (Taxotere ® Rhone Poulenc Rorer) is a semisynthetic taxoid produced from the needles of *Taxus baccata*. Paclitaxel and docetaxel have similar mechanisms of action. Cells exposed to taxanes cannot form a mitotic spindle.[12] This interferes with cell division and leads to cell death.

Chemotherapy may be used in the treatment of a range of cancers as a **first-line** treatment (initial systemic therapy following surgery (if appropriate)) or as a **second-line** treatment if the disease persists or relapses. When referring to metastatic or advanced breast cancer in this report, first-line refers to the first chemotherapy given after diagnosis of the metastatic or advanced stage of the disease, and second-line to chemotherapy given after this. **Adjuvant** therapy refers to chemotherapy following initial treatment by surgery or radiotherapy, to destroy any cancer cells that have spread. **Neoadjuvant** therapy refers to chemotherapy which is given before surgery.

Paclitaxel (Taxol®)
Paclitaxel is currently indicated for both breast and ovarian cancer in:

- The treatment of metastatic carcinoma of the breast in patients who have failed or are not candidates for standard anthracycline containing therapy.
- The primary treatment of carcinoma of the ovary, in combination with cisplatin, in patients with advanced disease or residual disease (> 1cm) after initial surgery.
- The secondary treatment of metastatic carcinoma of the ovary after failure of standard platinum containing therapy.
- There is also an indication for paclitaxel in non-small cell lung carcinoma

Docetaxel (Taxotere ®)
Docetaxel is currently indicated in

- The treatment of locally advanced or metastatic breast cancer (in combination with doxorubicin) in patients who have not previously received cytotoxic therapy for this condition.
- The treatment of locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent
- There is also an indication for docetaxel in non-small cell lung cancer.

2.2 CURRENT SERVICE PROVISION

Chemotherapy Used In Ovarian Cancer

Table 2 provides a summary of some of the chemotherapeutic agents used in the treatment of ovarian cancer, their toxicities and mode of administration.

Table 2 Summary of chemotherapeutic agents

Drug	Mode of action	Toxicity/side effects	Administration
5-fluorouracil	Anti-metabolite - prevents normal cell division	Toxicity unusual but may include myelosuppression, mucositis Nausea and vomiting Diarrhoea Dermatological toxicity Cerebellar syndrome	IV over 4 hours
Carboplatin	Binds to DNA, forms interstrand cross-links and intrastrand adducts	Myelosuppressive, especially thrombocytopenia. Nausea and vomiting. Side effects less severe than with cisplatin	Intravenous over 15 to 60 minutes
Cisplatin	Binds to DNA, forms interstrand cross-links and intrastrand adducts	Severe nausea and vomiting Nephrotoxicity Myelotoxicity Ototoxicity Peripheral neuropathy Hypomagnaemia Visual disturbances	Pre-treatment hydration mandatory Intravenous over 6 to 8 hours
Cyclophosphamide	Metabolite alkylates to DNA	Myelosuppression Haemorrhagic cystitis Nausea and vomiting Alopecia Cardiomyopathy (rare) "Allergic" interstitial pneumonitis	By mouth or intravenous over 5 to 15 minutes. Increased fluid intake advised
Docetaxel	Promotes microtubule assembly and arrests cell cycle in G_2 and M phases	Hypersensitivity Fluid retention	Premedication with dexamethasone by mouth for 5 days Intravenous over 1 hour
Doxorubicin	Cytotoxic, anthracycline antibiotic. Intercalation to DNA double helix; topoisomerase II mediated DNA damage; production of oxygen free radicals which cause damage to DNA and cell membranes	Nausea and vomiting Myelosuppression Alopecia Mucositis Cumulative cardiac toxicity; Dose related acute ECG changes Severe tissue damage if extravasated	Intravenous over 2 to 3 minutes
Methotrexate	Anti-metabolite - inhibits the enzyme dihydrofolate reductase.	Myelosuppression Mucositis Pneumonitis	By mouth, intravenous, intramuscular, intrathecally. Folinic acid following administration helps to prevent mucositis or myelosuppression.
Mitomycin	Cytotoxic antibiotic	Delayed bone marrow toxicity	Administered at 6 weekly

		Lung fibrosis Renal damage	intervals
Paclitaxel	Promotes microtubule assembly and arrests cell cycle in G_2 and M phases	Hypersensitivity Myelosuppression Peripheral neuropathy Cardiac conduction defects with arrhythmias Alopecia Myalgia/arthralgia	Premedication with corticosteroid, antihistamine and histamine H_2-receptor antagonist 3 hour or 24 hour infusion
Vinblastine	Vinca alkaloid. Reversible inhibition of mitosis. Binds to microtubule protein, ultimately inhibiting formation of mitotic spindles	Peripheral or autonomic neuropathy Abdominal pain Constipation Myelosuppression Alopecia Severe local irritation	Intravenous over 1 minute
Vinorelbine	Vinca alkaloid Reversible inhibition of mitosis. Binds to microtubule protein, ultimately inhibiting formation of mitotic spindles	Peripheral or autonomic neuropathy Abdominal pain Constipation Myelosuppression Alopecia Severe local irritation	Injection

2.3 DESCRIPTION OF NEW INTERVENTION

Ovarian Cancer

A previous systematic review undertaken for the National Institute for Clinical Excellence[1] concluded that the use of paclitaxel in combination with platinum as first-line treatment for ovarian cancer was supported by the best available evidence, and this treatment combination had potentially acceptable cost-effectiveness ratios. This report is an update of that systematic review, taking into account new evidence which has come to light since publication of the original review in early 2000.

A number of reports have evaluated the effectiveness of the taxanes in the treatment of ovarian cancer. In 1996, a Development and Evaluation Committee (DEC) report **recommended** the use of paclitaxel as a first-line chemotherapeutic agent in the treatment of ovarian cancer. [13] This recommendation was to be reviewed after 12 to 18 months.

Additionally, the Trent DEC committee evaluated the use of paclitaxel and cisplatin as a first-line treatment in ovarian cancer and recommended "that paclitaxel should be available for patients within national controlled trials. . . and for other patients at the discretion of clinicians". [14] Subsequently, this decision was supported in a supplementary document. [15]

An earlier DEC report investigated the second and third-line use of paclitaxel in advanced ovarian cancer. The report concluded that there was insufficient evidence to recommend "the use of paclitaxel for second-line chemotherapy after standard platinum chemotherapy has failed". [16] However, "the use of paclitaxel for third-line chemotherapy (by heavily pre-treated patients), when other chemotherapy agents have failed" was considered "beneficial but high cost." [16]

The role of chemotherapy, including paclitaxel, in the treatment of ovarian cancer was discussed in the recent NHS Executive Guidelines for Commissioning Cancer Services for Gynaecological cancers. [2] It was recommended that paclitaxel plus carboplatin should be

standard therapy for women with advanced ovarian cancer. It was advised that this recommendation should be reviewed when the results of the ICON3 trial were mature.

Projected Unit Cost

Paclitaxel
NHS List Price excluding VAT: 30 mg vial: £124.79 100 mg vial: £374.00

Recommended dosage for first-line ovarian cancer therapy: 135mg/m^2

Assuming average body surface area of 1.75m^2, required dose for ovarian cancer:
= 236.25mg can be given from 2 x 100mg vials and 2 x 30 mg vials

Total cost per cycle: £997.58

This costing does NOT include any premedication or other medication required to manage adverse events e.g. G-CSF for neutropenia.

Licensed Indications, Contraindications and Warnings

Paclitaxel
The following indications, contraindications and warnings are taken from the manufacturer's submission.[17]

Therapeutic indications

Ovarian carcinoma
The primary treatment of carcinoma of the ovary, in combination with cisplatin, in patients with advanced disease or residual disease (> 1 cm) after initial laparotomy.

The secondary treatment of metastatic carcinoma of the ovary after the failure of standard platinum-containing therapy.

Recommended dosage: Primary treatment of ovarian carcinoma
A combination regimen is recommended consisting of paclitaxel 135mg/m^2 administered over 24 hours followed by cisplatin 75 mg/m^2 , with a three-week interval between courses.

Recommended dosage: Secondary treatment of ovarian and breast carcinoma
The recommended dose of paclitaxel is 175mg/m^2 administered over a period of 3 hours with a 3-week interval between courses.

Subsequent doses of paclitaxel should be administered according to individual patient tolerance.

Paclitaxel should not be readministered until the neutrophil count is ≥ 1.5 x 10^9/L and the platelet count is ≥ 100 x 10^9/L. Patients who experience severe neutropenia (neutrophil count < 0.5 x 10^9/L for ≥ 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses.

All patients must be premedicated with corticosteroids, antihistamines and H_2 antagonists prior to paclitaxel.

Contra-indications
Paclitaxel is contra-indicated in patients with severe hypersensitivity reactions to paclitaxel or any other component of the formulation, especially polyethoxylated castor oil.

Paclitaxel is contra-indicated during pregnancy and lactation.

Paclitaxel should not be used in patients with baseline neutrophils < 1.5 x 10^9/L.

Special warnings and special precautions for use
Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists.

Taxol should be given *before* cisplatin when used in combination.

Hypersensitivity reactions: Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angiodema and generalised urticaria have occurred in < 1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine mediated. In the case of severe hypersensitivity reactions, paclitaxel should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.

Haematological: Bone marrow suppression (primarily neutropenia) is the dose limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to a level ≥ 1.5 x 10^9/L and the platelets recover to a level ≥ 100 x 10^9/L.

Cardiovascular: Severe cardiac conduction abnormalities have been reported rarely. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. Hypotension, hypertension and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

Nervous system: Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is unusual. In severe cases, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel.

Patients with liver impairment: There is no evidence that the toxicity of paclitaxel is increased when given as a 3 hour infusion to patients with mildly abnormal liver function. No

data are available for patients with severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment.

Paclitaxel is not recommended for patients with severely impaired hepatic function.

Other: Since paclitaxel contains dehydrated alcohol (396 mg/mL), consideration should be given to possible central nervous system and other effects.

Special care should be taken to avoid intra-arterial administration of paclitaxel. In animal trials investigating local tolerance, severe tissue reactions occurred following intra-arterial administration.

3 EFFECTIVENESS AND COST-EFFECTIVENESS

3.1 METHODS OF THE REVIEW

Search strategy
The following databases were searched for relevant literature:

- MEDLINE
- EMBASE
- CancerLit
- Cochrane Controlled Trials Register
- National Research Register

More detailed information about the search strategy is presented in Appendix 2. Results of the database searches were deduplicated against results of the database searches for the original review, and only references which were not found in the original searches were assessed for inclusion.

Bibliographies of all retrieved articles were searched for additional references. Manufacturer and sponsor submissions made to the National Institute for Clinical Excellence (NICE) were also reviewed to identify any additional trials. The internet was searched for information on ongoing trials (see Appendix 2).

Inclusion and exclusion criteria
Titles (and where possible abstracts) of trials identified from all searches and sources (see Appendix 2) were assessed independently by two reviewers for relevance. If either reviewer considered the paper to be potentially relevant, a full paper copy of the manuscript was obtained. Each full paper copy was reassessed for inclusion using the same criteria as for the original review, which were as follows:

Interventions

a) Paclitaxel (Taxol ® Bristol-Myers Squibb) used either alone or in combination with other drugs as part of a chemotherapy regimen
b) Other standard chemotherapy regimens. For ovarian cancer these include non-platinum drugs such as cyclophosphamide, doxorubicin (Adriamycin), and platinum (cisplatin and carboplatin) either alone or in combination.[9]

The use of taxanes as part of high dose regimens with autologous stem cell support was not considered. Trials comparing only different paclitaxel regimens (either in terms of dose, period of administration or combination) were not included.

Participants
(See Appendix 1 for definition of stages)

Women with ovarian cancer

i) Early (FIGO stage I)
ii) Advanced (FIGO stages II to IV)

Outcomes

a) Overall response (complete response + partial response)
b) Progression free survival
c) Overall survival
d) Symptom relief
e) Quality of life
f) Adverse effects
g) Cost

Design

a) Randomised, controlled trials comparing paclitaxel to a standard chemotherapy regimen
b) Full economic evaluations

Trials comparing only different doses or period of infusion of taxanes were not included.

Trials that did not meet all of the criteria were excluded and their bibliographic details listed in Appendix 8, along with the reason for exclusion. Information relating to inclusion of trials highlighted by the industry submissions is presented in Appendix 9. Any disagreements were discussed in order to obtain a consensus and if no agreement was reached a third reviewer was consulted.

Data extraction strategy

Data extraction was conducted by one reviewer using predefined data extraction forms in a Microsoft Access database and checked by a second reviewer. Any disagreement was resolved by consensus and if this was not reached a third reviewer was consulted.

The type of data that was extracted and summarised included: specific details about the interventions, the population investigated and the outcome measures used. Trials that had been reported in multiple publications were collated and reported only once.

Where sufficient data were presented an estimation of the treatment effect along with the 95% confidence interval (CI) was calculated for each individual trial. Where possible this was done on an intention to treat basis. For dichotomous outcome measures the relative risk (RR) or hazard ratio (HR) was calculated and for continuous outcomes the median or mean difference (MD) was used. For survival data or other time-to-event data the hazard ratio was reported where presented in the included trial. If Kaplan Meier curves were presented, the p value of the log rank test was presented, where performed. Median survival times were also reported, where given in the trial.

In order to assess the economic data in terms of the clinical effectiveness of the intervention (i.e. the direction of the cost-effectiveness data and the magnitude of effectiveness data), each trial was given a summary grading (A-I) according to the level and direction of dominance (i.e. whether the intervention of interest should be preferred over the comparator). Extended dominance indicates that both the effectiveness data and the economic data support the use of either the intervention or the comparator and the decision on resource allocation is clear. When either the economic or the effectiveness data supports the intervention/comparator, the dominance is said to be partial or weak and a decision can still be made. However, if there is no dominance indicated then further incremental cost analysis may be required in order to estimate the incremental cost-effectiveness ratio. This is important in helping the decision-

making process. The following matrix (Figure 1) illustrates all of the possible permutations, and was used to assign each trial a summary grading.

Figure 1 Incremental cost of treatment compared to control[18, 19]

		Health outcomes +	o	-
	+	A	B	C
Costs	o	D	E	F
	-	G	H	I

	Strong dominance for decision in either direction (i.e. in favour of the intervention or comparator)
	Weak dominance for decision
	Non-dominance; no obvious decision

Code	Implication for intervention	Direction of the cost-effectiveness data and the magnitude of effectiveness data
A	Trade off	Higher costs but better outcomes (incremental analysis required)
B	Reject	Higher costs and no difference in outcomes (partial dominance in favour of the comparator)
C	Reject	Higher costs and poorer outcomes (extended dominance in favour of the comparator)
D	Accept	No difference in costs and improved outcomes (partial dominance in favour of the intervention)
E	Neutral	No difference in costs and no difference in outcomes
F	Reject	No difference in costs and poorer outcomes (partial dominance in favour of comparator)
G	Accept	Lower costs and improved outcomes (extended dominance in favour of the intervention)
H	Accept	Lower costs and no difference in outcomes (partial dominance in favour of the intervention)
I	Trade off	Lower costs but poorer outcomes (incremental analysis required)

Quality assessment strategy

The methodological quality of each included trial was assessed using predefined checklists. Two reviewers conducted this process independently. Any disagreements were resolved by consensus and a third reviewer was consulted if required. Quality criteria included: method of randomisation, allocation concealment, baseline comparability of identified prognostic characteristics (which were identified as being treatment free interval, disease bulk, number of previous regimens, age, histology and performance status), presentation of eligibility criteria, reporting of co-interventions, loss to follow-up <20%, handling of withdrawals and use of intention to treat analysis. Blinding was also assessed, although it is acknowledged that blinding is often impossible in trials of cancer treatment.

