Topotecan (Hycamtin®) for the treatment of recurrent and stage IVB carcinoma of the cervix

Single Technology Appraisal (STA) submission to the National Institute for Health and Clinical Excellence

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GlaxoSmithKline

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Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
CI	Confidence interval
CR	Complete response
CTC	Common toxicity criteria
DNA	Deoxyribonucleic acid
EMEA	European Medicines Agency
ES	Effect size
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics
GI	Gastrointestinal
ICER	Incremental cost-effectiveness ratio
HIF	Hypoxia-inducible factor
HR	Hazard ratio
HRQOL	Health-related quality of life
ITT	Intention-to-treat
IV	Intravenous
NNT	Number needed to treat
OS	Overall survival
Pbo	Placebo
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SEM	Standard error of mean
SF-36	Short Form-36
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
WBC	White blood cell

Acknowledgements

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Section A

1. Description of technology under assessment

1.1 Brand name and therapeutic class

Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

> ***Generic name:*** *topotecan*
>
> ***Brand name****: Hycamtin®*
>
> ***Approved name****: Hycamtin 1 mg and 4 mg powder for concentrate for solution for infusion*
>
> ***Therapeutic class****: Antineoplastic and immunomodulating agent. ATC Code L01XX17.*

1.2 UK marketing authorisation

Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

> *Topotecan received UK marketing authorisation for the treatment of cervical carcinoma on 22 November 2006 and was launched in March 2007.*

1.3 Indication(s) in the UK

What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

> *Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination.*
>
> *Other licensed indications for IV topotecan monotherapy are:*[1]

- *For patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy (date of licence: 12 November 1996).*
- *For patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate (date of approval: 13 January 2006).*

1.4 Current use in the NHS

To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Discussions with clinical experts highlight an increasing use of topotecan in combination with cisplatin in Scotland and Wales after SMC and AWMSG recommendations. This has been confirmed by IMS data (Appendix 4).

There are currently no ongoing clinical trials for topotecan in the UK for the proposed cervical indication. Topotecan solution for infusion has been available for use in this indication in the UK since March 2007.

1.5 Regulatory approval outside the UK

Does the technology have regulatory approval outside the UK? If so, please provide details.

Hycamtin solution for infusion has approval in all EU countries involved in the Centralised procedure (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK). The other countries where Hycamtin solution for infusion has regulatory approval are: Argentina, Australia, Bahrain, Belarus, Brazil, Canada, Chile, China, Colombia, Croatia, Dominican Republic, Ecuador, Egypt, El Salvador, Hondurus, Hong Kong, Iceland, India, Israel, Jamaica, Jordon, Kazakhstan, Kenya, Kuwait, Lebanon, Macedonia, Madagascar, Malaysia, Moldova, Namibia, New Zealand, Nicaragua, Norway, Oman, Pakistan, Panama, Qatar, Russia, Saudi-Arabia, Singapore, South Africa, South Korea, Switzerland, Syria, Taiwan, Thailand, Trinidad and Tobago, Turkey, UAE, USA, Ukraine, Venezuela, Maldives.

1.6 Additional health technology assessment in the UK

Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Topotecan has received the following recommendations:

Scottish Medicines Consortium (SMC) – November 2007

Topotecan (Hycamtin®) is accepted for restricted use within NHS Scotland in combination with cisplatin for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. It is restricted to patients who are cisplatin-naïve.

In an open-label study, overall and progression-free survival was significantly longer for topotecan in combination with cisplatin compared with cisplatin alone. Haematological adverse events were more common in the topotecan in combination with cisplatin group.

The economic submission demonstrated that topotecan in combination with cisplatin was cost effective compared to cisplatin alone in cisplatin-naïve patients. However, the manufacturer's justification of the treatment's cost in relation to its health benefit was not deemed sufficient to gain acceptance by SMC for use in patients with previous exposure to cisplatin.

All Wales Medicines Strategy Group (AWMSG) – February 2008

Intravenous topotecan (Hycamtin®) is recommended for use within NHS Wales in combination with cisplatin, for the treatment of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. It is restricted for use in patients who are cisplatin-naïve.

Topotecan (Hycamtin®) should only be initiated by specialists experienced in the treatment of cervical cancer.

Topotecan (Hycamtin®) is not presently recommended for shared care.

1.7 Formulation(s) available

For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

> *For the cervical indication, topotecan is presented as a powder which is reconstituted into a solution for infusion. Two vial sizes are available; containing 1 mg or 4 mg of topotecan (as hydrochloride). The excipients are tartaric acid, mannitol, hydrochloric acid and sodium hydroxide.*

1.8 Proposed course of treatment

What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

> *The recommended dose of topotecan is 0.75 mg/m^2/day administered as 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the topotecan dose. This treatment schedule is repeated every 21 days for six courses or until progressive disease. In randomized controlled trials the median number of cycles given was four, with actual number of cycles completed ranging from zero to seven.*

1.9 Acquisition cost of the technology

What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

> *The list price of topotecan is £97.65 per 1 mg vial and £290.62 per 4 mg vial[2]*
>
> *The list price of cisplatin is £24.50 per 50 mg vial; £50.22 per 100 mg vial.[2]*

1.10 Setting for the use of the technology

What is the setting for the use of the technology?

> *The use of topotecan should be confined to units specialised in the administration of cytotoxic chemotherapy and should only be administered under the supervision of a physician experienced in the use of chemotherapy.[2]*

1.11 Additional aspects for consideration

For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Topotecan should be used in combination with cisplatin. As with any cytotoxic agent, topotecan should only be administered under the supervision of a physician experienced in using chemotherapy, and its use is dependent on the ability to manage haematological toxicity. Prior to initiating topotecan, the patient must have a confirmed neutrophil count ≥ 1.5 x 10^9/L, platelet count of ≥ 100 x 10^9/L and haemoglobin level ≥ 9g/dL (after transfusion if necessary). These are usual tests for chemotherapeutic regimens.

2. Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

The decision problem considered is the clinical and cost-effectiveness of topotecan in combination with cisplatin, relative to platinum-based single and combination chemotherapy regimens, in women with carcinoma of the cervix recurrent after radiotherapy and patients with stage IVB disease.

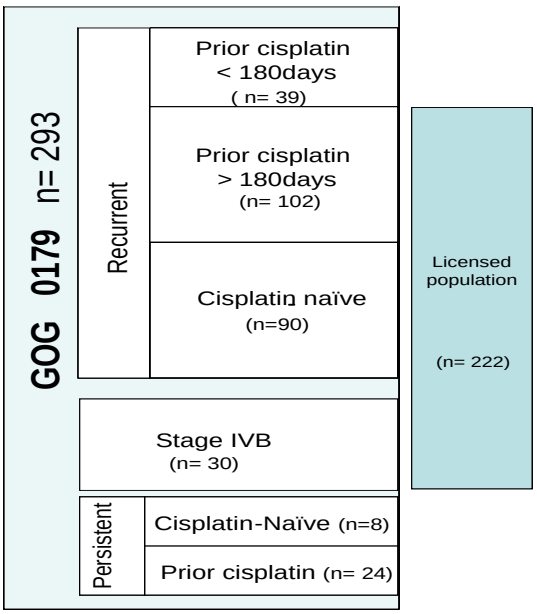
2.1 Intervention

Topotecan (Hycamtin®) in combination with cisplatin, administered intravenously for 6 courses or until disease progression.

2.2 Population

The population under consideration is women with carcinoma of the cervix recurrent after radiotherapy and patients newly presenting with stage IVB disease. This population reflects the majority of patients selected for study GOG-0179,[3] the pivotal clinical trial which is the primary evidence base supporting topotecan in combination with cisplatin in this setting. The licensed indication excludes patients with persistent disease, as well as stating that patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination. The duration of the cisplatin free interval required is not explicit in the indication, but is assumed to be at least 180 days, consistent with analyses presented in Section 5.1 of the SmPC, which show that the survival benefits are greater in patients with recurrence after 180 days. In the indicated population chemotherapy is used as palliative care when curative surgery and/or radiotherapy are unsuitable. Figure 1 shows the licensed population in relation to the population studied in GOG-179. Full study results are presented in the clinical section for the intention-to-treat population; the economic evaluation considers patients within the licensed population sub-group, as well as other sub-groups of interest.

Figure 1: Licensed population in relation to study population from GOG-179



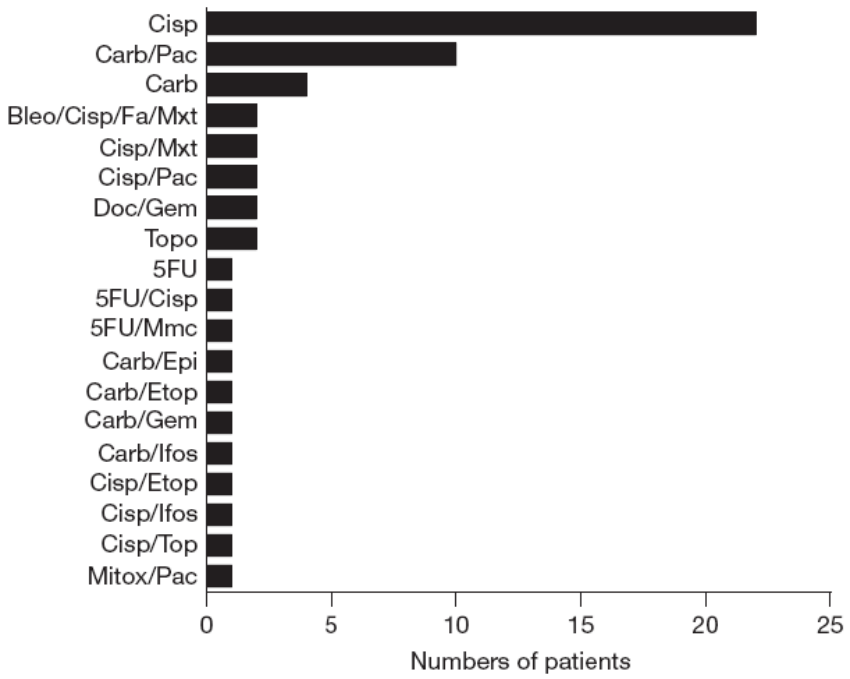
2.3 Comparators

In line with the decision problem outlined in the final scope, this submission considers platinum-based single and combination chemotherapy regimens as comparators.

An analysis of the IMS Oncology Analyzer database was conducted, capturing data from Q3 2004 until Q3 2008. This analysis (Figure 2 and Appendix 4) demonstrates that cisplatin monotherapy constitutes the key alternative intervention in the population in which combination therapy with topotecan and cisplatin is licensed. Carboplatin is also used in the treatment of recurrent or stage IVB cervical cancer, mainly in combination with paclitaxel, despite neither agent being licensed in this therapy area, and despite no data from randomized controlled trials to support their use in the cervical cancer indication. The IMS data suggest that a number of other agents are used infrequently in this setting, including cisplatin in combination with paclitaxel.

Feedback from UK clinicians confirms this pattern of treatment in clinical practice, but suggests that the use of paclitaxel in combination with cisplatin may be higher than suggested by the Oncology Analyzer database. For this reason, and to provide an approximate indication of the performance of topotecan versus a platinum-based combination regimen, the combination of paclitaxel and cisplatin is addressed in the submission. Due to the limited and inconsistent use of other treatments they are not considered as key comparators in this appraisal of topotecan.

Figure 2. Chemotherapy regimen at the point of eligibility for topotecan in combination with cisplatin



5-FU: 5-fluorouracil; Bleo: bleomycin; Carb: carboplatin; Cisp: cisplatin; Doc: docetaxel; Epi: epirubicin; Etop: etoposide; Fa: folinic acid; Gem: gemcitabine; Ifos: ifosfamide;Mitox: mitoxantrone; mmc: mitomycin C; Mxt: methotrexate; Pac: paclitaxel; Topo: topotecan

2.4 Outcomes

The key study considered in this submission is GOG-0179, a phase III randomized controlled clinical trial evaluating the efficacy and safety of topotecan in combination with cisplatin compared with cisplatin alone. Outcome measures are listed below:

Primary endpoint - overall survival

Secondary endpoints - progression-free survival, response rates (complete response, and partial response), adverse effects of treatment, and health related quality of life (FACT-G).

A second study (GOG-0169) investigating paclitaxel in combination with cisplatin versus cisplatin monotherapy was identified through a systematic review of the literature, and is presented in an indirect comparison with topotecan in combination with cisplatin, via the common cisplatin monotherapy arms. The outcome compared was overall survival.

2.5 Economic analysis

A systematic review of the literature found no existing economic evaluations of topotecan in cervical cancer. Two unpublished economic analyses are presented:

1. <u>Primary analysis: Comparison of topotecan in combination with cisplatin vs. cisplatin monotherapy</u>

   This is a trial based analysis using GOG-0179 data. To reflect the licensed population the base case analysis excludes patients with persistent disease (32 patients in the trial, 11% of the ITT population) and also those patients without a sustained cisplatin-free interval (SFCI), (39 patients, 13% of the ITT population). This population is termed the *Licensed population* (see below).

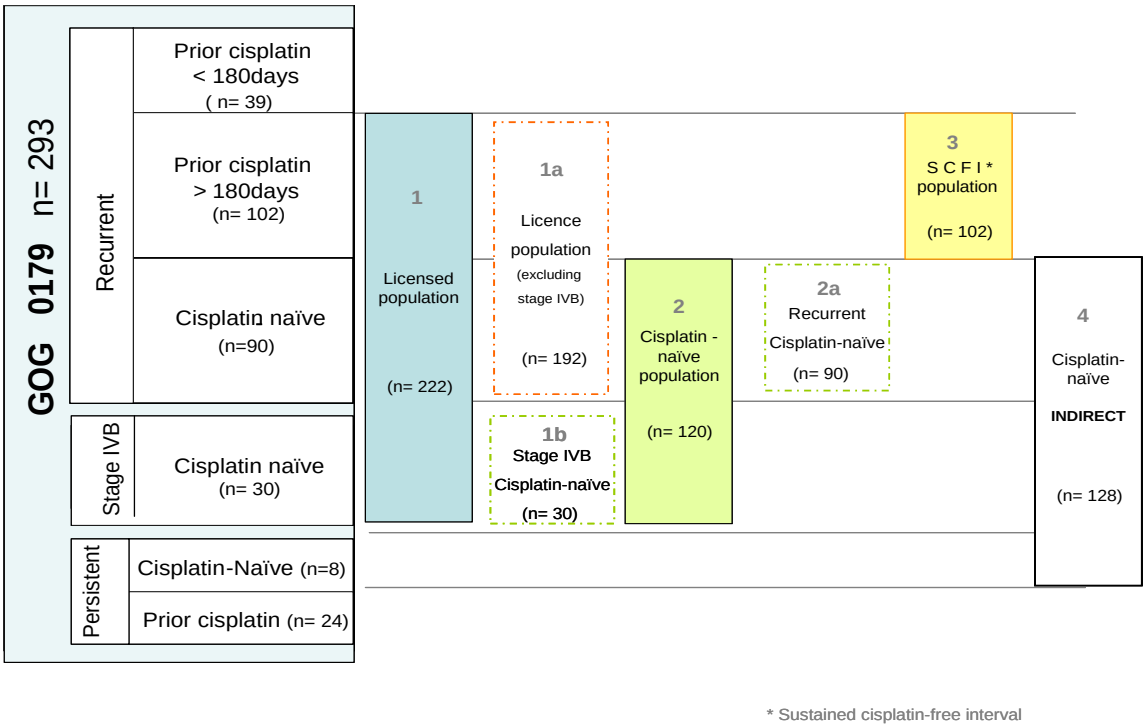
   The *Licensed population* consists of several further key subgroups (1, 2, 3, below) which have been analysed separately.

   The groups are summarized below:

   1. *Licensed population, consisting of:*
      - *1a. Licensed population excluding IVB patients*
      - *1b. Stage IVB patients (by definition cisplatin-naïve, as they are newly presenting)*
   2. *Cisplatin-naïve population, consisting of:*
      - *2a. Cisplatin-naïve recurrent population*
      - *(1b. Stage IVB patients)*
   3. *Patients with a sustained cisplatin-free interval (SCFI; >180 days)*

   The schematic overleaf shows the licensed population (1), plus the sub-groups of interest, in relation to the GOG-0179 population.

Figure 3. GOG-179 study population and sub-groups of interest



Outcomes and costs are evaluated over a 36-month time horizon beginning with the start of treatment, which reflects the follow-up period in the study, as well as the lifetime of the vast majority of patients in the study. Costs are considered from an NHS and PSS perspective. All costs and outcomes are discounted at 3.5% per annum.

The key outcomes in the direct analysis are:

- Mean costs
- Life years gained (LYG)
- Quality-adjusted life years (QALYs)
- Incremental cost per life year gained
- Incremental cost per quality-adjusted life year gained

2. <u>Secondary analysis: Comparison of topotecan in combination with cisplatin vs. paclitaxel in combination with cisplatin</u>

Whilst the IMS data presented in Figure 2 suggest that the use of this combination is scarce in UK clinical practice, this regimen has been studied in two RCTs, GOG-0169 and GOG-0204. The systematic review of clinical literature did not identify any randomized clinical trial data for carboplatin in combination with paclitaxel in cervical cancer. The cisplatin/paclitaxel combination is the only one for which adequate data are available for an economic evaluation. This analysis is therefore intended to provide an approximate indication of the performance of topotecan versus a platinum-based combination regimen.