Methods of analysis/ synthesis
Results of data extraction and quality assessment are presented in structured tables and also as a narrative summary. Where new trials were found which impact on the results of the original review, the results of the original review are also presented.

3.2 RESULTS OF CLINICAL EFFECTIVENESS ANALYSIS

3.2.1 Excluded trials

Thirty-four papers were excluded after the full publications had been assessed for inclusion. Seven contained taxane therapy in both trial arms,[20-26] seven were non-systematic reviews,[27-33] six looked at second-line therapy for advanced ovarian cancer,[34-39], one did not look at taxanes,[40] one was a letter about an included study[41] and five were case series or were uncontrolled trials.[42-46] Details of excluded trials are given in Appendix 7. One systematic review[47] was excluded but checked for references to RCTs or economic evaluations.

Two newly published full reports of studies included in the original review were excluded because they contained no further information.[48, 49]

3.2.2 Included trials

Six further trials were found for the update report which looked at paclitaxel in combination with a platinum compound for first-line treatment of advanced ovarian cancer.[50-56] Three of these trials were included in the original review but have since been updated.[50-52, 56] These three trials are referred to as OV10,[50, 51] GOG111[56] and ICON3.[52] Two of the other trials were small trials which may be reports from single centres of a multicentre trial, but insufficient information was given in the publications to confirm this.[53, 57#392] One was an interim analysis.[53, 57] The other trial was a larger trial which is only published as a conference abstract and only reports toxicity.[55]

In the original report, four RCTs were found (Table 10), three of which (OV10, GOG 111 and GOG 132) assessed the effectiveness of paclitaxel combined with cisplatin and one (ICON3) which assessed the effectiveness of paclitaxel combined with carboplatin. ICON3 was stated to be an interim analysis.

Table 3 New included trials on taxanes for advanced ovarian cancer

Trial	Participants	Intervention	Control A	Control B
OV10 (updated)[50, 51]	Age: Median 58 both groups Type of cancer: Advanced epithelial ovarian cancer. Stage of cancer: FIGO stage II (B-C), III and IV Prior treatments: No previous chemotherapy or radiotherapy. Exclusion criteria: WHO PS= 4; inadequate bone marrow or renal function; complete bowel obstruction or presence of brain metastasis; history of medically significant atrial or ventricular arrhythmias; congestive heart failure; a documented myocardial infarction within 6 months preceding randomisation; active infection or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment. Further details: Initial surgical procedure within less than 8 weeks of recruitment. Optimal or suboptimal surgery included. Tumour grade: well defined n=57; moderately well defined n=178; poorly defined n=389; missing or N/A n=56. Less than 10% of the patient population had FIGO stage IIB or IIC disease, and roughly one third had optimal residual disease (<1cm).	Paclitaxel combined with cisplatin N:342 Dose: T at 175 mg/m2 as 3-hour infusion and P at 75mg/m2 Number of cycles: Median = 6 (range 0-10) Length of cycles: 3 weeks Premedication: dexamethasone 20mg; ranitidine 50 mg iv; diphenhydramine 50 mg iv Prophylactic anti-emetics and oral magnesium recommended	Cyclosphamide plus cisplatin N:338 Dose: C at 750mg/m2 followed by P at 75mg/m2 Number of cycles: Median = 6 (range 0-10) Length of cycles: 3 weeks Prophylactic anti-emetics and oral magnesium recommended	
ICON3 (updated)[52]	Age: Median 58.9 years Type of cancer: Invasive ovarian epithelial cancer Stage of cancer: FIGO stage I-IV Prior treatments: Surgery (total abdominal hysterectomy, bilateral salpingo-oophorectomy and thorough staging were recommended as minimal surgical procedures) Inclusion/ exclusion criteria: Not received any previous radiotherapy or chemotherapy. Informed consent. Further details: 9% FIGO stage I, 11% FIGO stage II, 64% FIGO stage III, 16% FIGO stage IV. Residual bulk of disease: none or microscopic 30%, <2cm 24%, >2cm 46%. Differentiation: poor 52%, moderate 33%, well 11%. Histological cell type: serous 53%, mucinous 7%, endometrious 16%, clear cell 6%, undifferentiated 7%, other 10%.	Paclitaxel/ carboplatin N: 701 Dose: Paclitaxel 175mg/m2 in a 3 hr infusion, Carboplatin min 5(GFR+25)mg (determined by area under curve method) Number of cycles: 6 Length of cycles: 3 weeks	Carboplatin N: 943 Dose: Min 5(GFR+25)mg (determined by area under curve method) Number of cycles: 6 Length of cycles: 3 weeks Prophylactic anti-emetics	Cyclophosphamide/ doxorubicin/ cisplatin N: 421 Dose: Cyclophosphamide 500mg/m2, doxorubicin 50mg/m2, cisplatin 50mg/m2 Number of cycles: 6 Length of cycles: 3 weeks Prehydration Prophylactic anti-emetics
GOG111 (updated)[56, 58-64]	Age: Median 59 both groups. Inclusion criteria: Pathologically verified epithelial ovarian cancer. Borderline cancers excluded. Stage III (suboptimal) and IV. GOG PS 0 to 2. Prior treatments: No prior radiotherapy or chemotherapy. Further details: GOG 0: 27-31% GOG 1: 53-54% GOG 2: 17-19% Stage III: 64-67% Stage IV: 33-36% Measurable disease: TP: 54% CP: 57% Sub-optimal: residual mass > 2cm: None	Paclitaxel (135mg/m^2) + cisplatin (75mg/m^2) Paclitaxel: 24 hour infusion; followed by cisplatin 6 x 3 week cycle Premedication: dexamethasone 20mg; ranitidine 50 mg iv; diphenhydramine 50 mg iv	cyclophosphamide (750mg/m^2) + cisplatin (75 mg/m^2) 6 x 3 week cycles	

Gennatas[53, 57]	Type of cancer: Advanced ovarian cancer Stage of cancer: FIGO stage IIIa, IIIb, IIIc and IV	Cisplatin plus paclitaxel N: 43 Dose: Cisplatin 75mg/m2 and paclitaxel 175mg/m2 (infusion time not stated). Number of cycles: 6 Length of cycles: Not stated	Cisplatin plus cyclophamide N: 42 Dose: Cisplatin 75mg/m2 and cyclophosphamide 700mg/m2 Number of cycles: 6 Length of cycles: Not stated
Simsek[54]	Age: PC 56.2 yrs (range 25-76), CC 58.4 yrs (range 33-80) Type of cancer: Advanced ovarian cancer. Prior treatments: Surgery. Those with optimal cytoreductive surgery were included as well as those without. Further details: Stage III and IV epithelial ovarian tumours in which optimal debulking surgery was performed. Type of tumour: serous CP 8/15, CC 6/15; mucinous CP 0 CC 4; endometriosis CP 6, CC 4; other CP 1, CC 3.	Paclitaxel/ cisplatin N:15 Dose: Paclitaxel 135mg/m2 (infusion time not stated), Cisplatin 75mg/m2 Number of cycles: Not stated Length of cycles: Not stated	Cisplatin/ cyclophosphamide N:17 Dose: Cisplatin 75mg/m2, cyclophosphamide 750mg/m2 Number of cycles: Not stated Length of cycles: Not stated
Wolf[55]	Age: 57 years (27-79). Type of cancer: Advanced ovarian cancer. Orior treatments: Not stated. Further details: Stage IIb (n=18), III (n=148) and IV (n=46).	Paclitaxel/ carboplatin N: 106 Dose: Paclitaxel 175mg/m2 (infusion time not stated), Carboplatin AUC 6. Number of cycles: 6 Length of cycles: 4 weeks	Carboplatin/ cyclophosphamide N: 106 Dose: Carboplatin AUC 6, Cyclophosphamide 600mg/m2. Number of cycles: 6 Length of cycles: 4 weeks

Table 4 Included trials in the original review on taxanes for advanced ovarian cancer

	Participants	**Intervention**	**Control A**	Control B
GOG 132[65]	Age: Median 59.4 -60.1 years Inclusion criteria: Histologically confirmed ovarian epithelial cancer. Borderline cancers excluded. Stage III (suboptimal) or Stage IV. GOG PS 0 to 2. Prior treatments: No prior radiotherapy or chemotherapy. Further details: GOG 0: 27-31% GOG 1: 55-56% GOG 2: 14-17% Stage III: 65-73% Stage IV: 27-35% Measurable disease: T: 62% P: 61% TP: 62% Sub-optimal: None	T: paclitaxel (200mg/m^2) T: 24 hour infusion 6 x 3 week cycles Premedication: dexamethasone 20mg; cimetidine 50 mg iv; diphenhydramine 50 mg iv	P: cisplatin (100mg/m^2) 6 x 3 week cycles Hydration Prophylactic anti-emetic	TP: paclitaxel (135mg/m^2) + cisplatin (75mg/m^2) T: 24 hour infusion followed by P. 6 x 3 week cycles Premedication: dexamethasone 20mg; cimetidine 50 mg iv; diphenhydramine 50 mg iv Prophylactic anti-emetic

3.2.3 Description of included trials

All six included trials looked at paclitaxel combined with a platinum compound for the first-line treatment of advanced ovarian cancer.[50-57] Three included trials were updated reports of trials in the original review.[50-52, 56] The other three were new trials which were either reported in conference proceedings as abstracts[53, 55, 57] or were reported in Turkish;[54] in all cases only limited details could be extracted for this review.

Four trials looked at paclitaxel combined with cisplatin[50, 51, 53, 54, 56, 57] while the largest trial (ICON3[52]) and another trial (Wolf[55]) looked at paclitaxel combined with carboplatin. The dose of paclitaxel used in four trials was 175mg/m^2[50, 52, 53, 55] but in GOG111 and the foreign language trial it was lower at 135mg/m^2.[54, 56] The four trials which combined paclitaxel with cisplatin used cyclophosphamide combined with cisplatin as a comparator.[50, 51, 53, 54, 56, 57] One trial used a slightly lower dose of cyclophosphamide (700mg/m^2) than the other three (750mg/m^2).[53, 57] The large trial which combined paclitaxel with carboplatin had two comparator groups.[52] The investigator could choose which comparator group a patient might be assigned to before randomisation took place. The more popular comparator was single agent carboplatin (n=1421, of whom 943 were allocated control), and the less popular comparator was cyclophosphamide combined with doxorubicin and cisplatin (n=653, of whom 421 were allocated control). The smaller trial which combined paclitaxel with carboplatin[55] used cyclophosphamide 600mg/m2 combined with carboplatin as a comparison group.
Mean age of participants in the four trials where age was reported ranged from 56.2 to 58.9 years.[50, 52, 54, 55] Three trials restricted inclusion to participants with FIGO stage III or IV (i.e. more advanced) ovarian cancer,[53, 54, 56, 57, 64] two trials also included women with FIGO stage II ovarian cancer[50, 51, 55] (although less than 10% of participants in these trials had stage II disease) and the largest trial also included women with FIGO stage I disease, although the majority of women (80%) in this trial had stage III or IV disease.[52] The two largest trials, OV10[50, 51] and ICON3,[52] seem to have included slightly different participants with around 33% and 54% respectively having optimal residual disease following surgery, less than 10% in OV10 having FIGO stage II disease and around 20% in ICON3 having FIGO Stage I or II disease. 57% and 52% respectively had poorly defined or differentiated disease. The other two trials did not give many details about participants although the foreign language trial stated that participants with and without optimal cytoreductive surgery were included.[54]

The other trial of taxanes for first-line treatment of ovarian cancer which was included in the original review, GOG 132,[65] also restricted inclusion to women with FIGO Stage III or IV ovarian cancer. The trial looked at paclitaxel 135mg/m2 combined with cisplatin 75mg/m2. GOG 132 used single agent cisplatin (100mg/m2) as a comparator. GOG 132 has been criticised previously for allowing participants to cross-over to the alternate treatment arm before disease progression and without documenting the cross-over, thus confounding the trial results. OV10 also allowed some cross-over of treatment before disease progression but this was documented.

3.2.4 Quality of included trials

Details of the validity assessment of included trials are presented in Appendix 5.
It is important to note that one of the included trials was an interim analysis and its results should therefore be interpreted with caution.[53, 57] One of the six included trials (ICON3) reported sufficient information on both the generation of the randomisation code and concealment of allocation to trial arm.[52] Four of the included trials may have had adequate concealment of allocation but insufficient detail was reported.[50, 51, 54-56] All six trials stated the number of participants randomised and four reported some identified important baseline characteristics[50-52, 54, 56] (one trial (OV10) reported all but one of the most important baseline characteristics[50, 51]). Trial groups were reported as being comparable at baseline for all characteristics measured in one trial (OV10)[50, 51] and for some characteristics in two other trials (ICON3[52] and GOG111[56, 64] Trial inclusion criteria were reported in full in OV10 and

GOG111, in part in ICON3 and not at all in the other three trials. One trial (ICON3)[52] identified co-interventions which may have impacted on the trial results and in the foreign language trial it was unclear whether this information was reported.[54] The OV10 trial reported that for some outcomes, outcome assessors were blind, and that administrators and participants were not blind.[50] It was unclear whether this information was reported in the foreign language trial,[54] the Wolf trial reported that it was 'blinded' and the other three trials did not report whether blinding took place.[52, 53, 56, 64] All six trials reported outcomes for more than 80% of randomised participants. Three of the six included trials did not report outcomes for all participants who withdrew,[52, 53, 55] two did[50, 56, 64] and in the foreign language trial it was unclear whether this information was reported.[54] The three largest trials, GOG111,[56, 64] OV10[50] and ICON3,[52] undertook an intention to treat analysis on some outcomes. One of the smaller trials did not undertake an intention to treat analysis[53] and in the foreign language trial and Wolf it was unclear whether this information was reported.[54, 55]

Overall, the quality of reporting of the included trials was either good or difficult to assess. The three larger trials (GOG111, OV10 and ICON3) were of good quality while the three smaller trials gave insufficient details for validity to be properly assessed.

3.2.5 Assessment of effectiveness

Latest results for GOG111, ICON3 and OV10 will be presented under 'New data'; earlier results of these trials from the original report which have been superseded will not be presented.

Overall response rates

New data

Two out of six trials presented data on response rates.[50, 53, 57] One trial showed no significant difference between groups for any response outcome,[53] while the other trial (OV10) showed a significant difference in favour of the paclitaxel arm for overall and complete response and for progressive disease.[50] One trial did not report response rates but did report a 'tumour positive' result on second look laparoscopy for 4 out of 8 participants in the intervention group versus 6 out of 11 participants in the control group.[54] The same trial also reported that serum Ca^{125} levels fell to normal in a shorter time in the paclitaxel than in the control group.

Data from original report

Overall response rates (complete response + partial response) were presented for GOG 111 and GOG 132. When comparing the paclitaxel plus platinum arm with the control arm, no significant difference in response rates was found in GOG 111. However, cisplatin alone had a superior response rate compared to combined cisplatin and paclitaxel in GOG 132 (RR: 0.62 (95% CI: 0.53, 0.73)). A greater proportion (over 90%) of patients in GOG 132 were evaluable for response compared with GOG 111 (about 60%) or OV10 (about 50%).

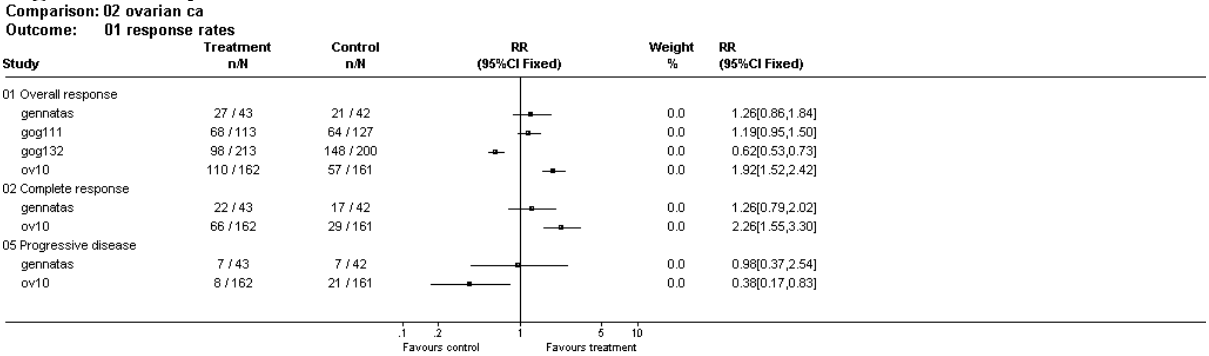
Table 5: Summary of response rates - new and original data combined

Outcome	Trial	Intervention	Control	RR (95% CI)
Overall response	OV10[50]	110/162	57/161	1.92 (1.52, 2.42)*
	Gennatas[53]	27/43	21/42	1.26 (0.86, 1.84)
	GOG 111	68/113	64/127	1.19 (0.95, 1.50)

	GOG 132	98/213	148/200	0.62 (0.53, 0.73)**
Complete response	OV10[50] Gennatas[53]	66/162 22/43	29/161 17/42	2.26 (1.55, 3.30)* 1.26 (0.79, 2.02)
Progressive disease	OV10[50] Gennatas[53]	8/162 7/43	21/161 7/42	0.38 (0.17, 0.83)* 0.98 (0.37, 2.54)

*significant difference in favour of intervention
**significant difference in favour of control

Figure 2: Response rates



NB. For the outcome 'progressive disease' a RR <1 favours treatment. For all other response outcomes a RR >1 favours treatment.

Progression free survival (PFS)

New data

The two larger trials (OV10 and ICON3) reported progression free survival. Both presented Kaplan Meier curves. OV10 found a highly significant difference between groups in favour of paclitaxel at around 24 months follow-up time, with a log rank test giving a p value of 0.0005. At a median follow-up of 39 months,[51] OV10 reported a median progression-free survival of 15.3 months in the paclitaxel arm and 11.5 months in the control arm (logrank p=0.0005, Hazard Ratio = 0.71, 95% CI: 0.58, 0.87). ICON3 however found no significant differences between the groups, presenting a hazard ratio of 0.94 (95% CI: 0.84, 1.05, log rank p=0.24) corresponding to an absolute improvement in 1 year PFS in the paclitaxel group of 2% (95% CI: –1%, 5%). When hazard ratios were calculated separately for each control group there was still no significant difference between the groups.
In OV10, 20 participants in the intervention group received second-line therapy before disease progression compared to 14 in the control group.

Data from original report

Kaplan Meier curves were presented for each of the trials. Two analyses were presented for GOG 111.[17] As the protocol did not exclude maintenance therapy prior to clinical evidence of progression, the results presented here are based on the curve where patients had been censored at time of subsequent therapy if this was given prior to evidence of clinical progression. Such patients were considered to have progressed. Median time to progression for the paclitaxel/platinum combination ranged from 14.1 months (GOG 132) to 16.6 months (GOG 111). The GOG 111 trial reported significantly greater median times to progression for the paclitaxel arm than the control: 16.6 months versus 13 months. No probability levels were given for GOG 132 but patients treated with single agent platinum appeared to survive longer without progression.

Overall survival

New data

The three larger trials (GOG111, OV10 and ICON3) also reported overall survival. Both OV10 and ICON3 presented Kaplan Meier curves. GOG111 update was presented only as a conference abstract. OV10 found a highly significant difference between groups in favour of paclitaxel at 24 months follow up time, with a log rank test giving a p value of 0.0016, and again at 39 months follow-up median survival was 36 months in the paclitaxel arm versus 26 months in the control arm (logrank p=0.0016, Hazard Ratio = 0.73, 95% CI: 0.60, 0.89). GOG111 at a median follow-up of 6.5 years also found a significant survival benefit in favour of paclitaxel (Hazard Ratio 0.70, 95% CI: 0.57, 0.87). However, ICON3 again found no significant difference between groups at 34 months follow up (HR 0.96, 95% CI 0.84, 1.09, p=0.53). The hazard ratio was still not significant when calculated for each control group separately and translated into an absolute difference in 2 year survival of 1% (95% CI –3%, 5%).

Data from original report

Kaplan Meier curves were presented for each of the trials.

Median length of survival for patients treated with the paclitaxel/platinum combination ranged from 26.6 months (GOG 132) to 35.7 months (GOG 111). The GOG 111 trial reported significantly greater median survival times for the paclitaxel arm than the control: 35.7 months versus 24.2 months. No probability levels are given for GOG 132 but patients treated with single agent platinum appeared to survive longer (30.2 months).

Table 6: Summary of time to event outcomes – new and original data combined

Outcome	Trial	Intervention N	Intervention median (95% CI)	Control N	Control median
Time to progression/ Progression free survival (months)	OV10[50] ICON3[52] GOG 111 GOG 132	342 710 113 213	15.3 17.1 16.6 14.1	338 1364 127 200	11.5* 16.1 13* 16.4
Overall survival (months)	OV10[50] ICON3[52] GOG 111 GOG 132	342 710 113 213	35.6 37.6 35.7 (29.5, 39.3) 26.6	338 1364 127 200	25.8* 36.1 24.2 (20.6, 29.9)* 30.2

*significant difference in favour of intervention

Compliance

New data

Data on compliance were not presented for two of the included trials: Gennatas and Simsek. In OV10, 52/339 participants in the paclitaxel arm versus 71/336 participants in the control arm did not complete all cycles of therapy. More participants in the control arm did not complete therapy because of disease progression, than in the taxane arm (47/336 (control) versus 23/339 (taxane) RR 0.49 (0.30, 0.78)). ICON3 does not give data on compliance by trial arm but gives an overall figure of >80% participants completing all cycles of therapy. The principal reasons for not completing therapy were disease progression, toxicity, death and patient preference (in order of magnitude).

Data from original report

Patient compliance and reasons for discontinuation of therapy may give an indication of the acceptability of treatment. However, because all these trials were open label, there may have been different pressures on or by patients to either continue treatment or cross-over depending on the arm. Compared with the other trials, in GOG 132, fewer patients in the platinum only arm completed all cycles. Adverse events were the reason most frequently given by this group, followed by withdrawal of consent.

Adverse events

New data

Simsek[53] did not report actual figures but reported that the intervention caused haematological toxicity more severe than the control but with use of amifostine and/ or G-CSF, neutropenia was managed 'without problems'. It was also reported that alopecia, allergic reactions and peripheral toxicity were more common in the intervention than control arm and that gastrointestinal toxicity was about the same in both arms.

For the remaining three trials that reported adverse events, only ICON3 compared paclitaxel/ carboplatin to single agent carboplatin control. Significantly more fever, alopecia and neurosensory and neuromotor events were experienced by participants in the paclitaxel arm, and significantly less haematological toxicity.

Comparison of paclitaxel/ platinum to combined cisplatin control found the following differences. Participants in the paclitaxel group experienced significantly more flushing, 'lokositz' (perhaps a haematological event), severe hypersensitivity reactions, myalgia, neurosensory and neuromotor events, and alopecia than participants in the control groups. Participants in the control groups experienced significantly more haematological toxicities including neutropenia and thrombocytopenia, nausea and vomiting than participants in the intervention groups.

Wolf[55] compared paclitaxel/ carboplatin to cyclophosphamide/ carboplatin and found more alopecia and neurotoxicity in the paclitaxel arm and more haematological problems in the control arm.

Data from original report

The reports were not consistent in the way adverse events were reported – the results of GOG132 were impossible to interpret. A significantly greater incidence of neutropenia was found in the paclitaxel arm than the control arm of GOG 111. Cardiovascular adverse events were only reported in GOG 111. Significantly more cardiovascular side effects were reported in the paclitaxel than control arm of GOG 111. OV10 reported a greater incidence of hypersensitivity reactions in the paclitaxel than control arm, despite premedications, and GOG111 reported a greater incidence of allergic reactions in the paclitaxel arm than control arm.

Table 7: Summary of adverse events (G3/4) new and original data combined

Outcome	Trial	Intervention n/N	Control n/N	Relative Risk (95% CI)
Single agent platinum control				
All haematological toxicities	ICON3 (carbo)[52]	86/478	233/943	0.73 (0.58, 0.91)*
Fever	ICON3 (carbo) [52]	24/240	15/500	3.33 (1.78, 6.24)**
Neurosensory	ICON3(carbo)[52]	73/478	4/943	36.00 (13.24, 97.9)**

Neuromotor	ICON3 (carbo) [52]	5/240	1/500	10.42 (1.22, 88.7)**
Nausea/ vomiting	ICON3 (carbo)[52]	34/478	70/943	0.96 (0.65, 1.42)
Alopecia (G3)	ICON3(carbo)[52]	298/478	29/943	20.27 (14.07, 29.2)**
'Other' (including ototoxicity, renal, cardiac, stomatitis)	ICON3 (carbo)[52]	27/478	36/943	1.48 (0.91, 2.41)
Combined carboplatin control				
Nausea/ vomiting	Wolf[55]	8/106	14/106	0.57 (0.25, 1.31)
Mucositis	Wolf[55]	2/106	0/106	5.00 (0.24, 102.93)
Neurotoxicity	Wolf[55]	15/106	0/106	31.00 (1.88, 511.54)**
Alopecia	Wolf[55]	76/106	29/106	2.62 (1.88, 3.65)**
Leucopenia	Wolf[55]	15/106	29/106	0.52 (0.29, 0.91)*
Thrombocytopenia	Wolf[55]	5/106	23/106	0.22 (0.09, 0.55)*
Anaemia	Wolf[55]	4/106	22/106	0.18 (0.06, 0.51)*
At least 1 blood transfusion	Wolf[55]	21/106	46/106	0.46 (0.29, 0.71)*
Received platelets	Wolf[55]	1/106	10/106	0.10 (0.01, 0.77)*
Combined cisplatin control				
Discontinuations	OV10[50]	22/342	15/338	1.45 (0.77, 2.75)
All haematological toxicities	ICON3 (CAP)[52] Simsek[54]	46/232 1/15	94/421 2/17	0.89 (0.65, 1.22) 0.57 (0.06, 5.64)
Neutropenia	OV10[50] Simsek[54] GOG 111)[56, 58-64]	218/339 3/15 92/190	244/336 6/17 80/207	0.89 (0.80, 0.98)* 0.57 (0.17, 1.88) 1.16 (1.07, 1.26)**
Febrile neutropenia	OV10[50]	9/339	10/336	0.89 (0.37, 2.17)
Fever	ICON3 (CAP) [52]	19/146	58/252	0.57 (0.35, 0.91)*
Infections	GOG 111)[56, 58-64]	14/190	12/207	1.13 (0.68, 1.87)
Leucopenia	GOG 111)[56, 58-64]	73/190	73/207	1.0 (0.88, 1.12)
Thrombocytopenia	OV10[50] GOG 111)[56, 58-64]	9/339 10/190	25/336 9/207	0.36 (0.17, 0.75)* 1.05 (0.57, 1.94)
Flushing	Simsek[54]	9/15	1/17	10.20 (1.46, 71.4)**
Anaemia	GOG 111)[56, 58-64]	13/190	2/207	1.39 (0.79, 2.46)
Severe hypersensitivity reactions	OV10[50]	15/339	5/336	2.97 (1.09, 8.09)**
'Lokositz'	Simsek[54]	8/15	0/17	19.12 (1.20, 305.7)**
Anorexia	GOG 111)[56, 58-64]	1/196	3/213	0.72 (0.21, 2.53)
Arthralgia/ myalgia Arthralgia (G3) Myalgia (G3)	GOG 111)[56, 58-64] OV10[50] OV10[50]	2/196 9/339 21/339	1/213 2/336 0/336	1.63 (0.28, 9.65) 4.46 (0.97, 20.49) 42.62 (2.59, 701)**
Neurosensory	ICON3(CAP)[52] OV10[50] GOG 111)[56, 58-64]	35/232 67/339 5/196	12/421 4/336 2/213	5.29 (2.80, 10.00)** 16.60 (6.12, 45.01)** 2.45 (0.77, 7.81)
Neuromotor	ICON3 (CAP) [52] OV10[50]	2/146 16/339	2/252 2/336	1.73 (0.25, 12.12) 7.93 (1.84, 34.22)**
Allergy	GOG 111)[56, 58-64]	5/196	0/213	20.64 (1.21, 352)**
Nausea/ vomiting Nausea Vomiting	ICON3 (CAP)[52] GOG 111)[56, 58-64] OV10[50] OV10[50]	20/232 12/196 51/339 37/339	79/421 13/213 68/336 61/336	0.46 (0.29, 0.73)* 0.93 (0.55, 1.56) 0.74 (0.53, 1.03) 0.60 (0.41, 0.88)*
Diarrhoea	GOG 111)[56, 58-64]	4/196	2/213	1.90 (0.57, 6.40)
Stomatitis	OV10[50]	2/339	0/336	4.96 (0.24, 102.9)

Alopecia (G3)	ICON3(CAP)[52] OV10[50]	159/232 173/339	271/421 72/336	1.06 (0.95, 1.19) 2.38 (1.89, 3.00)**
Urinary toxicity	Simsek[54]	3/15	5/17	0.68 (0.19, 2.38)
Ototoxicity	OV10[50] GOG 111)[56, 58-64]	8/339 0/196	14/336 3/213	0.57 (0.24, 1.33) 0.08 (0.00, 1.47)
'Other' (including ototoxicity, renal, cardiac, stomatitis)	ICON3 (CAP)[52] GOG 111 (cardiac))[56, 58-64]	13/232 13/196	21/421 5/213	1.12 (0.57, 2.20) 2.72 (1.34, 5.51)**