Since patient level clinical trial data were not available for GOG-0169 it was not possible to exclude patients with persistent disease, or those with a sustained cisplatin-free interval to achieve consistency with the licensed indication for topotecan. In order to

match the patients from the two studies as far as possible the overall ITT population of GOG-0169 and all cisplatin-naïve patients from the GOG-0179 study (including those with persistent disease) are compared in the indirect analysis (shown as sub-group 4 in Figure 3).

This is a modelled analysis using GOG-0179 and GOG-0169 data. Outcomes and costs are evaluated over a 24-month time horizon beginning with the start of treatment, which reflects the follow-up period in study GOG-0169. Costs are considered from an NHS and PSS perspective. All costs and outcomes are discounted at 3.5% per annum.

Survival is unadjusted as it was not feasible to apply quality adjustments to the available aggregate-level GOG-0169 data in the same manner as QALYs were calculated at the patient-level in the direct analysis.

The key outcomes in the indirect analysis are:

- Treatment costs
- Administration costs
- Follow-up costs
- Costs of adverse events
- Life years gained (LYG)
- Incremental cost per life year gained

2.6 Special considerations and other issues

Additional sub-group analyses

The following prospectively planned subgroup analyses will be considered in the clinical section only. In these analyses patient survival will be evaluated according by:

- prior radiotherapies (no RT, RT without radiosensitiser, RT with cisplatin as a radiosensitiser, RT with radiosensitisers other than cisplatin)
- race (Caucasian vs. black vs. others)
- GOG performance status (PS 0 vs. 1 vs. 2)
- histology (adenocarcinoma vs. squamous cell carcinoma)
- age (<65 years vs. ≥ 65 years)

Additional evidence for paclitaxel in combination with cisplatin

New evidence has been recently presented from study GOG-204[4] which included a head to head comparison between topotecan in combination with cisplatin vs. paclitaxel in combination with cisplatin. However, there is very limited information currently available in the public domain. Given the relevance of the data, the available data from this study is used in a sensitivity analysis in the indirect comparison described above.

Lack of utility data collected in clinical trial

Since the clinical trial protocol did not mandate the use of a health-related quality of life instrument from which utility estimates can be directly measured, e.g., EQ-5D, the base case analysis uses utility estimates mapped from FACT-G data collected in study GOG-0179.

A systematic literature search in MEDLINE and HEED was conducted for publications presenting utility data for patients with cervical cancer. None of the studies identified contained utilities describing the health states encountered during the course of the trial-based analysis, notably response, stable disease, progression and various degrees of haematological toxicity. Therefore, they were of no value to determine the utility changes associated with treatment outcomes, or to differentiate treatments according to quality as well as quantity of survival. Utilities for advanced breast cancer elicited from nurses were used in a sensitivity analysis to explore the impact of different utilities in the direct economic evaluation.[5]

Section B

3 Executive summary

Topotecan for the treatment of recurrent carcinoma of the cervix

Background information

Cervical cancer is the second most common malignant neoplastic disease among women worldwide; however, in countries with efficient screening, advanced disease is relatively rare.[6] Overall, there are approximately 38,000 new cases of cervical cancer a year within the European Union (EU) and 17,000 associated deaths.[1] The standardised incidence rate for cervical cancer is 8.4 per 100,000 females in the UK as a whole, and 2,803 new cases were diagnosed in the UK in 2005 making it the twelfth most common cancer in women and accounting for around 2% of all female cancers. In women under 35 years in the UK, cervical cancer is the most common cancer after breast cancer, and there were 671 new cases of cervical cancer diagnosed in this population in 2005.[7] In 2006, there were 949 deaths from cervical cancer in the UK.

In the UK, most patients are diagnosed with early disease when surgery may be curative. In more advanced non-metastatic disease, radiotherapy may be administered with curative intent. For recurrent or metastatic disease, treatment is, in most cases, palliative. Stage IVB cervical cancer is the most advanced form of the disease, in which the cancer has spread further than the pelvic region to more distant organs, such as the lungs.[1] The median survival for stage IVB cervical cancer is very low, at approximately 9 to 10 months, with 30% survival at 1 year and 2 to 5% survival at 2 years.[8] The objectives of treatment of cervical cancer that is recurrent after radiotherapy or in stage IVB are to improve overall survival (OS) and progression-free survival (PFS) whilst providing an acceptable toxicity profile and maintaining or improving patient quality of life (QoL).

Cisplatin has long been considered the most effective platinum-based chemotherapy for the treatment of recurrent or advanced cervical cancer[9-13]. Patients with cervical cancer that is recurrent after radiotherapy or with stage IVB disease are usually treated with cisplatin, either alone or in combination with other chemotherapies. In recent years, use of combination therapies, particularly paclitaxel or topotecan in combination with either cisplatin or carboplatin has increased; although no combinations have been explicitly licensed for this indication other than topotecan in combination with cisplatin.[1]

Topotecan:

Topotecan (Hycamtin®) acts by inhibiting topoisomerase I, an enzyme that is required for DNA replication, leading to cell death. This results in DNA damage, inducing apoptotic cell death predominantly in replicating cells such as tumour cells.[1] The UK marketing authorisation for topotecan in the treatment of cervical carcinoma was received on 22 November 2006.

Eligible population:

Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease.[1] Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination. For the purposes of this submission the duration of the cisplatin free interval required is assumed to be at least 180 days. This is consistent with analyses presented in Section 5.1 of the SmPC, (Appendix 1) which show that the survival benefits are greater in

patients with recurrence after 180 days. This period is referred to hereafter as the sustained cisplatin-free interval (SCFI).

Comparators

Quantifying the extent to which platinum-based chemotherapies are used within the relevant patient population continues to be problematic due to the non-availability of local or national NHS audit data. This submission has therefore used the most current IMS Oncology Analyzer dataset available (October 2003 to September 2008) (Appendix 4). This dataset unveils an important variation in current clinical practice in the NHS as there seems to be a multiplicity of platinum-based chemotherapies being prescribed to women with recurrent or advanced cervical cancer.

Notwithstanding this variance, it was apparent from the results from the IMS study that a) cisplatin monotherapy constitutes the most common treatment used in this population (in 39% of patients), and b) carboplatin-based regimens are also used in the treatment of recurrent or stage IVB cervical cancer, although this agent is unlicensed in this therapy area and there is little clinical evidence supporting its use. In addition, discussions with clinical experts show that in current clinical practice the use of cisplatin and paclitaxel in patients with advanced or recurrent cervical cancer is not unusual (even though the combination is not formally licensed in this setting).

Other platinum-based combinations, including cisplatin in combination with gemcitabine or vinorelbine, are inconsistently used in clinical practice and have very limited clinical trial evidence.

Therefore the key comparator considered in this submission is cisplatin monotherapy. Carboplatin in combination with paclitaxel provides a second key comparator, but the lack of clinical trial data evaluating this combination regimen precludes further analyses to be conducted. Paclitaxel in combination with cisplatin is considered as a third comparator.

Comparative clinical effectiveness

A systematic review was performed to identify the comparative clinical evidence available for topotecan and its comparators (platinum-based single- and combination regimens).

Three clinical trials evaluating the use of topotecan in this setting were identified

- GOG-0179 - a phase III randomized controlled clinical trial in which topotecan in combination with cisplatin was compared with cisplatin alone
- GSK-CRT-234 - a Phase II single-arm study investigating the safety and efficacy of topotecan combined with cisplatin.
- GOG-0204 - a randomized controlled clinical trial reported in abstract form which included a head-to-head comparison of four cisplatin-containing combinations (paclitaxel, vinorelbine, gemcitabine and topotecan).

One further clinical trial which compared cisplatin in combination with paclitaxel with cisplatin monotherapy (GOG-0169) was identified.

Therefore, the key clinical evidence evaluating the combination therapy of topotecan and cisplatin versus cisplatin monotherapy can be derived from the GOG-0179 randomized clinical trial[3,6] Data for the clinical and cost-effectiveness evaluation of cisplatin in combination with topotecan versus other platinum-based combination regimens are provided

by GOG-0169 and GOG-0204. No randomized, controlled evidence evaluating the use of carboplatin either as monotherapy or part of combination regiments in the target population was identified.

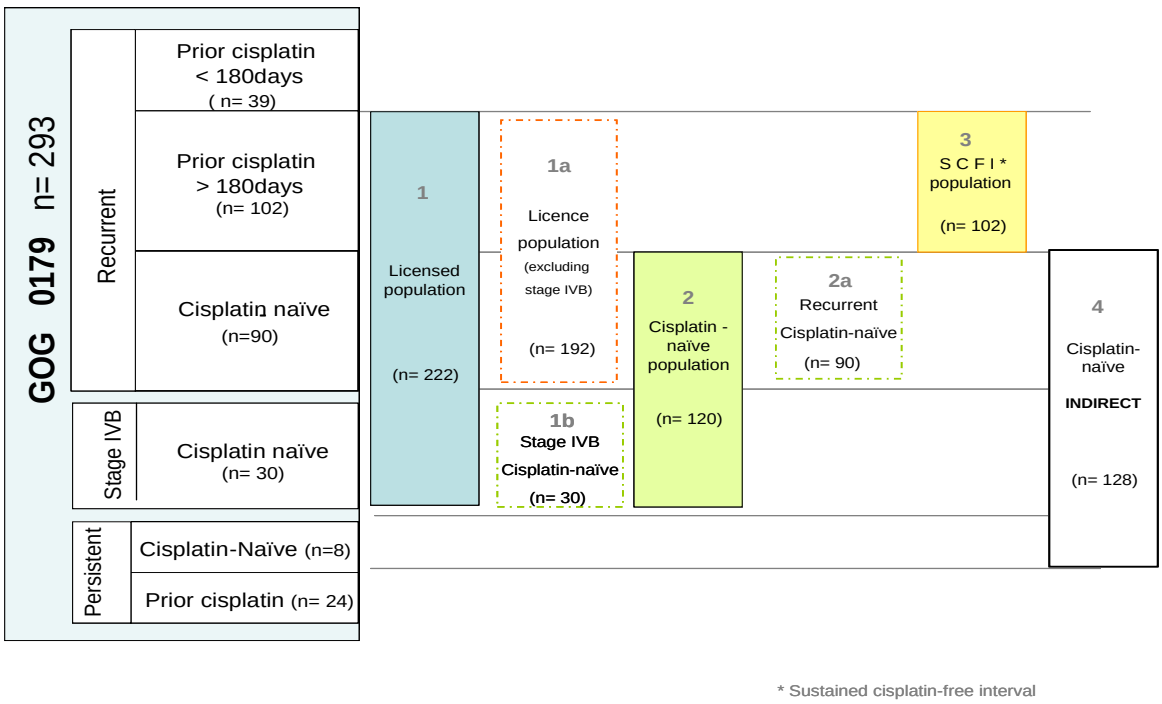
Topotecan in combination with cisplatin versus cisplatin alone

GOG-0179 was an independent trial including 293 women with stage IVB, recurrent or persistent carcinoma of the cervix who were unsuitable for curative treatment with surgery and/or radiotherapy. Treatment with topotecan in combination with cisplatin resulted in significantly longer median overall survival than treatment with cisplatin alone (9.4 vs 6.5 months; hazard ratio, HR: 0.76, 95% confidence interval, CI: 0.59 to 0.98; p=0.033), with a predictable and manageable safety profile. There was no evidence suggesting that reported QoL and adverse event scores changed over time across regimens, after adjusting for baseline scores and age at entry.

Additional subgroup analyses were undertaken for this submission as the GOG-0179 trial includes patients outside the licence for topotecan in combination with cisplatin. Specifically, the indication excludes patients with persistent disease, as well as those with a short cisplatin free interval prior to recurrence. The subgroups and their relevance to GOG-0179 are shown in Figure 4. In a subgroup representing the total licensed population (subgroup 1), median overall survival in GOG-0179 was 11.9 versus 7.3 months (topotecan in combination with cisplatin versus cisplatin, HR: 0.65, p=0.0041). Other subgroups were analysed and a trend favouring patients receiving the combination regimen was identified (see section 6.4 for detailed results). In particular, results suggest that patients considered as cisplatin-naïve (subgroup 2) experienced greater benefits (median overall survival was 14.5 versus 8.5 months in those treated with topotecan in combination with cisplatin and cisplatin monotherapy, respectively (HR 0.58, p=0.0098))

To date, topotecan and cisplatin is the only combination regimen to have demonstrated a statistically significant survival advantage versus cisplatin in patients with cervical cancer recurrent after radiotherapy or with stage IVB disease.

Figure 4: Schematic of study population and subgroups analysed



Topotecan in combination with cisplatin versus paclitaxel in combination with cisplatin

The systematic review also identified a Phase III randomised controlled trial of paclitaxel in combination with cisplatin versus cisplatin alone in patients with stage IVB recurrent or persistent carcinoma of the cervix (GOG-0169).[14] This study showed a beneficial trend in overall survival favouring the combination regimen but it failed to reach statistical significance. Although there were some differences in the baseline characteristics of the patients recruited to GOG-0179 and GOG-0169, indirect comparisons were attempted using the common comparator (cisplatin; Section 6.6). A hazard ratio statistic, together with confidence intervals, was generated which was, in effect, the comparison of cisplatin in combination with topotecan and cisplatin in combination with paclitaxel with respect to the median survival time. The calculated hazard ratio of 0.87, with confidence interval of 0.62 to 1.23 favours the cisplatin/topotecan combination, but also shows that no statistical difference exists between the two treatments.

An abstract presented at the 2008 American Society of Clinical Oncology Meeting reported a randomised trial in patients with stage IVB, recurrent or persistent cancer not amenable to cure (GOG-0204).[4] This trial included a head to head comparison of four cisplatin-containing combinations (paclitaxel, vinorelbine, gemcitabine and topotecan). In April 2007, a planned interim analysis recommended early closure of GOG-0204 since all experimental arms were unlikely to demonstrate a significant advantage compared with paclitaxel in combination with cisplatin. There is very limited information currently available in the public domain for GOG-0204. However, the overall survival HR for cisplatin plus topotecan versus cisplatin plus paclitaxel was 1.268 (Var[In(HR)]: 0.021), in favour of the paclitaxel combination. Given the relevance of the results, the available data from this study is used in a sensitivity analysis in the indirect comparison described above. Discussion on the potential imitations associated with the scarce data available and the differences in study populations are also reported.

Safety

In the GOG-0179 trial a total of 140 patients were exposed to topotecan in combination with cisplatin. The most common toxicities associated with topotecan include myelosuppression, nausea and vomiting, mucositis, rash, and hepatotoxicity. The incidence of grade 3 and 4 neutropenia and leucopenia was higher in the topotecan and cisplatin combination arm compared to the cisplatin alone arm. Similar toxicity issues were reported in the CRT-234 study. Most complications were manageable with antibiotics, protocol specific dose modifications, and the addition of G-CSF (filgrastim) on subsequent treatment cycles.

Topotecan has been used in a large number of patients over the last few years and pharmacovigilance assessments evaluating the post-marketing exposure to topotecan have reported that the benefit/risk profile of topotecan continues to be favourable [14].

Cost-effectiveness of topotecan

Relative to cisplatin monotherapy, the combination of topotecan and cisplatin is a cost effective therapy in patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. The baseline estimate of the incremental cost per QALY gained for the licensed population was £17,974. Probabilistic sensitivity analyses suggest that the likelihood of topotecan in combination with cisplatin having an incremental cost-utility ratio lower than £20,000/QALY is slightly over 50% in this scenario (nearly 90% for a threshold of £30,000/QALY). In patients with recurrent or Stage IVB disease who were cisplatin-naïve the ICER was £10,928/QALY, with a probability of being cost effective at a willingness to pay of £20,000/QALY of over 85%. Exclusion of patients presenting with Stage IVB disease had a marginal impact on the cost effectiveness of the topotecan/cisplatin

combination, increasing it by approximately £1,000/QALY for the licensed population, and decreasing it by just over £2,000/QALY in the cisplatin-naïve population. In patients who had received prior cisplatin, but who had a sustained cisplatin free interval of over 180 days (SCFI), the cost utility ratio for topotecan in combination with cisplatin was £32,463/QALY, with a probability of cost effectiveness at a £30,000/QALY threshold of over 50%. Whilst the ICER for this particular subgroup (SCFI) is beyond the current NICE threshold for cost-effectiveness, results should be viewed in the context of the Institute's provisions for end of life medicines.