*significant in favour of intervention
**significant in favour of control

Figure 3: Adverse events – single agent carboplatin control

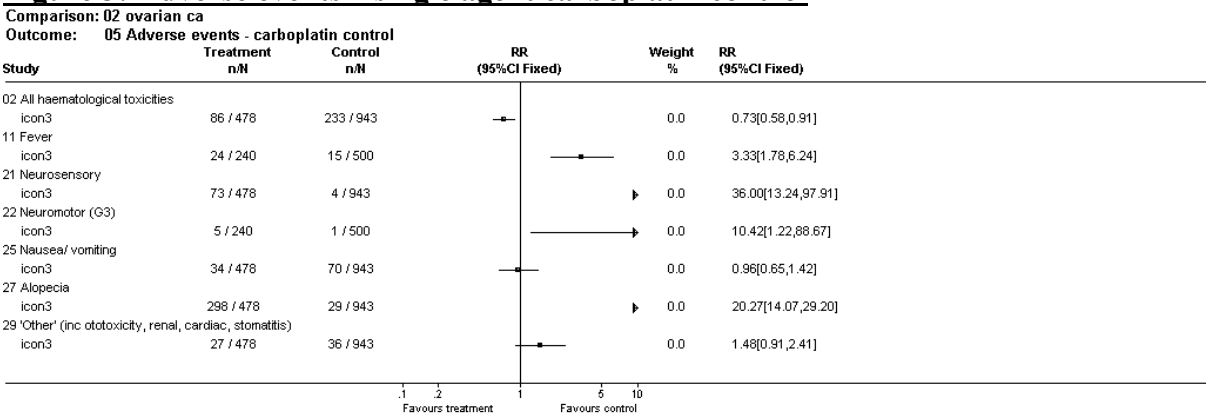


Figure 4: Adverse events – combined carboplatin control

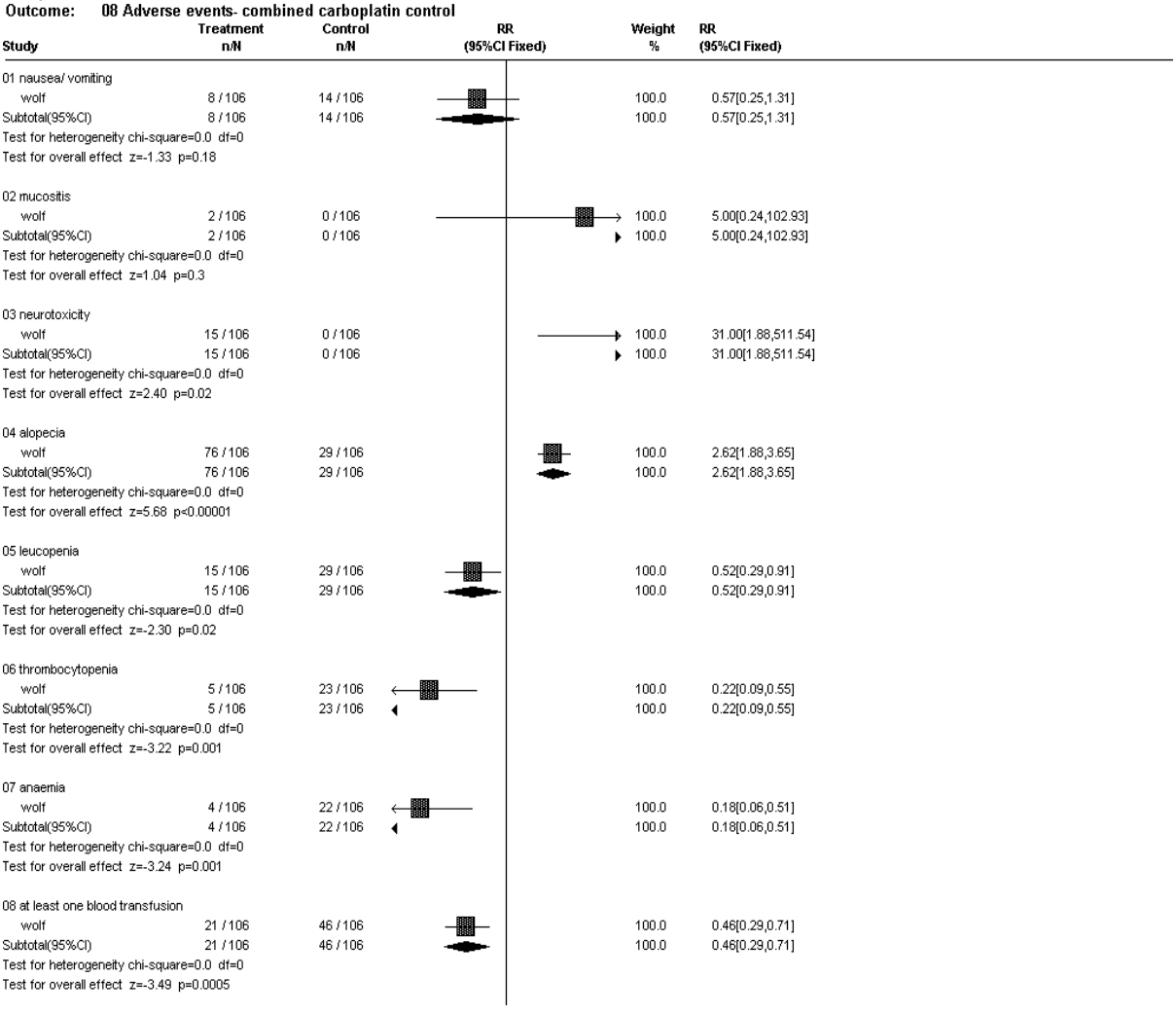
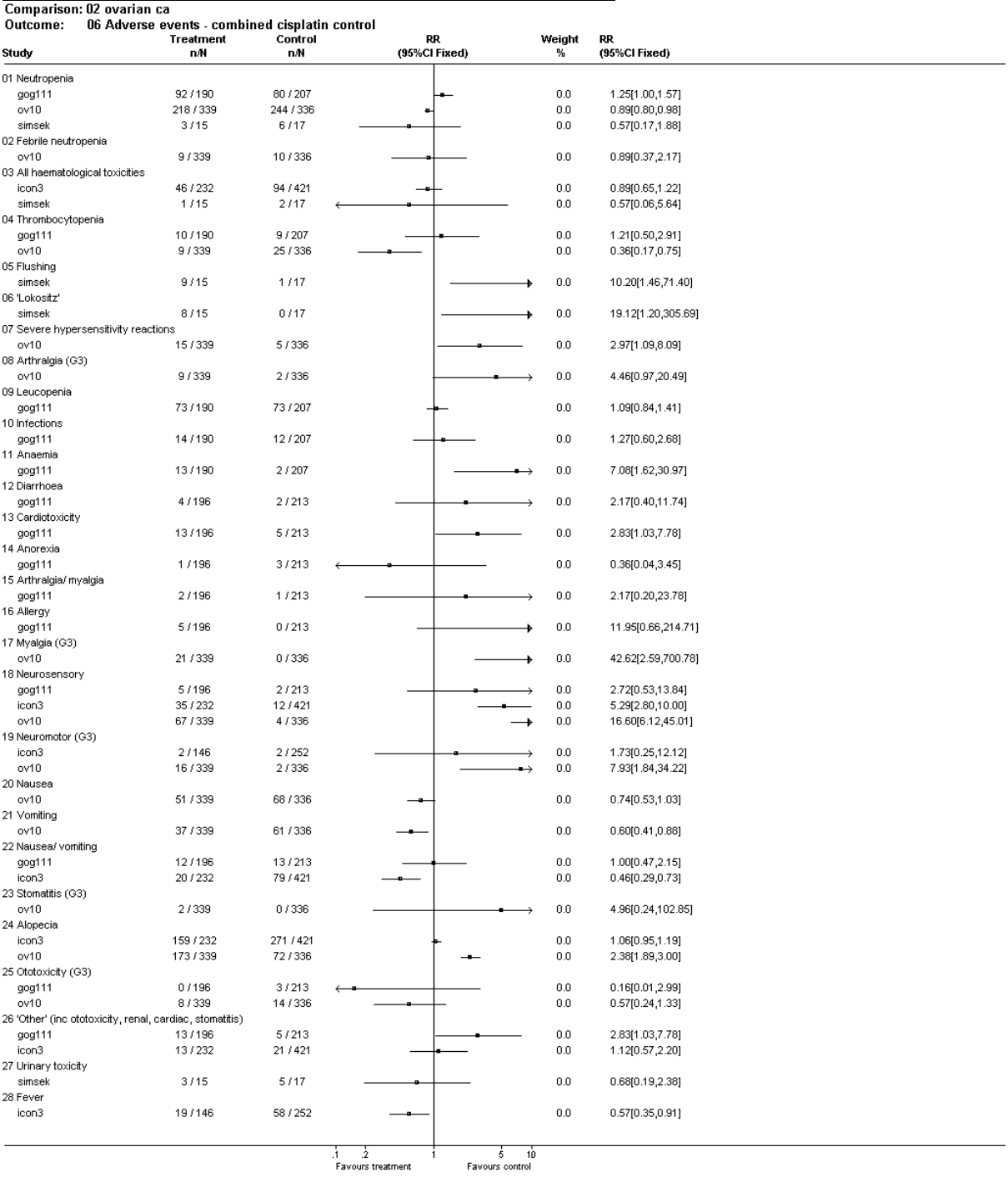


Figure 5: Adverse events – combined cisplatin control



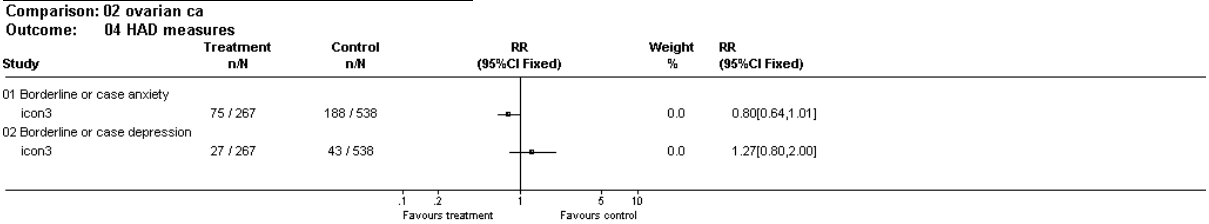
Quality of life

New data

Quality of life was not reported as such in any of the six included trials, however, anxiety and depression were measured in ICON3 using the Hamilton Anxiety and Depression scale at 6 months follow-up.[52] Borderline or case anxiety was reported in 28% of the intervention group versus 35% of the control groups (combined). Depression was reported in 10% of the intervention group versus 8% of the control groups (combined). There were no significant differences between the groups (Figure 9).

Data from original report
With the exception of GOG 111, none of the trials reported quality of life. There was no significant difference in the number of participants in either arm having lower performance status scores during the study compared with base-line (RR: 1.33 (95%CI: 0.86, 2.07)).

Figure 10: Anxiety and depression



Subgroups and sensitivity analyses
OV10[50] used a Cox regression analysis to adjust for known prognostic factors. Hazard ratios were presented for rate of progression at 24 months follow-up (0.74, 95% CI: 0.63, 0.88) and rate of death at 24 months follow-up (0.73, 95% CI: 0.60, 0.89) i.e. the advantage of the paclitaxel arm remained qualitatively unchanged. Sensitivity analyses were not presented for the 39 month follow-up data.
Subgroup analysis in ICON3[52] found no clear evidence that the paclitaxel arm was more or less effective than control in any subgroup for progression free survival or overall survival. Subgroups examined were: randomisation group, number of patients entered by each centre, age, FIGO stage, residual bulk, histological cell type and differentiation. A possible trend was seen in overall survival in favour of centres recruiting more than 50 participants.

Summary of effectiveness data
Six trials were found, three of which were updates of trials previously included in the original review (GOG111, OV10 and ICON3),[50-52, 56] one was a new trial with carboplatin/ paclitaxel combined,[55] one was an interim report[53, 57] and one was a foreign language report of a trial with a very small sample size.[54] The quality of the reporting of the three larger trials[50-52, 56] was deemed to be good and the quality of the reporting of the smaller trials[53-55, 57] was difficult to assess. Four trials looked at paclitaxel combined with cisplatin[50, 51, 53, 54, 56, 57] and two looked at paclitaxel combined with carboplatin[52, 55] for the first-line treatment of advanced ovarian cancer.

The interim report showed no significant differences between groups for any response outcomes, while OV10 found significant differences in favour of paclitaxel therapy for overall response, complete response, partial response and progressive disease. Three trials did not report response rates but one (Simsek[54]) indicated a favourable result in serum levels of Ca^{125}.

The two larger trials reported progression free survival; one (OV10) was highly significant in favour of paclitaxel and the other (ICON3) found no significant differences between groups. Similar results were found in these two trials plus the GOG111 update for overall survival, with OV10 and GOG111 finding a significant result in favour of the paclitaxel arm and ICON3 finding no significant differences between groups.

Participants in the intervention group experienced significantly more flushing, 'lokositz' (perhaps a haematological event), severe hypersensitivity reactions, myalgia, neurosensory and neuromotor events, and alopecia than participants in the control groups. Participants in the control groups experienced significantly more haematological toxicities including neutropenia and thrombocytopenia, nausea and vomiting than participants in the intervention groups. ICON3 was the only trial which reported measures of anxiety and depression, and found no significant differences between groups.

3.3 RESULTS OF ECONOMIC ANALYSIS

3.3.1 Excluded evaluations

Six economic evaluations were excluded after the full manuscripts had been assessed for inclusion. Three reported costs only, not effectiveness,[66-68] one was a non-systematic review,[69] one looked at second-line therapy for advanced ovarian cancer[70] and one was a descriptive study.[71] Further details of excluded evaluations are given in Appendix 8.

3.3.2 Included evaluations

New data

Two conference abstracts were found on economic evaluations of paclitaxel combined with a platinum compound as first-line therapy for advanced ovarian cancer.[72, 73] Both were based on the RCT known as OV10.[50]

The manufacturers, Bristol Myers Squibb, submitted an economic evaluation based on GOG111 which had previously been submitted in confidence to the original review. In this version the methods and clinical outcomes were the same but the costs were updated to current levels. The updated results are reported briefly in the section entitled 'Summary of economic data' below.

3.3.3 Description of included evaluations

Two new economic evaluations were found of paclitaxel combined with cisplatin versus cyclophosphamide combined with cisplatin as a first-line treatment for women with advanced ovarian cancer.[72, 73] Both were found in literature searches for the Bristol-Myers Squibb submission rather than in CRD searches. Both were abstracts from conference proceedings (ASCO 2000). Both were based on the RCT OV10. Both were cost effectiveness analyses.

Source of effectiveness data

Both evaluations derived effectiveness data from the same RCT (OV10).[50] One evaluation[72] used a subset of participants included in the RCT (those from Canadian centres only) for effectiveness outcomes for the economic evaluation and the other used all trial participants for effectiveness outcomes.[73]

Health outcomes

Clinical effectiveness of paclitaxel combined with cisplatin for advanced ovarian cancer was estimated using progression free survival and overall survival derived directly from the RCT

in one evaluation,[72] and using overall survival estimated using both a restricted means analysis and a parametric Weibull model in the other.[73]

Measures of benefit
Benefit was measured in terms of life years gained in both evaluations, and in terms of progression free life years gained in the Canadian evaluation.[72]

Resource use
Resource use data was collected during the RCT for both economic evaluations – for one, from Canadian centres only,[72] and for the other, from a subset of participants recruited by EORTC institutes.[73] In one evaluation it is stated that information was obtained from ambulatory and inpatient units.[72]

Costs
In the all-patient evaluation,[73] costs assessed comprised of direct treatment costs i.e. drugs for chemotherapy, hospital stays and day clinic visits during treatment and follow-up, outpatient visits, concomitant medication, surgery and second-line chemotherapy after progression. Unit cost figures were based on the tariffs of the Belgian health insurance system. Costs were reported in 1998 prices.

In the Canadian evaluation,[72] unit costs were based on detailed data from a major academic medical centre. These data were then used to generate total costs for each case from randomisation to death, excluding costs of drugs for second-line therapy.

Synthesis
The estimated costs and benefits were synthesised using incremental cost per life year gained for the Canadian evaluation[72] and incremental cost effectiveness ratios (ICERs) per life year gained for the all-patient evaluation.[73] In the all-patient evaluation, the impact of uncertainty was assessed by bootstrapping and the results expressed in terms of a cost-effectiveness acceptability curve. In the Canadian evaluation no sensitivity analysis was reported to have been undertaken.

3.3.4 Quality of the included evaluations

Both evaluations were reported only as abstracts from conference proceedings and so a lot of details were missing. The viewpoints of the analyses were not clearly stated and/ or justified. The Belgian evaluation[73] suggested that the comparator used in OV10 may be less than optimal, which casts doubt on the reliability of the results of the economic evaluation. It was not explained why cost-effectiveness analyses rather than cost-utility analyses were used. The Belgian evaluation did not state all primary outcomes measured for the economic evaluation. Discounting was not described in either trial and the Belgian evaluation did not fully report details of currency or price adjustment for inflation or currency conversion. The cost year and perspective of the Canadian evaluation[72] were not stated. The model used in the Belgian evaluation was not well described. Details of statistical tests and sensitivity analyses used were not fully described in either evaluation.

Neither evaluation seems to be applicable to the NHS setting. Both are based on effectiveness data which may not be valid. Costs were collected during the trial for each economic evaluation.

3.3.5 Assessment of cost-effectiveness

Clinical benefit

Canadian evaluation[72]
Median progression free survival 17 months versus 10.1 months.
Median overall survival 36.8 months versus 25.6 months.

Belgian evaluation[73]
Overall survival significantly higher in paclitaxel arm (HR 0.73, 95% CI: 0.60, 0.89)

Costs

Canadian evaluation[72]
Mean cost per patient: paclitaxel/ cisplatin US$30,774
cisplatin/ cyclophosphamide US$18,515

Belgian evaluation[73]
Mean cost per patient paclitaxel/ cisplatin 933,000 BF (= US$25,353*)
Mean cost per patient cisplatin/ cyclophosphamide 668,000 BF (= US$18,152*)
*Conversions carried out by NHSCRD reviewers, using exchange rate given in paper.

Synthesis of cost and benefit

Canadian evaluation[72]
Cost per LYG paclitaxel/ cisplatin versus cisplatin/ cyclophosphamide US$13,315
Cost per progression free LYG p/c versus c/c US$21,321

Belgian evaluation[73]
ICER per LYG (restricted means analysis):
Paclitaxel/ cisplatin vs cisplatin/ cyclophosphamide 0.31 years, 855,000 BF (=US$23,234*)
ICER per LYG (Weibull model):
p/ c vs c/ c 0.79 years, 335,000 BF (=US$9,103*).
*Conversions carried out by NHSCRD reviewers, using exchange rate given in paper.

Both evaluations found paclitaxel/ cisplatin to be both more costly and more effective than cyclophosphamide/ cisplatin, giving it a matrix score of 'A' (incremental analysis required).

Sensitivity analysis

No results were reported for either evaluation.

Implications for practice

Canadian evaluation[72]
The authors state that the paclitaxel/ cisplatin combination has acceptable cost-effectiveness in the treatment of women with advanced ovarian cancer.

Belgian evaluation[73]
The authors state that compared to other accepted treatments analysed with Belgian data, the estimated values of ICER per LYG seem quite low, so the paclitaxel/ cisplatin combination in ovarian cancer would be considered cost-effective.

Data from original report

In the original review, there were nine cost-effectiveness analyses and three cost-utility analyses of paclitaxel as first-line therapy for advanced ovarian cancer. Two UK evaluations used carboplatin rather than cisplatin.
In the original review, the range of incremental costs per life year gained found in two UK cost-effectiveness evaluations comparing paclitaxel plus cisplatin to carboplatin was £7,173 to £12,417, which was within the range reported for all evaluations comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin (£3,960 to £13,360). All nine cost-effectiveness analyses found paclitaxel treatment to be more costly and more effective than control treatment, giving it a matrix score of 'A' (incremental analysis required).
In the cost-utility analyses the range of incremental cost per QALY gained was £5,273 to £11,269. All three scored 'A' on the matrix as they were both more costly and more effective than comparator treatments.

Summary of economic data
For the update report, two new economic evaluations were found,[72, 73] both of which were based on subgroups of OV10.[50] One was set in Canada[72] and one in Belgium;[73] both reports were not applicable to the NHS. The Canadian evaluation found the cost per LYG for paclitaxel/ cisplatin versus cisplatin/ cyclophosphamide to be US$13,315 and the cost per progression free LYG for paclitaxel/ cisplatin versus cyclophosphamide/ cisplatin was US$21,321.
The Belgian evaluation found ICER per LYG for paclitaxel/ cisplatin vs cisplatin/ cyclophosphamide using a restricted means analysis to be US$23,234 and using a Weibull model to be US$9,103.
Both economic evaluations suggest that paclitaxel is a cost-effective treatment (matrix score 'A'), if the findings of OV10 are valid. If the findings of OV10 are not valid, as suggested in this report, these economic analyses are not valid either and must be disregarded.

The updated submission from Bristol Myers Squibb reported an additional 0.702 life years at an incremental cost of £7,074 per life year gained and an additional 0.459 years free of disease progression at an incremental cost of £10,808 per progression-free life year gained with Taxol/ carboplatin versus carboplatin. These figures are based on the assumption that cisplatin and carboplatin in combination with Taxol were similar in efficacy. This is not necessarily an appropriate assumption and means that the figures reported are based on an indirect comparison rather than data reported directly from RCTs.

In the original review, the range of incremental costs per life year gained found in two UK cost-effectiveness evaluations comparing paclitaxel plus cisplatin to carboplatin was £7,173 to £12,417, which was within the range reported for all evaluations comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin (£3,960 to £13,360). All nine cost-effectiveness analyses found paclitaxel treatment to be more costly and more effective than control treatment, giving it a matrix score of 'A' (incremental analysis required).
In the cost-utility analyses the range of incremental cost per QALY gained was £5,273 to £11,269. All three scored 'A' on the matrix as they were both more costly and more effective than comparator treatments.
Most of the evaluations, apart from the first two mentioned, used similar treatments to those used in GOG 111 and OV10, which may invalidate their findings (see above).

4. DISCUSSION

4.1 Main findings

Four RCTs were identified in the original report, with 3770 participants. The update searches identified a further six RCTs, of which three were new (one was an interim report and one a very small trial, one was larger but only reported as a conference abstract) and three were updates of trials previously included in the original report (GOG111, OV10 and ICON3). In total, seven RCTs were included with 4108 participants. The studies were of moderate to good quality. Patients in two of the trials had significantly greater progression free survival and overall survival than controls, however the largest trial by far (ICON3) found no significant differences between groups. No significant differences were found between groups on quality of life measures. Paclitaxel patients experienced significantly less haematological toxicities in ICON3, but more fever, alopecia, neurosensory and neuromotor events than single agent carboplatin, and significantly more flushing, myalgia, neurosensory and neuromotor events, alopecia and severe hypersensitivity reactions than combined cisplatin control treatment. Combined cisplatin control was associated with significantly more haematological toxicities and nausea and vomiting than paclitaxel/ cisplatin. In the Wolf trial, paclitaxel was associated with significantly more alopecia and neurotoxicity than combined carboplatin/ cyclophosphamide control but significantly less haematological toxicity. In the original review in ICON3 a significantly greater incidence of neutropenia, cardiovascular adverse events, hypersensitivity and allergic reactions were seen in the paclitaxel than control arm despite premedications.

Economic evaluations based on the OV10 treatments (paclitaxel/ cisplatin versus cisplatin/ cyclophosphamide) found the paclitaxel combination to be cost effective (matrix score 'A'). However if there is no survival benefit, as indicated by ICON3, these evaluations would not be based on valid data and in fact the confidence intervals for cost per QALY would include infinity, making paclitaxel less cost-effective than the control treatments. An updated economic evaluation based on GOG111 reported incremental cost effectiveness ratios for taxol/ carboplatin versus carboplatin, which were not trial arms in GOG111.

4.2 Limitations of the review

The majority of included trials had some methodological problems and/or were insufficiently reported. It is important that trials are not only conducted well but also reported adequately.

Two ovarian cancer trials[52, 64] gave sufficient details of the generation of the randomisation sequence. Only one ovarian cancer trial[52] also reported details of concealment of allocation. Proper randomisation ensures that selection bias is avoided by ensuring that participants have a prespecified (very often equal) chance of being assigned to the experimental or control group. An adequate procedure for generating a random number list should therefore be used.[74] Fore knowledge of group assignments leaves the allocation sequence subject to manipulation by researchers and participants.[74] Concealed random allocation of interventions by an independent person who is not responsible for determining the eligibility of patients is therefore essential. Previous research has demonstrated that randomised and non-randomised controlled trials may produce different results.[75] RCTs that have used an

inadequate randomisation procedure or have not clearly demonstrated allocation concealment may overestimate the treatment effect size.[75]

No trial reported on blinding. Previous research has shown that non-blinded trials can overestimate the treatment effect.[76] Whilst blinding in cancer trials is acknowledged to be difficult or even impossible to undertake due to the nature of the disease and of the drugs being given, lack of blinding may have implications for administration of co-interventions, cross-over to the alternate treatment arm and any subjective clinician evaluated outcome measures such as alleviation of symptoms (if assessed, see below), response and QOL. It should at least be reported whether blinding took place or not, and trialists should be aware of these potential limitations inherent in cancer treatment trials where blinding cannot take place.

It is important in any trial that baseline characteristics are comparable between intervention groups. The most important baseline characteristics, as determined by the expert panel for previous NICE reviews for breast and ovarian cancer, were not all reported therefore it cannot be assumed that the participants in each treatment group did not differ.

Several trials did not report clearly the duration over which the treatment was given, which has both a cost and clinical impact.

Loss to follow-up was less than 20% in all trials. A high attrition rate means that the data presented for the remaining participants may not be representative of outcomes for the whole group. An intention to treat (ITT) analysis (where participants are analysed according to the groups to which they were initially randomly allocated, regardless of whether or not they dropped out, fully complied with the treatment or crossed over and received the other treatment) protects against attrition bias. Ignoring the findings of all withdrawals/dropouts and non-responders means that only those who fully complied with treatment were included in the analysis which could lead to an overestimation of the average treatment effect or, worse, a biased comparison if compliance level is influenced by effectiveness (although this may not be likely for intravenous therapy).

Information relating to outcome measures was sometimes poorly reported. For some outcomes, only percentages were reported, rather than actual numbers, making it difficult to calculate summary statistics and their confidence intervals, especially where it was not clear how many participants were being assessed for the outcome. Definitions of outcome measures were often not clearly stated (for example whether partial response referred to a 25% reduction or 50% reduction in size of a tumour) and often details of how outcomes were measured were not given either. This limits the comparability of trials.

Survival data were often presented inadequately with no hazard ratio or measure of its variance. Trial authors sometimes stated that there was a significant difference in survival, and gave p-values from a log-rank test but did not present median survival and its variance. Follow-up times were not always stated. The numbers included in the group comparisons at the end of survival curves were sometimes not given. The ideal measure of survival would be hazard ratios presented with standard errors or 95% confidence intervals. The second best measure would be Kaplan-Meier curves and a log rank test conducted, to see if there was a significant difference between the two curves, presented with the p value (the log rank test takes into account the data from the whole curve). The third best method would be to present

median survival, which is read from a single point (in time) along the Kaplan-Meier curves. It is also very important when reading the data from the curves to make sure that the difference between the curves at this point in time is representative of the whole curves (i.e. there may be a large difference between the curves at this point only with the curves merging close together before and after). Survival data tended to be better reported in the ovarian cancer trials than the breast cancer trials.

Response to treatment may not be a very relevant outcome measure in that it may not impact upon a patient's survival or quality of life. It is possible that tumour shrinkage may alleviate symptoms (especially pain) where these are present (however women with ovarian cancer may have few or no symptoms) and improve quality of life. However, quality of life outcomes were not addressed directly by most of the trials.

One source of publication bias is where trials which do not show the intervention to be effective or do not report significant findings do not get published. This may be due to the reluctance of the authors themselves or due to the editorial policies of journals. This can be a particular problem with industry sponsored trials with companies often only wanting to publish positive results relating to their products, or alternatively there may be a longer delay in publication of less positive findings.

4.3 Interim reports

One trial of paclitaxel for advanced ovarian cancer[53] was published as an interim report. The results of interim reports should be regarded with caution as they will be superseded by the results of the final report, which could be different.

4.4 Ongoing trials

A trial reported to be ongoing is the RM1273 trial comparing topotecan and cisplatin to paclitaxel and cisplatin in ovarian cancer.[77]

4.5 Missing outcomes

Quality of life was not reported for any trial and anxiety and depression outcomes were reported for ICON3 only.[52] It is arguable that for people with advanced ovarian cancer, data on quality of life and/ or relief of symptoms (especially pain) where these are present may be very important outcomes and should be reported more often.

4.6 Why is ICON3 different from the other ovarian trials?

It was stated in the original review that if the mature results of ICON3 did produce different results from OV10 and GOG 111 this would not invalidate the results of the latter two trials, as these were of good quality. It was also stated that the ICON3 trial included a far wider range of patients than the other two trials and that subgroup analysis may find that the effectiveness of paclitaxel depends on the stage of ovarian cancer. In this update report, it was acknowledged that ICON3, unlike the other two trials, included women with FIGO stage I ovarian cancer (i.e. less advanced). However only around 10% of trial participants had FIGO stage I ovarian cancer. 91% of participants in ICON3 were similar to participants in

OV10. Participants were also similar between ICON3 and OV10 in terms of the proportion with poorly differentiated or defined disease. Subgroup analysis carried out in the ICON3 trial found no significant heterogeneity in progression free or overall survival between trial participants in terms of FIGO stage, residual bulk, histological cell type or differentiation, indicating that these participant characteristics did not influence response to treatment.

ICON3 used a different platinum compound – carboplatin – to the other trials, which used cisplatin. Carboplatin is more commonly used in the UK. Three trials have shown no difference in the effect of carboplatin and cisplatin when compared as monotherapy,[11] however this may not be the case when they are used in combination. Interim reports from three trials comparing cisplatin/ paclitaxel against carboplatin/ paclitaxel do not show any significant differences in progression free survival (results for overall survival are not yet available).[78-80]

Control regimens differed between trials: GOG 111 and OV10 both used cyclophosphamide combined with cisplatin while ICON3 allowed a choice between single agent carboplatin and a combination of cyclophosphamide, doxorubicin and cisplatin. Analysis carried out by the authors of the ICON3 trial found significant heterogeneity between groups of trials with different control groups in progression free or overall survival, indicating that choice of control group may have influenced response to treatment.[81] It has been suggested previously that the choice of control arm in GOG 111 and OV10 may have been less effective than other control treatments.[82]

The other trial reported in the original report, GOG 132, was criticised for allowing substantial crossover from the control arm to taxanes prior to progressive disease being reported, resulting in possible confounding of results. The results of this trial were similar to those of ICON3, i.e. no significant differences between taxane and control groups. The authors of ICON3 report that heterogeneity between the trials is not accounted for by the extent of crossover and that the findings of GOG 132 may therefore be valid.[81]

It is worth noting that ICON3 recruited more patients than GOG111 and OV10 added together, even if only patients with gross macroscopic disease (>2cm in diameter at end of initial laparotomy) were counted.

In summary, two of the four best known trials report a significant advantage for paclitaxel combined with a platinum compound over control treatment, but the largest trial by far reports no significant advantage. No obvious reason for these differences can be found, although it may be the case that the control treatment used in the two trials which found in favour of paclitaxel was inadequate. This cannot be confirmed, however the body of evidence does not support the use of paclitaxel combined with a platinum compound.