The majority of deterministic sensitivity analyses (SAs) decreased the ICER, indicating that the base case estimate may be conservative. A key driver of uncertainty in this analysis was the estimation of utilities, and an alternative analysis using utilities derived from the literature increased the ICERs considerably in some scenarios. It should be noted, however, that use of health related quality of life data collected directly in the pivotal trial (GOG-0179) to generate utilities using a validated mapping technique, as employed in the base case analysis, is arguably the more robust approach. In a secondary, indirect comparison, topotecan in combination with cisplatin dominated paclitaxel/cisplatin in the base case. However, in a sensitivity analysis using alternative but preliminary data from a head to head clinical trial in which the two interventions were compared directly, the paclitaxel combination was shown to be cost effective versus topotecan/cisplatin (£982/LYG), suggesting that there is considerable uncertainty in this indirect comparison.

Resource implications for the NHS

Treatment with topotecan and cisplatin could be implemented in England and Wales at an initial cost to the NHS in year one of approximately £440,703 for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. This assumes a 100% uptake in the eligible population, and acquisition costs as well as resource use costs involved in the administration of topotecan in these patients. It should be noted that the introduction of topotecan is unlikely to require changes in the current health care infrastructure. Furthermore, the continued emphasis on disease prevention through cervical cancer screening and the advent of HPV vaccination in the UK will gradually reduce the number of women with cervical cancer including those with advanced disease.

Conclusions

Topotecan in combination with cisplatin provides a clinically and cost-effective treatment in women with recurrent or stage IVB cervical carcinoma. Whilst analyses of clinically-defined sub-groups suggest that topotecan in combination with cisplatin is particularly cost effective in patients with recurrent or Stage IVB disease who were cisplatin-naïve, this evaluation suggest that it is likely to be cost effective across the licensed population. We are therefore seeking a recommendation for its use in this group of patients who, otherwise, have very limited treatment options in the last stages of their disease.

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4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Overview of the disease condition

Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Aetiology

Cancer of the cervix is commonly in the form of squamous cell carcinoma which develops from the outer surface cells of the cervix and is associated with the human papilloma virus (HPV).[7] The cancer forms in tissues of the cervix and is usually slow-growing, may be asymptomatic, but can be found with regular Papanicolaou cytology (microscopic examination of cells scraped from the cervix).[15]

Co-factors that modify the risk among HPV-DNA positive women include the use of oral contraceptives for five or more years, smoking, high parity (five or more full term pregnancies) and previous exposure to other sexually transmitted diseases, such as Chlamydia trachomatis and herpes virus type 2. Women exposed to the human immunodeficiency virus (HIV) are at high risk of HPV infection, HPV-DNA persistency and progression of HPV lesions to cervical cancer.[16]

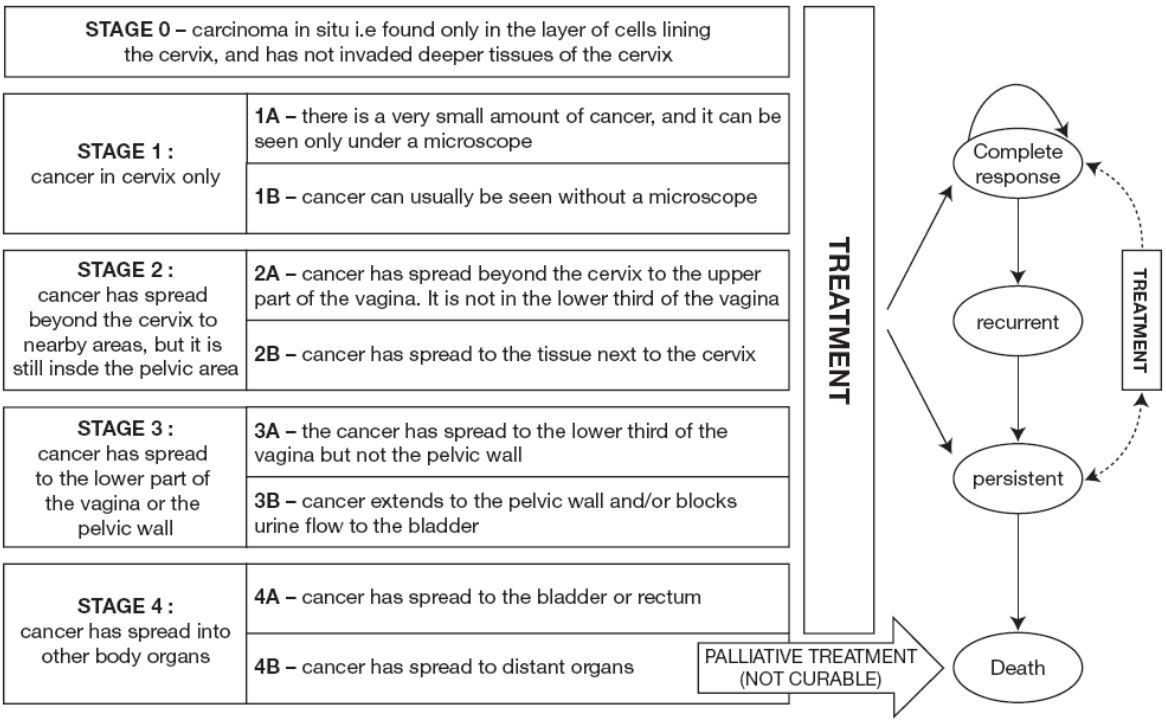
Staging of cervical cancer

Figure 5 presents an overview of the the various stages of cervical cancer based on the FIGO (International Federation of Gynecology and Obstetrics) system. Cancers are primarily staged at diagnosis by clinical examination, although some re-staging may occur after initial surgery (pathological or p-stage). Re-staging does not usually occur at later phases of the disease. Therefore, the terminology on the right-hand side of the Figure is used to describe the disease status after initial staging. If the patient is clear from visible signs of the disease, this is termed complete response. A patient who was free from disease but in whom cervical cancer has returned is considered to have recurrent disease. The licence for topotecan considers patients with cervical cancer recurrent after radiotherapy and patients with stage IVB disease. If a patient's diseased tissue was not entirely removed by surgery or the patient has no disease free periods, their disease is termed persistent. Chemotherapy may result in a complete response for the former of these two types of persistent disease.

Stage IVB cervical cancer is the most advanced form of the disease, in which the cancer has usually spread further than the pelvic region to more distant organs, such as the lungs.[1] Due to metastatic disease at the time of presentation, the median survival for stage IVB is very low: 9-10 months and 30% survival at 1 year and 2-5% survival at 2 years.[8] Due to improved screening and education, there has been a decline in the incidence of stage IVB disease and these patients represent only a small proportion of metastatic cervical cancer patients. In the study GOG-0179, only 30 patients (14 in the topotecan in combination with cisplatin arm and 16 patients in the cisplatin arm) had de novo stage IVB disease. As these are newly diagnosed cervical cancer patients, the baseline characteristics are different from those with recurrent disease i.e. distant metastases at the time of diagnosis, fast growing tumours and no previous chemotherapy and/or radiotherapy, the analysis of this group will be presented separate from those with recurrent disease.

The objectives of treatment in cervical cancer that is recurrent after radiotherapy or stage IVB disease are to improve overall survival (OS) and progression-free survival (PFS) whilst providing an acceptable toxicity profile and maintaining or improving patient quality of life (QoL).

Figure 5. FIGO Cervical cancer staging



Burden of illness

Cervical cancer is the second most common malignant neoplastic disease among women worldwide, however, in countries with efficient screening, advanced disease is relatively rare.[6] Overall, there are approximately 38,000 new cases of cervical cancer a year within the European Union (EU) and 17,000 associated deaths.[1]

In women under 35 years in the UK, cervical cancer is the most common cancer after breast cancer, and there were 671 new cases of cervical cancer diagnosed in this population in 2005.[7] The standardised incidence rate for cervical cancer is 8.4 per 100,000 females in the UK as a whole, and 2,803 new cases were diagnosed in the UK in 2005. In 2006, there were 949 deaths from cervical cancer in the UK.

The total annual cost, including resources and direct medical costs in the UK, from the NHS perspective, for the screening and management cervical cancer is £168.9 to £187.8 million which includes hospital visits, procedures and 1 year treatment costs.[5]

Treatment pathway and treatment options

In the EU, most patients are diagnosed with early disease when surgery may be curative. In more advanced non-metastatic disease, radiotherapy may be administered with curative intent. For recurrent or metastatic disease, treatment is, in most cases, palliative.