It has been suggested that taxanes may be most effective in those with bulky disease, although this was not seen on subgroup analysis in ICON3. If this opinion is widely held it may be worthwhile to conduct another RCT in those with bulky disease.

4.7 Economics

For the ovarian cancer review, two new economic evaluations were found,[72, 73] both of which were based on subgroups of OV10.[50] Both scored 'A' on the matrix (more costly and more effective).
Both economic evaluations suggest that paclitaxel is a cost-effective treatment if the findings of OV10 are valid.
In the original review, all nine cost-effectiveness analyses and all three cost-utility analyses found paclitaxel treatment to be more costly and more effective than control treatment, giving it a matrix score of 'A'.

Most of these evaluations used similar treatments to those used in GOG 111 and OV10, which may invalidate their findings.
If the findings of OV10 are not valid, as suggested in this report, these economic analyses are not valid either and must be disregarded. If the findings of ICON3 are valid and there is no difference in effectiveness between paclitaxel and non-paclitaxel containing treatments, the confidence limits of the cost-effectiveness estimate would include infinity and paclitaxel would definitely not be cost-effective.

For all evaluations, weaknesses in the estimates of effectiveness may affect the generalisability of the results.

4.8 How have the findings changed from the original report?

Two updated trials show a highly beneficial effect of paclitaxel combined with a platinum compound (OV10 and GOG111), one very small trial shows some beneficial effect (Simsek) but the largest trial plus one interim report show no effect (ICON3 and Gennatas). ICON3 is by far the largest trial but is the only trial of paclitaxel plus carboplatin to report response and survival data. In the original review, two trials showed a beneficial effect of taxane therapy (OV10 and GOG111) and two showed no beneficial effect (one being ICON3). The difference might be explained by differences in control treatments used, but this is inconclusive. It should be seriously considered whether single agent carboplatin should be used as first-line treatment for advanced ovarian cancer, rather than a taxane, given the unfavourable side effect profile of the taxanes and the economic data (if taxanes offer no survival benefit, the confidence interval for cost per QALY would include infinity).

4.9 Need for further research

It has been suggested that future RCTs should look at the administrative schedule of taxanes given as combination therapy, to determine whether the chemotherapeutic agents should be given together or sequentially.

If the results of ICON3 are believed to be correct then no further trials of paclitaxel for first-line treatment of advanced ovarian cancer should be needed. However if the results of ICON3 are not believed to be correct, a further trial comparing paclitaxel/ carboplatin to carboplatin restricting participants to those with bulky disease may be warranted.

5. CONCLUSIONS

- The updated results of the ICON3 trial show no beneficial effect of paclitaxel combined with carboplatin over carboplatin alone or CAP (cisplatin, cyclophosphamide, doxorubicin) for any subgroups. This is the largest trial and contradicts results found in two other, much smaller, well known trials of paclitaxel combined with cisplatin in the first-line treatment of advanced ovarian cancer, while adding weight to the results of one other RCT and an interim report. No obvious reason can be found for the discrepant results, although they may be due to differences in the control treatments. The evidence does not appear to support the use of paclitaxel in this context, and may provide a case for considering the use of carboplatin as first-line treatment for advanced ovarian cancer, rather than taxanes.

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APPENDIX 1: Staging of ovarian cancers

FIGO Staging for Epithelial Cancer of the Ovary[7]

Stage Ia-b may be referred to as early ovarian cancer; later stages may be referred to as advanced.

Stage I: Growth limited to the ovaries

Ia. One ovary

Ib Both ovaries involved

Ic, Ascites (an accumulation of fluid in the abdominal (peritoneal) cavity) present or positive peritoneal washings

Stage II: Growth limited to pelvis

IIa Extension to gynaecological adnexae (on or in a structure associated with the uterus such as on ovary, fallopian tube or uterine ligament)

Iib Extension to other pelvic tissues

Iic Ascites or positive washings

Stage III: Growth extending to abdominal cavity - including peritoneal surface seedlings, omentum
May be subdivided (a or b) by bulk of intra-abdominal mass

Stage IV: Metastases to distant sites (including hepatic parenchymal disease)

APPENDIX 2: SEARCH STRATEGIES AND RESULTS

Database	Host	Dates covered	Date searched	Hits	Full/ titles	Strategy name	Imported into Endnote
MEDLINE	Silverplatter/ARC	1999– 2001/10	28/11/01	116	Full	Meupdate.his	Yes
EMBASE	Silverplatter/ARC	1999 – 2001/10	28/11/01	136	Full	Emupdate.his	Yes
CancerLit	Silverplatter/ARC	1999 – 2001/10	28/11/01	33	Full	Meupdate.his	Yes
Cochrane Controlled Trials Register (CCTR)	CD-ROM	Issue 4: 2001	28/11/01	58	Full	Cctrstr.txt	Yes
National Research Register (NRR)	CD-ROM	Issue 3: 2001	28/11/01		Full Full	Nrrstr.his	No

After deduplication a total of 343 records were imported into an Endnote Library, Taxupdate4.enl,

No update limits were applied to EMBASE or MEDLINE as any duplicate records could be deleted at the Endnote stage of the searches. CancerLit does not allow limiting by update code therefore duplicate records were again deleted before entering into the Endnote Library. The CCTR and NRR allow searching of "new this issue" so this was applied to avoid duplication with previous searches.

EMBASE: Silverplatter Version. (1999 – 2001/10)

The search was rerun and the records limited to post 1999.
SilverPlatterASCII 3.0WINNSelected Databases

1. explode "Breast-Neoplasms"/ all subheadings
2. ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
3. ovar* near4 ((oncolog* or carcinoma*) in ti ab)
4. breast* near4 ((oncolog* or carcinoma*) in ti ab)
5. breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
6. explode "Ovarian-Neoplasms"/ all subheadings
7. (adnexa* near mass*)
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. "Paclitaxel"/ all subheadings
10. paclitaxel*
11. docetaxel*
12. taxol*
13. taxotere*
14. taxanes
15. #9 or #10 or #11 or #12 or #13 or #14
16. #8 and #15
17. explode "economic-evaluation"/ all subheadings
18. cost effect*
19. cost benefit*
20. economic evaluation*
21. technology assessment*
22. pharmacoeconomic*
23. cost util*
24. #17 or #18 or #19 or #20 or #21 or #22 or #23
25. #16 and #24
26. explode "Breast-Neoplasms"/ all subheadings
27. ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
28. ovar* near4 ((oncolog* or carcinoma*) in ti ab)
29. breast* near4 ((oncolog* or carcinoma*) in ti ab)
30. breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
31. explode "Ovarian-Neoplasms"/ all subheadings
32. (adnexa* near mass*)
33. #26 or #27 or #28 or #29 or #30 or #31 or #32
34. "Paclitaxel"/ all subheadings
35. paclitaxel*
36. docetaxel*
37. taxol*
38. taxotere*
39. taxanes
40. #34 or #35 or #36 or #37 or #38 or #39
41. #33 and #40
42. explode "Clinical-Trials"/ all subheadings
43. (clin* near trial*) in ti ab
44. ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
45. Placebos
46. placebo* in ti ab

47. random in ti ab
48. "randomized-controlled-trial"/ all subheadings
49. #42 or #43 or #44 or #45 or #46 or #47 or #48
50. #41 and #49
51. #50 or #25

MEDLINE: Silverplatter Version. (1999 - 2001/10)

The search was rerun and the records limited post 1999.
SilverPlatterASCII 3.0WINNSelected Databases

1. explode "Breast-Neoplasms"/ all subheadings
2. ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
3. ovar* near4 ((oncolog* or carcinoma*) in ti ab)
4. breast* near4 ((oncolog* or carcinoma*) in ti ab)
5. breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
6. explode "Ovarian-Neoplasms"/ all subheadings
7. (adnexa* near mass*)
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. "Paclitaxel"/ all subheadings
10. paclitaxel*
11. docetaxel*
12. taxol*
13. taxotere*
14. taxanes
15. #9 or #10 or #11 or #12 or #13 or #14
16. #8 and #15
17. "Cost-Benefit-Analysis"/ all subheadings
18. cost effect*
19. cost benefit*
20. cost util*
21. economic evaluation*
22. technology assessment*
23. pharmacoeconomic*
24. #17 or #18 or #19 or #20 or #21 or #22 or #23
25. #16 and #24
26. explode "Breast-Neoplasms"/ all subheadings
27. ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
28. ovar* near4 ((oncolog* or carcinoma*) in ti ab)
29. breast* near4 ((oncolog* or carcinoma*) in ti ab)
30. breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
31. explode "Ovarian-Neoplasms"/ all subheadings
32. (adnexa* near mass*)
33. #26 or #27 or #28 or #29 or #30 or #31 or #32
34. "Paclitaxel"/ all subheadings
35. paclitaxel*
36. docetaxel*
37. taxol*
38. taxotere*
39. taxanes

40. #34 or #35 or #36 or #37 or #38 or #39
41. #33 and #40
42. trial in pt
43. explode "Clinical-Trials"/ all subheadings
44. (clin* near trial*) in ti ab
45. ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
46. Placebos
47. placebo* in ti ab
48. random in ti ab
49. research-design
50. #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49
51. #41 and #50
52. #25 or #51

CancerLit: Silverplatter Version. (1999 - 2001/10)

The MEDLINE search strategy was used.
SilverPlatterASCII 3.0WINNSelected Databases

1. explode "Breast-Neoplasms"/ all subheadings
2. ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
3. ovar* near4 ((oncolog* or carcinoma*) in ti ab)
4. breast* near4 ((oncolog* or carcinoma*) in ti ab)
5. breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
6. explode "Ovarian-Neoplasms"/ all subheadings
7. (adnexa* near mass*)
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. "Paclitaxel"/ all subheadings
10. paclitaxel*
11. docetaxel*
12. taxol*
13. taxotere*
14. taxanes
15. #9 or #10 or #11 or #12 or #13 or #14
16. #8 and #15
17. "Cost-Benefit-Analysis"/ all subheadings
18. cost effect*
19. cost benefit*
20. cost util*
21. economic evaluation*
22. technology assessment*
23. pharmacoeconomic*
24. #17 or #18 or #19 or #20 or #21 or #22 or #23
25. #16 and #24
26. explode "Breast-Neoplasms"/ all subheadings
27. ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
28. ovar* near4 ((oncolog* or carcinoma*) in ti ab)
29. breast* near4 ((oncolog* or carcinoma*) in ti ab)
30. breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
31. explode "Ovarian-Neoplasms"/ all subheadings

32. (adnexa* near mass*)
33. #26 or #27 or #28 or #29 or #30 or #31 or #32
34. "Paclitaxel"/ all subheadings
35. paclitaxel*
36. docetaxel*
37. taxol*
38. taxotere*
39. taxanes
40. #34 or #35 or #36 or #37 or #38 or #39
41. #33 and #40
42. trial in pt
43. explode "Clinical-Trials"/ all subheadings
44. (clin* near trial*) in ti ab
45. ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
46. Placebos
47. placebo* in ti ab
48. random in ti ab
49. research-design
50. #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49
51. #41 and #50
52. #25 or #51

The Cochrane Controlled Trials Register (Issue 4: 2001)

The Cochrane Controlled Trials Register (CCTR) was searched via the Cochrane Library CD-ROM. The search strategy was run on each version of the Cochrane Library released since the initial search and records were limited to "new this issue".

1. PACLITAXEL*:ME
2. PACLITAXEL*
3. DOCETAXEL*
4. TAXOL*
5. TAXANES
6. TAXOTERE*
7. (((((#1 or #2) or #3) or #4) or #5) or #6)
8. OVARIAN-NEOPLASMS*:ME
9. ((CANCER* or ONOCOLOGY) or NEOPLASM*)
10. (((TUMOUR* or TUMOR*) or MALIGNAN*) or CARCINOMA*)
11. (BREAST or OVAR*)
12. BREAST-NEOPLASMS*:ME
13. (#8 or #12)
14. ((#9 or #10) and #11)
15. (#13 or #14)and (#7)

National Research Register CD-ROM (Issue 3: 2001)

The National Research Register (NRR) was searched via the CD-ROM. The search strategy was run on the latest version of the National research Register and records were limited to "new this issue". The results were then printed out for browsing.

1. PACLITAXEL*
2. DOCETAXEL*
3. TAXOL*
4. TAXANES
5. TAXOTERE*
6. #1 or #2 or #3 or #4 or #5

APPENDIX 3: DATA EXTRACTION SHEETS FOR EFFECTIVENESS TRIALS

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) Gennatas 2000[53, 57]	**Intervention:** Cisplatin plus paclitaxel **N:** 43 **Dose:** Cisplatin 75mg/m2 and paclitaxel 175mg/m2 **Number of cycles:** 6 **Length of cycles:** Not stated **Control:** Cisplatin plus cyclophamide **N:** 42 **Dose:** Cisplatin 75mg/m2 and cyclophosphamide 700mg/m2 **Number of cycles:** 6 **Length of cycles:** Not stated **Length of follow-up:** Not stated **Comments:** Treatment evaluation was done at the end of cycle 3 and 6.	**Age:** Not stated **Type of cancer:** Advanced ovarian cancer **Stage of cancer:** FIGO stage IIIa, IIIb, IIIc and IV **Stage of therapy:** Not stated **Prior treatments:** Not stated **Inclusion/ exclusion criteria:** Not stated **Further details:** None reported	**Intervention group n:** The number of participants with measurable or evaluable disease was 37. **Control group n:** The number of participants with measurable or evaluable disease was 33.	It was reported that paclitaxel/cisplatin combination causes hematological toxicity more severe than the cyclophosphamide/cisplastin combination. However with the use of Amifostine and /or G-CSF neutropenia was managed without significant problems. Alopecia, allergic reactions, and peripheral toxicity are also more common with paclitaxel/cisplastin than with cyclosphamide/cisplatin. Gastrointestinal toxicity was about the same in the two groups. No actual figures were presented.	**Authors' conclusions:** The preliminary analysis of this ongoing trial has revealed a superiority of the cisplatin and paclitaxel combination, which has not reached statistical significance so far. The toxicity of the two regimens is about the same but the cisplatin-paclitaxel combination requires more active supportive measures.

Results				
General comments:	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Interim findings as the trial was reported to be ongoing. There was no significant difference (p=0.512) in the response rate. The effect on progession-free survival and overall survival of the two regimens had not yet been evaluated.	**Outcome:** Complete response **Intervention:** 22/37 **Control:** 17/33	**Outcome:** Partial response **Intervention:** 5/37 **Control:** 4/33	**Outcome:** Stable disease **Intervention:** 3/37 **Control:** 5/33	**Outcome:** Progressive disease **Intervention:** 7/37 **Control:** 7/33

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) Wolf 1999[55]	**Intervention:** Carboplatin plus paclitaxel **N:** 106 **Dose:** Carbplatin AUC 6 and paclitaxel 175mg/m2 **Number of cycles:** 6 **Length of cycles:** 4 weeks **Control:** Carboplatin plus cyclophosphamide **N:** 106 **Dose:** Carboplatin AUC 6 and cyclophosphamide 600mg/m2 **Number of cycles:** 6 **Length of cycles:** 4 weeks **Length of follow-up:** Not stated **Comments:** Recruited from 1/95 to 1/98. All received antiemetic prophylaxis and the paclitaxel group also received antiallergic prophylaxis prior to chemotherapy.	**Age:** Mean 57 Years (range 27-79) **Type of cancer:** Advanced ovarian cancer **Stage of cancer:** FIGO stage IIb, III and IV **Stage of therapy:** First line **Prior treatments:** Not stated **Inclusion/ exclusion criteria:** FIGO stage IIb-IV, ECOG performance status 0-2, normal haematological, liver and renal function. **Further details:** FIGO II (n=18), FIGO III (n=148), FIGO IV (n=46).	Overall, 260 were recruited and randomised, 212 are available for documentation.	In the control arm all 6 cycles were given 88 times (83 times in paclitaxel arm), 4% broke off because of severe side effects (7% in paclitaxel arm). In the paclitaxel arm 5 patients developed an allergic shock after a few mL of infusion. Side effects (Grade 3 or 4): Paclitaxel / Control Nausea 8% / 13% Mucositis 2% / 0% Neurotoxicity 14% / 0% Alopecia 72% / 27% Leucopenia 14% / 27% Thrombocytopenia 5% / 22% Anaemia 4% / 21% In the control arm 46 patients had at least one blood transfusion compared to only 21 patients in the paclitaxel arm. 10 patients got platelets in the ocntrol arm compared to 1 in the paclitaxel arm.	**Authors' conclusions:** Both therapy schemes are well tolerated. The drop out rate due to side effects is very low. 5% of the patients receiving paclitaxel showed an acute allergic reaction that made further administration impossible. Haematological problems are the most common and might lead to blood or platelet transfusions or G-CSF administrations in both arms. Pancytopenia occurs more often in the control arm than the paclitaxel arm. Grade III/IV alopecia is seen more often in the paclitaxel arm as is grade I/II neurotoxicity. Slight nausea/ emesis is common in both arms, although antiemetic therapy was given.

Results				
General comments: The abstract states that a detailed analysis of response will follow.				

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) The ICON Collaborators 2000[52] **Trial ID:** **ICON3**	**Intervention:** Paclitaxel/ carboplatin (CP) N: 701 **Dose:** Paclitaxel 175mg/m2 in a 3 hr infusion, Carboplatin min 5(GFR+25)mg (determined by area under curve method) **Number of cycles:** 6 **Length of cycles:** 3 weeks **Control:** Carboplatin (C) **N:** 943 Dose: Min 5(GFR+25)mg (determined by area under curve method) **Number of cycles:** 6 **Length of cycles:** 3 weeks **Control 2:** Cyclophosphamide/ doxorubicin/ cisplatin (CAP) **N:** 421 **Dose:** Cyclophosphamide 500mg/m2, doxorubicin 50mg/m2, cisplatin 50mg/m2 **Number of cycles:** 6 **Length of cycles:** 3 weeks **Length of follow-up:**	**Age:** Median 58.9 years **Type of cancer:** Invasive ovarian epithelial cancer **Stage of cancer:** FIGO stage I-IV **Stage of therapy:** First-line **Prior treatments:** Surgery (total abdominal hysterectomy, bilateral salpingo-oophorectomy and thorough staging were recommended as minimal surgical procedures) **Inclusion/ exclusion criteria:** Histologically confirmed invasive ovarian cancer of epithelial origin with no concomitant or previous malignant disease likely to interfere with treatment or outcomes. Not received any previous radiotherapy or chemotherapy. Informed consent. **Further details:** 9% FIGO stage I, 11% FIGO stage II, 64% FIGO stage III, 16% FIGO stage IV. Residual bulk of disease: none or microscopic 30%, <2cm 24%, >2cm 46%. Differentiation: poor 52%, moderate 33%, well 11%. Histological cell type: serous 53%, mucinous 7%, endometrious 16%, clear cell 6%, undifferentiated 7%, other 10%. Pre-treatment intervention groups were well balanced in terms of the specified patient characteristics.	**Intervention group n:** 0 **Control group n:** 0	All grade 3/4 unless otherwise stated. Neuropathies only measured in non-Italian centres CP(701) C(943) CAP(421) Alopecia 457 29 271 Nausea/vomiting 54 70 79 Haematological 132 233 94 Fever 43 15 58 Sensory neuropathy (G2,3) 108 4 12 Motor neuropathy 7 1 2 Other (inc ototoxicity, renal, cardiac, stomatitis) 40 36 21	**Authors' conclusions:** Up to 3.5 years from treatment, single agent carboplatin, CAP and paclitaxel plus carboplatin are all safe and show similar effectiveness as first line treatments for women requiring chemotherapy for ovarian cancer. The considerably more favourable toxicity profile of single agent carboplatin by comparison with both CAP and paclitaxel plus carbolpatin suggests that this can be regarded as a reasonable option as first-line chemotherapy for ovarian cancer.

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
	Median 34 months **Comments:** Carboplatin dose calculated using area under curve method of Calvert et al. GFR is the glomerular filtration rate determined by radioisotope method or 24 hour urine collection. All drugs given on day 1 of each cycle. For control group 2, one centre used a cisplatin dose of 75mg/m2. Control group was chosen by investigator before randomisation. Of 4 randomising groups, 2 randomised 2:1 in favour of the control arm and 2 randomised 1:1. All centres randomising through the Scandinavian group used the higher dose of cisplatin in the CAP combination.				

Results				
General comments: No clear evidence that PC was more or less effective than control in any subgroup for either progression free survival or overall survival. Possible trend in overall survival in favour of centres recruiting >50pts. Treatments given on progression and before progression are listed in the paper. Overall survival: an analysis allowing for possible imbalances in pretreatment characteristics across the research and control arms (by Cox's proprtional hazards model) gave a hazard ratio of 0.92.	**Outcome 1** **Outcome:** Progression free survival **Intervention:** Median 17.1 months. Hazard ratio 0.94 (95% CI: 0.84, 1.05, p=0.24). Absolute improvement in 1 yr PFS = 2% (-1%, 5%) **Control:** Median 16.1 months. Carboplatin group. HR 0.95 (0.83, 1.08) CAP group. HR 0.91 (0.74, 1.11)	**Outcome 2** **Outcome:** Overall survival **Intervention:** Median 37.6 months. Hazard ratio 0.96 (0.84, 1.09. P=0.53). Absolute difference in 2 year survival 1% (-3%, 5%). **Control:** Median 36.1 months. Carboplatin group. HR 0.94 (0.80, 1.10). CAP group. HR 1.01 (0.80, 1.27).	**Outcome 3** **Outcome:** Anxiety and depression (HAD scale) (6 months) **Intervention:** Borderline or case anxiety 28%, depression 10% **Control:** Both groups combined: borderline or case anxiety 35%, depression 8%	

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) Piccart 2000[50] **Trial ID:** **OV10**	**Intervention:** Paclitaxel combined wuith cisplatin (TP) N:342 **Dose:** T at 175 mg/m2 as 3-hour infusion and P at 75mg/m2 **Number of cycles:** Median = 6 (range 0-10) **Length of cycles:** 3 weeks **Control:** Cyclosphamide plus cisplatin (CP) **N:**338 **Dose:** C at 750mg/m2 followed by P at 75mg/m2 **Number of cycles:** Median = 6 (range 0-10) **Length of cycles:** 3 weeks **Length of follow-up:** Accrual time 18months + followed-up further 24 months **Comments:** TP and CP were given as inpatient or outpatient regimens. A substitute of carboplatin for cisplatin (12% in TP arm and 9% in CP arm) was allowed in the following circumstances: severe renal toxicity; substantial hearing loss and/or WHO grade 3 or 4 neurotoxicity. In the latter case paclitaxel was also	**Age:** 22-85 years (TP median 58 range 23-79; CP median 58 range 22-85) **Type of cancer:** Advanced epithelial ovarian cancer. **Stage of cancer:** Stage II (B-C), III and IV **Stage of therapy:** First-line **Prior treatments:** Participants who had received previous chemotherapy or radiotherapy were excluded. **Inclusion/ exclusion criteria:** Women had to have their initial surgical procedure within less than 8 weeks of recruitment, which could consist of an optimal (≤ 1cm residual mass) or suboptimal (>1cm residual mass) tumour cytoreduction. Exclusion criteria: WHO performance status of 4; inadequate bone marrow or renal function; complete bowel obstruction or presence of brain metastasis; borderline ovarian tumours or abdominal carcinomas of unknown origin; history of medically significant atrial or ventricular arrhythmias; congestive heart failure; a documented myocardial infarction within 6 months preceding randomisation; a second malignant disease (with exception of an adequately treated in situ carcinoma of the uterine cervix or basal cell carcinoma of the skin); expected inadequacy of follow-up; or active infection or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment. **Further details:** Tumour grade: well defined n=57;	**Intervention group n:** 52 **Reasons:** 23 for progression, 22 for toxicity, 7 for other reasons. 4/342 participants were considered to be ineligible. **Control group n:** 71 **Reasons:** 47 for progression, 15 for toxicity, and 9 for other reasons. 8/338 were considered to be ineligible.	TP(n=339) CP(n=336) Neutropenia(G3,4) 218 244 Febrile neutropenia 9 10 Thrombocytopenia(G3,4) 9 25 Nausea(G3,4) 51 68 Vomiting (G3+4) 37 61 Stomatitis(G3) 2 0 Alopecia(G3) 173 72 Arthralgia(G3) 9 2 Myalgia(G3) 21 0 Neurosensory (G3,4) 67 4 Neuromotor (G3) 16 2 Ototoxicity (G3) 8 14 Severe hypersensitivity reactions 15 5	**Authors' conclusions:** There is strong and confirmatory evidence from two large randomised Phase III trials to support paclitaxel-cisplatin as the new standard regime for treatment of patients with advanced ovarian cancer.

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
	discontinued. In patients without disease progression, chemotherapy options permitted beyond 6 cycles included the following: CP arm - CP, cyclophoshamide-carboplatin, cyclophosphamide alone, ciplastin alone, and carboplatin alone; TP arm - paclitaxel-carboplatin, paclitaxel alone, cisplatin alone, carboplatin alone, and carboplatin and cyclophosphamide. The median cisplatin dose intensity achieved was significantly higher in the TP arm than in the CP arm: 24.4 versus 22.4mg/m2. More frequent cisplatin dose reductions or switch to carboplatin occurred in the TP arm.	moderately well defined n=178; poorly defined n=389; missing or N/A n=56. Less than 10% of the patient population had FIGO stage IIB or IIC disease, and roughly one third had optimal residual disease. Stratification factors included treating institution, FIGO stage, amount of residual disease, WHO status, and tumour grade.			

Results				
General comments: PFS was the primary end point. A Cox regression analysis was performed to adjust for known prognostic factors. It appeared that the 26% reduction in the instantaneous rate of progression (HR 0.74; 95% CI: 0.63 to 0.88) and 27% reduction in the instantaneous rate of death (HR 0.73; 95% CI: 0.60 to 0.89), associated with the paclitaxel-cisplatin treatment, remained qualitatively unchanged. 50 participants (CP:22, TP: 28) underwent interval debulking surgery and 154 (CP 68, TP: 86) had undergone second look surgery after randomisation.	**Outcome 1** **Outcome:** Median Progression Free Survival (PFS) in months (ITT analysis) **Intervention:** 15.5 **Control:** 11.5, log rank p=0.0005	**Outcome 2** **Outcome:** Median overall survival (months) ITT analysis **Intervention:** 35.6 **Control:** 25.8, log rank p=0.0016	**Outcome 3** **Outcome:** Received second-line therapy before disease progression **Intervention:** 20 **Control:** 14	**Outcome 4** **Outcome:** Complete response (CP)/ partial response (PR) (total) **Intervention:** 66/29 (n=162) **Control:** 44 (p=0.01, chi-squared test for CR)/28 (n=161) p=0.01, chi-squared test for total (CR+PR)
	Outcome 5 **Outcome:** Stable disease/ progressive disease **Intervention:** 19/8 (n=162) **Control:** 25/21 (n=161)			

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) Simsek 1999[54]	**Intervention:** Paclitaxel/ cisplatin (CP) N:15 **Dose:** Paclitaxel 135mg/m2, Cisplatin 75mg/m2 **Number of cycles:** Not stated **Length of cycles:** Not stated **Control:** Cisplatin/ cyclophosphamide (CC) **N:**17 **Dose:** Cisplatin 75mg/m2, cyclophosphamide 750mg/m2 **Number of cycles:** Not stated **Length of cycles:** Not stated **Length of follow-up:** Not stated	**Age:** PC 56.2 yrs (range 25-76), CC 58.4 yrs (range 33-80) **Type of cancer:** Advanced ovarian cancer **Stage of cancer:** Advanced **Stage of therapy:** First-line **Prior treatments:** Surgery. Those with optimal cytoreductive surgery were included as well as those without **Inclusion/ exclusion criteria:** Not stated **Further details:** Stage III and IV epithelial ovarian tumours in which optimal debulking surgery was performed. Type of tumour: serous CP 8/15, CC 6/15; mucinous CP 0 CC 4; endometriosis CP 6, CC 4; other CP 1, CC 3.	Not stated	**Intervention group:** **Control group:** CP(n=15) CC(n=17) Neutropenia G2,3 3 6 Urinary toxicity 3 5 Flushing 9 1 'Pansitopeni' 1 2 'Lokositoz' 8 0	**Authors' conclusions:** There is no difference between paclitaxel/ cisplatin combination and cisplatin/ cyclophosphamide combination in the treatment of stage III and IV epithelial ovarian tumours in which optimal debulking surgery had been performed.

Results				
General comments: Paper was in ?Turkish so could only extract some results from tables. There was a table reporting something to do with lymph nodes but not sure what exactly. Could not extract anything from the text. The trial was very small so it could be a single centre from a multicentre trial.	**Outcome 1**	**Outcome 2**		
	Outcome: 2nd look laparoscopy, tumour positive **Intervention:** 4/8 **Control:** 6/11	**Outcome:** Serum Ca125 levels **Intervention:** Fell to normal level in shorter time in CP than CC group		

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) McGuire 1999[56] **Trial ID:** **GOG111**	**Intervention:** Paclitaxel/ cisplatin (CP) N:184 Dose: Paclitaxel 135mg/m2, Cisplatin 75mg/m2 **Number of cycles:** Not stated **Length of cycles:** Not stated **Control:** Cisplatin/ cyclophosphamide (CC) **N:**202 **Dose:** Cisplatin 75mg/m2, cyclophosphamide 750mg/m2 **Number of cycles:** Not stated **Length of cycles:** Not stated **Length of follow-up:** Median 6.5 years	**Age:** CP 60 yrs; CC 59yrs **Type of cancer:** Advanced ovarian cancer **Stage of cancer:** Advanced **Stage of therapy:** First-line **Prior treatments:** No prior radiotherapy or chemotherapy **Inclusion/ exclusion criteria:** Stage III or IV epithelial ovarian cancer, women who had undergone a surgical procedure and were left with suboptimal (<1cm) residual disease. **Further details:** 49/386 eligible patients still alive at last contact.	Not stated	Not reported in this abstract	This updates overall survival experience of patients following 3 additional years of follow-up since the original publication. **Authors' conclusions:** The substitution of paclitaxel for cyclophosphamide in a cisplatin-based doublet is the preferred combination for first-line treatment of advanced epithelial ovarian cancer on the basis of overall survival.

Results			
General comments: This updates overall survival experience of patients following 3 additional years of follow-up since the original publication.	**Outcome 1** **Outcome:** Overall survival **Intervention:** Hazard ratio = 0.70 (95% CI: 0.57, 0.87), after adjusting for FIGO stage, performance score, clinically measurable disease and histologic cell type. Also report estimated probability of surviving 5 years to be 27% (95% CI: 20%, 33%) in paclitaxel arm versus 16% (95% CI: 11%, 21%) in control arm.		