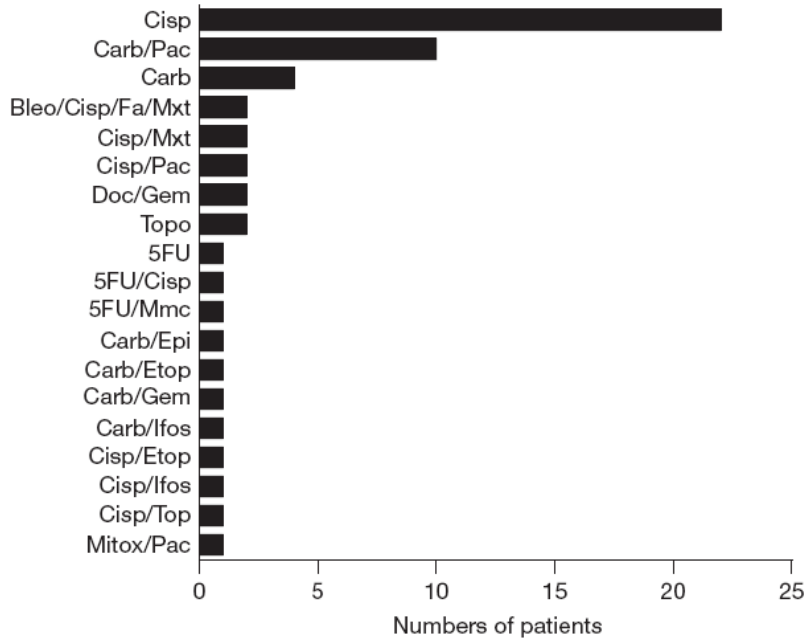
NICE has published full guidance on laparoscopic radical hysterectomy for early stage cervical cancer[17] and a technology appraisal on cervical cancer screening.[18] Radiotherapy has been used to control disease within the pelvis or to palliate metastatic sites. Cisplatin is the standard chemotherapy in the UK for the management of recurrent disease despite low response rates.[13] Topotecan in combination with cisplatin and paclitaxel in combination with cisplatin are both recommended in current UK-based treatment guidelines for recurrent or stage IVB cervical cancer, despite the latter not being licensed for this indication.[13] Other platinum-based combinations, including cisplatin plus gemcitabine and cisplatin plus vinorelbine, are not consistently used in clinical practice and have very limited clinical trial evidence.

A retrospective analysis of the IMS Oncology Analyzer database was conducted capturing data from Q3 2004 until Q3 2008. The IMS Oncology Analyzer links treatment to diagnosis enabling analysis beyond the scope of national prescribing costs. This database is the largest, most comprehensive commercially available oncology patient-record database. The full patient history is collected since diagnosis with complete timelines enabling all therapies to be sequenced even where multiple therapies are given concomitantly. In the absence of national audits of NHS patient treatment, the IMS Oncology Analyzer is arguably the most reliable source available for studying treatment pathways in cervical cancer.

The current submission uses the most current IMS Oncology Analyser dataset available at that time (October 2003 to September 2008), reported by IMS as moving annual totals (MAT) Q3 2004 to MAT Q3 2008 at which time the database reported case histories from 358 UK patients that had cervical cancer. From this sample 57 UK patients were considered to be eligible for treatment with topotecan and cisplatin.

This analysis (Figure 6 overleaf, and Appendix 4) demonstrated that carboplatin is also being used in the treatment of recurrent or stage IVB cervical cancer, although this agent is unlicensed in therapy area and its use is relatively poorly investigated in randomised controlled trials. The lack of standardisation in clinical practice highlights the need for NICE recommendations for the treatment of recurrent or stage IVB cervical cancer.

Figure 6. Chemotherapy regimen at the point of eligibility for topotecan in combination with cisplatin



5-FU: 5-fluorouracil; Bleo: bleomycin; Carb: carboplatin; Cisp: cisplatin; Doc: docetaxel; Epi: epirubicin; Etop: etoposide; Fa: folinic acid; Gem: gemcitabine; Ifos: ifosfamide;Mitox: mitoxantrone; mmc: mitomycin C; Mxt: methotrexate; Pac: paclitaxel; Topo: topotecan

4.2 Rationale for development

What was the rationale for the development of the new technology?

Topotecan (Hycamtin®) is an anti-tumour drug with topoisomerase I-inhibitory activity. It is a semisynthetic derivative of the pentacyclic alkaloid, camptothecin, which inhibits the nuclear enzyme topoisomerase I involved in DNA replication and the HIF.The latter mechanism is of particular interest in cervical cancer, because the tumour tends to be either bulky or present in radiated fields, which often results in tumour hypoxia.

An unmet therapeutic need remains for patients with stage IVB, recurrent or persistent cervical cancer since a single standard of chemotherapy care has not yet been defined by randomised controlled trials.

To date, topotecan in combination with cisplatin is the only licensed combination regimen that has demonstrated a statistically significant survival advantage versus cisplatin in patients with cervical cancer recurrent to radiotherapy or with stage IVB disease.

4.3 Principal mechanism of action

What is the principal mechanism of action of the technology?

Topotecan (Hycamtin®) is an anti-tumour drug with topoisomerase I-inhibitory activity. It is a semisynthetic derivative of the pentacyclic alkaloid, camptothecin, which inhibits the nuclear enzyme topoisomerase I involved in DNA replication and the HIF. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks.The HIF mechanism is of particular interest in cervical cancer, because the tumour tends to be either bulky or present in radiated fields, which often results in tumour hypoxia.

4.4 Suggested place for the technology

What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Cisplatin has long been considered the most effective drug in the treatment of recurrent or advanced cervical cancer.[9-12] Patients with cervical cancer that is recurrent after radiotherapy or with stage IVB disease are usually treated with this agent, either alone or in combination with other chemotherapies. In recent years, use of combination therapies, particularly paclitaxel plus carboplatin, paclitaxel plus cisplatin and topotecan plus cisplatin has increased; although no combinations have been explicitly licensed for this indication other than topotecan in combination with cisplatin.[1]

Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination. There is no consensus on the concept of cisplatin-naïvety and this is a key issue given the increasing number of women receiving cisplatin as a radiosensitiser. (i.e. whether patients receiving cisplatin as a radiosensitiser should still be considered as cisplatin naïve unlike those treated with cisplatin chemotherapy). Although the length of the treatment-free interval is not explicit in the SmPC, we have assumed a period of 180 days for this submission; in line with the GOG-0179 analyses presented in Section 5.1 of the SmPC (see Appendix 1).

4.5 Issues relating to current practice

Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

IMS data from Q3 2004 to Q3 2008 (Appendix 4) have demonstrated that a number of unlicensed products are being used in the treatment of recurrent or stage IVB cervical cancer in the UK, even though there is limited clinical evidence to justify their use. The IMS data suggest that there is a lack of consensus among oncologists regarding the chemotherapy regimens that should be used in this therapy area. Established chemotherapies may be favoured instead of following an evidence-based approach. This highlights the need for NICE recommendations in this therapy area.

4.6 Relevant guidelines or protocols

Provide details of any relevant guidelines or protocols.

NICE guidance

NICE has published full guidance on laparoscopic radical hysterectomy for early stage cervical cancer[17] and a technology appraisal on cervical cancer screening.[18] The main strategy for the prevention of cervical cancer is the programme of regular cervical smear testing and treatment of any pre-cancerous lesions. The Cervarix® HPV vaccine, which has a protective effect on cervical cancer, is currently recommended by the Department of Health for girls at 11-12 years of age.[18] NICE states that, if cervical cancer does develop, it can be treated with surgery, radiotherapy, chemotherapy, or a combination of these treatments. Surgery and radiotherapy are the main treatments for cancer of the cervix in its early stages and chemotherapy is used as palliative care when curative surgery and/or radiotherapy are unsuitable in recurrent and stage IVB cervical cancer.

Scottish Medicines Consortium (SMC) guidance

The SMC published the following recommendations:[19]

Topotecan (Hycamtin®) is accepted for restricted use within NHS Scotland in combination with cisplatin for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. It is restricted to patients who are cisplatin-naïve.

In an open-label study, overall and progression-free survival was significantly longer for topotecan in combination with cisplatin compared with cisplatin alone. Haematological adverse events were more common in the topotecan in combination with cisplatin group.

The economic submission demonstrated that topotecan in combination with cisplatin was cost effective compared to cisplatin alone in cisplatin-naïve patients. However, the manufacturer's justification of the treatment's cost in relation to its health benefit was not deemed sufficient to gain acceptance by SMC for use in patients with previous exposure to cisplatin.

All Wales Medicines Strategy Group (AWMSG) guidance

The AWMSG published the following recommendations:[20]

Intravenous topotecan (Hycamtin®) is recommended for use within NHS Wales in combination with cisplatin, for the treatment of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. It is restricted for use in patients who are cisplatin-naïve.

Topotecan (Hycamtin®) should only be initiated by specialists experienced in the treatment of cervical cancer.

Topotecan (Hycamtin®) is not presently recommended for shared care.

Scottish Intercollegiate Guidelines Network (SIGN) guidelines

The Scottish Intercollegiate Guidelines Network (SIGN) 2008 guidelines[13] for the management of cervical cancer provide a range of therapeutic options for patients with recurrent cervical cancer whose first line treatment has failed. These include surgery (salvage), chemotherapy and palliative treatment only. Topotecan in combination with

cisplatin, and paclitaxel in combination with cisplatin are both recommended in the SIGN guidelines for recurrent or stage IVB cervical cancer.[13] Alternative chemotherapy agents are not recommended by SIGN for this patient group. The use of topotecan in combination with cisplatin is restricted to patients who are cisplatin naïve.

5 Equity and equality

The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, evidence on differential treatment effects in population groups, and epidemiological evidence on risks or incidence of the condition in population groups. Evidence submitters are asked to consider whether the chosen decision problem could be impacted by the Institute's responsibility in this respect; including in considering subgroups and access to recommendations that use a clinical or biological criterion.

5.1 Identification of equity and equalities issues

A decision to make topotecan in combination with cisplatin available to patients who present with advanced cervical cancer would address several equity issues. First, it would benefit patients in the lowest socioeconomic classes, who benefit the least from screening programmes due to lower take-up rates. Second, it would benefit cohorts of women currently aged 18 years and over who, by virtue of age, do not qualify for the national human papilloma virus (HPV) programme introduced in September 2008 to vaccinate girls now aged 12-13 years and offer catch-up vaccination to 13-18 year old girls. Third, positive guidance would be consistent with the Institute's recent criteria for appraisal of end-of-life treatments. Fourth, it may help redress the relatively poor prognosis for diagnosed cervical cancer in England and Wales, as compared to other European nations.

Deprivation

An association between cervical cancer and deprivation is well-known. Although the current three-yearly screening programme prevents 84% of the cervical cancers that would develop without screening in women aged 25-49 years,[7] a 2004 study by Northumberland University found a clear link between low screening take-up and ward deprivation status.[21] This may in part account for the link between social class and cervical cancer. Long-term data drawn from 1% of the England and Wales population indicate that cervical cancer incidence is considerably higher among women of working age in manual than those in non-manual occupations.[7]

Intergenerational equity

Women presenting with advanced cervical cancer are likely to be aged 40 years or over (Appendix 4). Currently presenting cohorts have had little or no opportunity to benefit from recent preventive innovations, such as cervical screening with liquid-based cytology and vaccination against HPV, and thus may have faced greater lifetime risk of disease than younger cohorts face in the current era. The provision of improved treatment for presenting cases would advance the cause of equity by addressing an intergenerational imbalance.

End-of-life provision

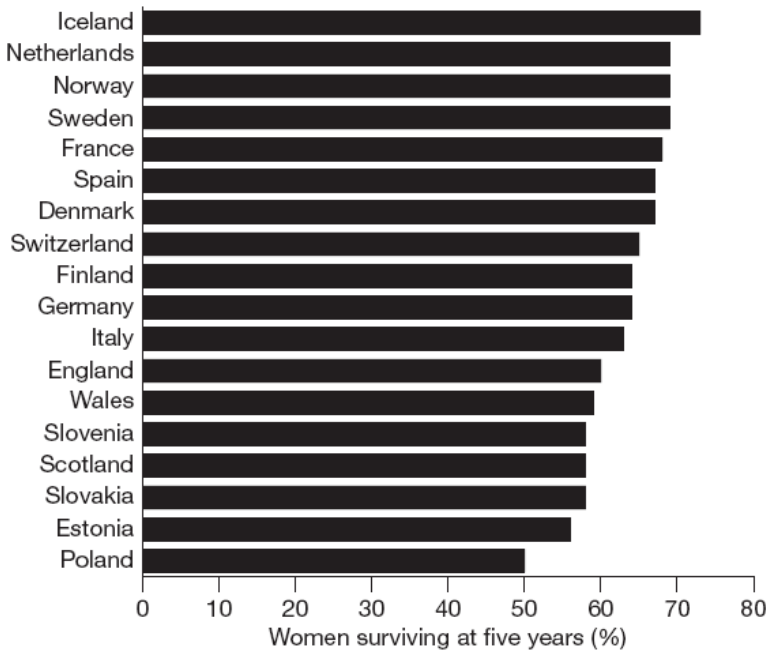
The target population has a life expectancy of less than 24 months. As described elsewhere in this submission, median life expectancy of patients treated with topotecan in combination with cisplatin is 4.6 months greater than those treated with cisplatin alone (licensed population). No alternative treatment with with a statistically significant improvement in survival compared to cisplatin alone is available. Topotecan in combination with cisplatin is licensed and indicated for small patient populations, amounting to an estimated 470 women

per year. The use of topotecan in combination with cisplatin therefore appears broadly to meet the Institute's key criteria for special appraisal of end-of-life treatments. Whilst we believe that topotecan is likely to be cost-effective within the current framework for NICE decision making, we would suggest that when considering uncertainty around these estimates that the committee should take into account that this medicine is also likely to meet the requirements of the institute's provisions for end of life medicines.

International considerations

Across Europe, differences in outcomes in cervical cancer have been reported in a longitudinal population study of over 73,000 women with cervical cancer by the EUROCARE working group. It was found that survival rates for women diagnosed between 1983 and 1994 improved steadily up to 1999, but that the improvement was not uniform, with the UK being amongst one of the countries showing little or no improvement in five-year survival rates. Survival rates in England were better than those in Wales and Scotland, but still lagged behind those the rest of Western Europe and all of the Northern European countries surveyed.[22] The study was published in 2007 and reported in a BMJ editorial which graphically represented the results, which are reproduced below.[23]

Figure 7. Age standardised survival at five years in European women aged 15 to 99 with cervical cancer*[23]



*Cancer diagnosed 1983 to 1994; women followed up to 1999

We recognize that there are likely to be many factors underlying these figures. However, they highlight why access to medicines with survival benefit remains important if the relative position of UK patients compared to the rest of Europe are to improve, consistent with the Cancer Reform Strategy.

How has the analysis addressed these issues?

No specific equity dimensions were explored in the economic analysis.

6 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUOROM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. Formal assessments of heterogeneity should be included.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.

6.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Appendix 2, section 10.2.

A systematic review of the literature was undertaken to identify published data on the clinical efficacy of topotecan and comparator products in the treatment of patients with recurrent after radiotherapy or stage IVB carcinoma of the cervix. The search was designed to identify all clinical data published since the Cancer Care Ontario systematic review in 2006[24] The Cancer Care Ontario systematic review searched MEDLINE (1966 to February 2006), EMBASE (1980 to February 2006), the Cochrane Library (Cochrane Database of Systematic Reviews (2006 Issue 1), and Cochrane Controlled Trials Register (2006 Issue 1)), the Canadian Medical Association Infobase, and the National Guidelines Clearinghouse. The conference proceedings of the American Society of Clinical Oncology (1995-2005) and the European Society of Medical Oncology (2002-2005) were also searched.

The Cancer Care Ontario systematic review was used as a source of studies published before 2006 as the methodology was sufficient to capture all relevant studies of topotecan and comparator products. The inclusion and exclusion criteria of the systematic review are

presented in Section 6.2.2. Additional information on the systematic review methodology, including search strategies and first/second pass checklists, is presented in Appendix II.

Systematic searches of MEDLINE, EMBASE and EMBASE Alert were conducted using DataStar on the web (http://www.datastarweb.com). The Cochrane Collaboration Library, including The Central Register of Controlled Trials was searched at http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html

In addition, The Centre for Reviews and Dissemination (CRD), including the UK National Health Service Economic Evaluation Database (NHS EED) was searched at http://www.york.ac.uk/inst/crd/crddatabases.htm, the Canadian Medical Association Infobase and Health Economic Evaluations Database (HEED) at WILEY InterScience were searched. The following conference websites were also searched:

- American Society of Clinical Oncology 2005-2008 (Cancer Care Ontario systematic review 1995-2005)

- European Society of Medical Oncology 2005-2008 (Cancer Care Ontario systematic review 2002-2005)

All searches were conducted on 18 December 2008. The general search strategy is presented in Appendix 2; this search strategy was modified to reflect the requirements of the individual databases. The electronic databases were searched for all years available for the cost analysis and restricted to 2006 onwards for the clinical search.

6.2 Study selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Evidence on topotecan in combination with cisplatin

Pivotal Phase III data:

GOG-0179

Long HJ, Bundy BN, Grendys EC, Benda JA, McMeekin DS,Sorosky J, Miller DS, Eaton LA, and Fiorica JV. Randomized Phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Journal of Clinical Oncology 2005; 23; 21:4626-4633.