Trial details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (Year) Trope 1999[51] Trial ID: OV10	**Intervention:** Paclitaxel/ cisplatin (CP) N:338 **Dose:** Paclitaxel 175mg/m2, Cisplatin 75mg/m2 **Number of cycles:** Median 6 **Length of cycles:** 3 weeks **Control:** Cisplatin/ cyclophosphamide (CC) **N:**300 **Dose:** Cisplatin 75mg/m2, cyclophosphamide 750mg/m2 **Number of cycles:** Median 6 **Length of cycles:** 3 weeks **Length of follow-up:** 39 months (median)	**Age:** PC 58 yrs, CC 58 yrs **Type of cancer:** Advanced ovarian cancer **Stage of cancer:** Advanced **Stage of therapy:** First-line **Prior treatments:** Surgery. **Inclusion/ exclusion criteria:** Stage IIb-Stage IV suboptimally or optimally debulked ovarian cancer. **Further details:** Not stated.	Not stated	Not reported in this abstract.	Updates previous publications (median follow-up 28 months) to 39 months for the outcomes progression-free survival and overall survival. Conference abstract only. **Authors' conclusions:** This large intergroup randomised trial confirmed the GOG111 findings showing an improved overall and progression-free survival with paclitaxel/ cisplatin compared with cyclophosphamide/ cisplatin.

Results				
General comments: Similar results were obtained when adjusting for prognostic variables.	**Outcome 1**	**Outcome 2**		
	Outcome: Progression free survival **Intervention:** 15.3 months **Control:** 11.5 months (logrank p=0.0005, Hazard Ratio = 0.71 (95% CI: 0.58, 0.87)).	**Outcome:** Overall survival **Intervention:** 36 months Control: 26 months (logrank p=0.0016, Hazard Ration = 0.73 (95% CI: 0.60, 0.89)).		

APPENDIX 4: DATA EXTRACTION SHEETS FOR ECONOMIC EVALUATIONS

Trial details	Source of data	Method for estimation of benefits/ costs	Results/ statistical analysis	Assessment of uncertainty	Comments
Walker 2000[72] **Research question:** To compare cost-effectiveness of paclitaxel-cisplatin versus cyclophosphamide-cisplatin given post-operatively in women with advanced epithelial ovarian cancer **Type of economic evaluation:** Cost effectiveness analysis **Country/ currency:** US $ **Cost year:** Not stated **Perspective:** Not stated **Trial population:** Women with advanced epithelial ovarian cancer **Interventions (including comparator):** Paclitaxel/cisplatin (TP) versus cyclophosphamide/cisplatin (CP)	**Source of effectiveness data:** Single RCT (Subset of Intergroup OV10) **Source of cost data:** Prospective/concurrent.	**Valuation for clinical outcomes or benefits:** Clinical outcomes used included progression free survival (PFS) and overall survival (OS) at a median follow-up of 38.5 months. Analyses were based on a subgroup of Canadian participants (160/680). Life years gained (LYG). **Estimation of costs:** Analysis was based on a subgroup of participants (160/680) recruted by one of the Intergroups (NCIC-CTG). Itemised resource use was obtained for all patients at each Canadian centre including information from ambulatory and inpatient units. Unit costs were based on detailed data from a major academic medical centre. These data were then used to generate total costs for each case from randomisation to death (excluding costs of drugs for second-line therapy) **Modelling:** No model used	**Clinical outcome/ benefits:** Median PFS (months) was 17 in TP group and 10.1 in CP. Median OS (months) was 36.8 in TP group and 25.6 in CP. **Costs:** Mean patient cost (US$) for TP group was 30,774 and in the CP group was 18,515. **Synthesis of costs and benefits:** The incremental cost per life-year gained based on median overall survival was $13,135 for the TP group in comparison to CP. The excess of total costs per progression -free life year gained through the trial was $21,321. **Statistical analysis:** Not stated	**Sensitivity analysis:** None reported	**Authors' conclusions:** The cost effectiveness for the gain in overall survival from TP is well below the commonly cited threshold for cost-effective care of $50,000 per incremental life-year of overall survival, often considered as the benchmark for such interventions to be acceptable. It is also noted that the TP-treated participants incurred significantly higer costs in the post-recurrence phase than the CP-treated participants. TP has acceptable cost-effectiveness in the treatment of women with AOC. **Direction of result:** A (more costly, more effective) **Implications for practice:** None stated. **Comments:** Published as a conference abstract, not many details given.

Trial details	Source of data	Method for estimation of benefits/ costs	Results/ statistical analysis	Assessment of uncertainty	Comments
Neymark 2000[73] **Research question:** To assess the cost-effectiveness from the point of view of the Belgian health insurance system of paclitaxel/ cisplatin compared to cyclophosphamide/ cisplatin as first-line treatment of patients with advanced ovarian cancer. **Type of economic evaluation:** Cost effectiveness analysis **Country/ currency:** Belgian francs (BF) **Cost year:** 1998 **Perspective:** Belgian health insurance system **Trial population:** Patients with advanced ovarian cancer **Interventions (including comparator):** Paclitaxel/cisplatin (TP) versus cyclophosphamide/cisplatin (CP)	**Source of effectiveness data:** Single Phase III RCT (European-Canadian intergroup RCT, OV10) **Source of cost data:** Prospective/concurrent (resource use data collected during the trial).	**Valuation for clinical outcomes or benefits:** The mean survival was estimated using both a restricted means analysis and by using a parametric model (Weibull). Life years gained (LYG). **Estimation of costs:** The cost estimates were based on a subgroup of participants (231/680) recruited by EORTC institutes. The costs assessed comprised of direct treatment costs, i.e. the drugs for chemotherapy, hospital stays and day clinic visits during treatment and follow-up, outpatient visits, concomitant medication, surgery, and second-line chemotherapy after progression. Unit cost figures were based on the tariffs of the Belgian health insurance system. Costs were reported in 1998 prices (BF, 1 $US=36.8 BF using 1998 PPPs (OECD)). **Modelling:** Parametric (Weibull) model. Restricted means analysis.	**Clinical outcome/ benefits:** Overall survival was significantly increased in the TP arm, with a Hazard Ratio of 0.73 (95% CI: 0.60 to 0.89). Only incremental benefits were reported. LYG: 0.31 years using restricted means and 0.79 years using Weibull models. **Costs:** Average total costs were 933,000 BF in the TP arm and 668,000BF in the CP arm. **Synthesis of costs and benefits:** The estimated increase in mean survival and the corresponding incremental cost effectiveness ratios (ICER per life year gained) became, respectively: 0.31 year and 855,000BF (restricted means) and 0.79 year and 335,000BF (Weibull)	**Sensitivity analysis:** Not undertaken. **Statistical analysis:** The impact of uncertainty was assessed by bootstrapping, and the results were expressed in terms of a cost-effectiveness acceptability curve.	**Authors' conclusions:** The maximum value of ICER considered acceptable by society is not known. Compared to other accepted treatments analysed with Belgian data, the estimated values of ICER per life year gained seem quite low, so TP in ovarian cancer would be considered cost **Direction of result:** A (more costly, more effective) **Implications for practice:** None stated. **Comments:** Published as a conference abstract, not many details given.

APPENDIX 5: Validity Assessment for effectiveness trials

Ovarian cancer

Trial	Random procedure adequate	Allocation concealed	No. random stated	Baseline details	Baseline comp. achieved	Eligibility criteria	Co-interventions stated	Follow-up ∃80%	Outcome of withdrawals	ITT
Gennatas, 2000[53, 57]	not stated	not stated	yes	no	not stated	no	no	yes	no	no
ICON3 Collaborators 2000[52]	Good. Minimisation, central computer.	yes	yes	partially	Yes	partially	yes	yes	Not applicable	yes
McGuire 1999[56]	Not stated	Not stated	yes	no	unclear	partially	no	yes	unclear	unclear
Piccart 2000[50] and Trope 2000[51]	not stated	unclear	yes	partially (all but treatment free interval)	Yes	yes	no	yes	yes	partially
Simsek 1999[54]	not stated	unclear	yes	partially	unclear	unclear	unclear	yes	unclear	unclear
Wolf 1999[55]	Not stated	Not stated	yes	partially	unclear	partially	yes	yes	unclear	unclear

APPENDIX 6: Validity assessment of economic evaluations

	Ovarian cancer	
Quality check list	**Walker 2000[72]**	**Neymark 2000[73]**
Trial question		
The viewpoint(s) of the analysis are clearly stated and justified (e.g. provider, institution, societal)	No	not justified
Selection of alternatives		
Relevant alternatives are compared	yes	unclear, pos. suboptimal treatment acc. to trial
The alternatives being compared are clearly described	no, but is within trial	no not in abstract
The rationale for choosing the alternative programmes or interventions compared is stated	No	not stated
Form of evaluation		
The choice of form of economic evaluation is justified in relation to the question addressed	No	not stated
Effectiveness data		
The source(s) of effectiveness estimates used are stated (e.g. single trial, review, delphi panel)	yes	yes ref not gven though
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness trials)	no but avail. with trial	not stated
Benefit measurement and valuation		
The primary outcome measure(s) for the economic evaluation are clearly stated (i.e. cases detected, life years, QALYs, willingness to pay etc.)	yes	not stated - not all
Methods to value states and other benefits are stated (e.g. time trade off, standard gamble)	not applicable	not stated
Details of individuals from whom valuations were obtained are given	yes	not stated - but in the trial data
The relevance of productivity changes to the trial question is discussed	No	not stated
Productivity changes (if included) are reported separately	not applicable	not applicable
Costing		
Quantities of resources are reported separately from their unit costs (e.g. days in hospital)	not applicable	not stated
Methods for estimation of quantities are described	No	not applicable
Currency and price data are reported	no, just currency	yes
Details of currency or price adjustments for inflation or currency conversion are given	No	partially
Modelling		
Details of any model used are given (i.e. decision tree model, epidemiology model, regression model etc)	not applicable	only the name
The choice of model used and the key parameters on which it is based are justified	not applicable	not stated
Adjustments for timing of costs and benefits		
Time horizon of costs and benefits is stated	No	not stated

The discount rate(s) is stated	No	not stated
The choice of rate is justified	not applicable	not stated
A convincing explanation is given if cost or benefits are not discounted	not applicable	not applicable
Allowance for uncertainty		
Details of statistical tests and confidence intervals are given for stochastic data	No	no
The approach to sensitivity analysis is given (i.e. multivariate, univariate, threshold analysis etc)	No	partially - name methods used
The choice of variables for sensitivity analysis is justified	not applicable	no
The ranges over which the variables are varied are stated	No	no
Presentation of results		
Incremental analysis is reported	yes	yes
Major outcomes are presented in disaggregated and aggregated form	No	no
Applicable to the NHS setting	No	no

APPENDIX 7: EXCLUDED TRIALS

Trial	Intervention	Participants	Trial design	Reason for exclusion
Aiba, 2000[28]	✓	✓	✓	Non-systematic review. Japanese.
Andersson, 2000[37]	×	✓	✓	2nd line therapy. Taxane in both arms.
Astier, 2000[66]	×	✓	×	Cost analysis, not taxanes.
Atkins, 2000[41]	✓	✓	✓	Letter about an included study (OV10)
Bilgrami, 2000[44]	✓	✓	×	No control group.
Boddy, 2000[26]	×	✓	✓	Taxanes in both arms.
Caushaj, 2000[40]	×	✓	×	Not about taxanes.
Ceruti, 1999[45]	✓	✓	×	No control group
Culine, 1999[38]	✓	✓	×	Unclear whether randomised. 2nd line therapy.
Culine, 1999[33]	✓	✓	×	Non-systematic review.
de Matteis, 2000[43]	✓	✓	×	Case series.
Di Leo, 2000[22]	×	✓	×	Taxanes in both trial arms.
du Bois, 2000[27]	✓	✓	×	Non-systematic review. 2nd line therapy for ovarian cancer.
du Bois, 2000[30]	×	✓	×	Non-systematic review. Anthracyclines.
Hogberg, 2001[47]	✓	✓	×	Systematic review. Checked for references.
Kreis, 2000[46]	✓	✓	×	Case series.
Lamb, 1998[69]	✓	✓	×	Non-systematic review.
Lehoczky, 2001[39]	✓	✓	×	Non-systematic review. In Hungarian.
Leung, 1999[36]	✓	✓	×	Second-line therapy for ovarian cancer.
Luoma, 1998[35]	✓	✓	✓	Second-line therapy for ovarian cancer.
Mabro, 1999[31]	✓	✓	×	Non-systematic review.
Martin, 2000[71]	✓	✓	×	Economic – descriptive only.
Miller, 1999[21]	×	✓	×	Taxanes in both trial arms.
Morris, 2000[67]	×	✓	×	Cost trial (not effectiveness).
Nabholtz, 2000[29]	✓	✓	×	Non-systematic review.
Paridaens, 2000[48]	✓	✓	✓	Full report of trial included in original review – contains no further data
Piccart, 2000[34]	✓	✓	✓	Second-line therapy for ovarian cancer.
Redaelli, 1999[25]	✓	✓	×	Taxanes in both trial arms.
Rozek, 1999[68]	✓	✓	×	Cost analysis (not effectiveness).
Schroder, 1999[23]	✓	✓	×	Taxanes in both trial arms.
Sezer, 2000[42]	✓	✓	×	Not a trial (letter about a trial).
Sjostrom, 1999	✓	✓	✓	Full report of trial included in

				original review – contains no further data
Skarlos, 1997[20]	✓	✓	×	Taxanes in both trial arms.
Spicer, 1999[24]	✓	✓	×	Taxanes in both trial arms.
Stinson, 1999[70]	✓	✓	×	Second-line therapy for ovarian cancer.
Tiuliandin, 1999[32]	✓	✓	×	Non-systematic review.

APPENDIX 8: MANUFACTURERS' SUBMISSIONS

Bristol-Myers Squibb (paclitaxel)

The submission from Bristol-Myers Squibb included one RCT[83] which met review inclusion criteria but was another report of a trial included in the original review. The manufacturer's submission also identified publications from ICON3,[84] OV10,[50] GOG-132[85] and CISCA.TAX.18.[86] Only the ICON3 and OV10 publications had changed status since the original review, and these had already been identified in the literature searches and included (in the case of ICON3 a fuller report had been obtained from the trial authors).[52] The manufacturers also identified the following trials which were excluded for the following reasons:

Andersson et al.[87]	Taxanes in both trial arms.
Aravatinos et al.[88]	Taxanes in both trial arms.
Torri et al.[89]	Taxanes in both trial arms.
Piccart et al.[34]	Second-line treatment of ovarian cancer.
Markman et al.[90]	Taxanes in both trial arms.

A sixth trial was identified which did meet the review inclusion criteria and was included.[53] Two economic analyses (abstracts of) did meet review inclusion criteria and were included (Walker et al, 2000[72] and Neymark et al, 2000[91]).

A further submission by Bristol Myers Squibb in November 2001 identified no new RCTs. Meta-analyses were performed of the four largest trials (OV10, GOG111, GOG132 and ICON3) and pooled hazard ratios presented, however the 'hazard ratio' for the GOG111 study appeared to be the same as the relative risk presented in the GOG111 publication. Relative risk estimate is not the same as a hazard ratio as it does not take time-to-event data into account. The industry submission claims that the pooled hazard ratio is in favour of Taxol, but in fact the 95% confidence intervals include 1.00 for both progression-free and overall survival , showing no significant difference between taxol and comparator arms for these outcomes.

An economic evaluation which was provided in the submission appeared to be the same as that provided in the original submission but updated with current costs. This was noted in the cost-effectiveness section.