For additional information on this trial, see sections 6.3 to 6.7.

Additional evidence:

GOG-0204

Hand searching of conference abstracts identified the following trial:

Monk BJ, Sill M, McMeekin DS et al. A randomized phase III trial of four cisplatin (CIS) containing doublet combinations in stage IVB, recurrent or persistent cervical carcinoma: a Gynecologic Oncology Group (GOG) study. J Clin Oncol 2008;26.

The very limited data available in the public domain for study GOG-0204 (beyond a conference abstract and presentation) preclude a formal critical appraisal of its methodological robustness. However, available information on study characteristics and results will be fully discussed considering this 4-arm study included cisplatin plus topotecan and cisplatin plus paclitaxel among the comparators evaluated.

GOG-0204 included a head to head comparison of four cisplatin-containing combinations (paclitaxel, vinorelbine, gemcitabine and topotecan). A planned interim analysis recommended early closure of GOG-0204 as all experimental arms were unlikely to demonstrate a significant advantage compared to paclitaxel plus cisplatin.

Approximately 70% of patients had previously received cisplatin as a radiosensitiser in GOG-0204. This is consistent with the expansion of brachytherapy, sensitised with cisplatin, as a standard of care for first-line cervical cancer treatment; however, baseline data regarding cisplatin free interval of subjects or its impact on efficacy is not yet available in the public domain. Cisplatin free interval is an important factor in the efficacy of subsequent cisplatin-containing combination therapies. Cisplatin and topotecan have a synergistic effect, and in patients who have received prior cisplatin it is known that the combination is more effective in patients with a sustained platinum-free interval. Lack of accessible data regarding cisplatin free interval may pose some limitations such as the inability to perform subanalyses of efficacy in sustained cisplatin-free interval versus unsustained cisplatin free interval. Therefore, it is not possible to identify whether the trends seen in the study are typical of all patient subpopulations.

As discussed above, one of the limitations of the GOG-0204 trial was that it was closed early as all experimental arms were unlikely to demonstrate a significant advantage of any individual combination. An additional limitation of this trial is that the majority of patients (55% in paclitaxel arm, 53% in topotecan arm) were of PS 0, with no patients of PS 2 included and this status is not representative of the overall patient population. In GOG-0179, patients were recruited with PS of 0,1 and 2. In both arms 47% had PS 0, 45% had PS 1 and 8% were PS 2. Though the relative proportions of different performance statuses are not strikingly different, they are different enough between trials to have exerted a pull on the trends and possibly go some way towards explaining why the GOG-0204 results do not tally with the findings of GOG-0169 and GOG-0179.

With these limitations in mind, the HR for overall survival for topotecan in combination with cisplatin versus paclitaxel in combination with cisplatin in GOG-0204 was 1.268 (Var[ln(HR)]: 0.021), a non-significant trend. The corresponding HR for overall survival data for vinorelbine in combination with cisplatin versus paclitaxel in combination with cisplatin was 1.147 (Var[ln(HR)]: 0.026). The HR for overall survival data for gemcitabine in combination with cisplatin versus paclitaxel in combination with cisplatin was 1.322 (Var[ln(HR)]: 0.025). GOG-0204 also demonstrated a non-significant trend for QoL, response rate and PFS in favour of paclitaxel in combination with cisplatin.

Evidence on platinum-based single and combination interventions (comparators)

GOG-0169

Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF, Rocereto TF. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Journal of Clinical Oncology 2004; 22;15:3113-3119. Details of this study are included in section 6.4.

Additional evidence:

The Cancer Care Ontario systematic review[24] identified three additional trials evaluating carboplatin: carboplatin versus iproplatin[25,26] and carboplatin versus teniposide.[27] As none of these trials included the common comparator arm of cisplatin, an indirect comparison with GOG-0179 was not possible.

6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Eligible studies were randomised clinical trials, or systematic reviews and meta-analyses in which treatment with topotecan or platinum-based single and combination regimens were investigated in female patients of any race with cancer of the cervix recurrent after radiotherapy or stage IVB disease. Eligible treatments were:

- Topotecan in combination with cisplatin
- Platinum-based single and combination chemotherapy regimens (discussed in section 6.6 of this submission).

6.2.3 List of relevant RCTs

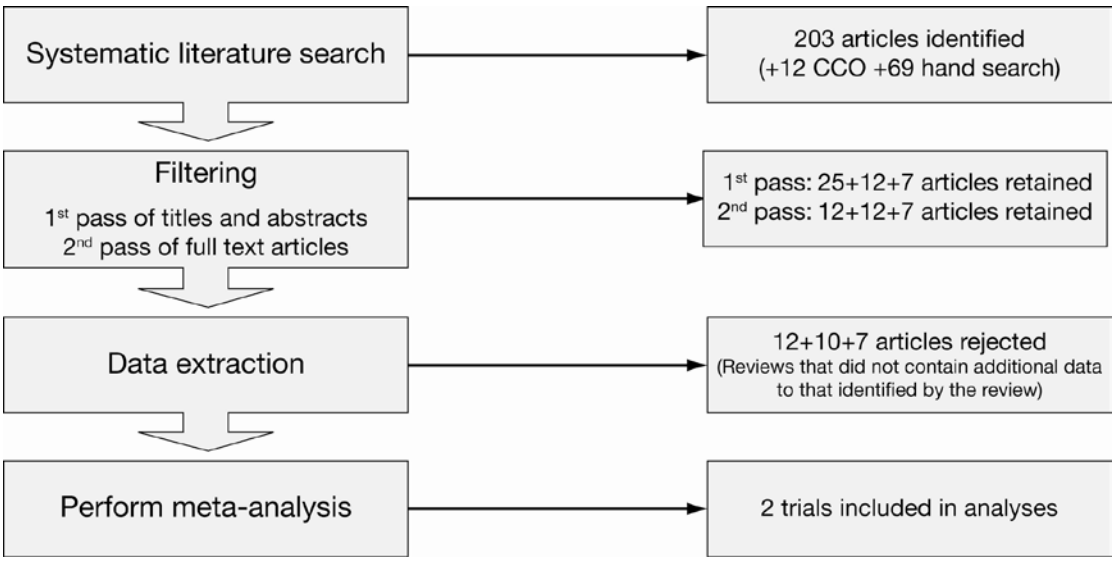
List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUOROM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUOROM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Figure 8 presents a flow diagram of the numbers of studies included and excluded at each stage of the systematic review. GOG-0179 and GOG-0169 were eligible for meta-analysis (section 6.6).

Figure 8. A flow diagram of the process and findings of the systematic review*



*69 conference abstracts were identified at the systematic literature search stage
CCO: Cancer Care Ontario systematic review[24]

6.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

GSK-CRT-234

Fiorica J, Holloway R, Ndubisi B, Orr J, et al. Phase II trial of topotecan and cisplatin in persistent or recurrent squamous and nonsquamous carcinomas of the cervix. Gynecologic Oncol 2002; 85: 89-94.

This GSK-funded trial was not identified by the systematic review as it is not an RCT. However, this phase II study has been incorporated in this submission as it provides important supportive data on topotecan. GSK-CRT-234 was a single arm Phase II study designed to test the safety and efficacy of topotecan in combination with cisplatin in patients with persistent or recurrent squamous cell or non-squamous cell cervical cancer. This study generated data which supported the licence application for topotecan in combination with cisplatin and on which the design of study GOG-0179 was based. The results demonstrated that topotecan plus cisplatin was safe and well tolerated in the evaluable (n=32) population. Efficacy was also shown, with a median overall survival of 10 months, an overall response rate (RR) of 28%, and a median duration of response of five months. As mentioned above GSK-CRT-234 is included in this submission dossier as supporting data only.

6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

Table 1 overleaf provides an overview of ongoing trials for topotecan that are expected to conclude within the next 12 months.

Table 1. Ongoing trials for topotecan

Study name	Phase	Patient population	Primary objectives	Planned number of patients	Trial duration	Start of trial	End of trial	Progress (as reported on htto://clinicaltrial.gov)
GSK-UMN-2001LS041 Adjuvant topotecan and cisplatin with concurrent radiation therapy for advanced cervical cancer	I	Advanced cervical cancer Stages IIB, IIIA, IIIB, IVA, + Stage IB or IIA with risk factors	toxicity	15		Feb 2005	Feb 2012	Ongoing, but not recruiting
UCI 03-33 Feasibility of weekly IV topotecan and cisplatin with concurrent pelvic radiation in the treatment of stages IB2-IVA cervical carcinoma	II	Primary, previously untreated invasive cervical cancer stage IB2-IVA	Feasibility and safety	12	5 years	April 2004	Jan 2009	Recruiting
GOG-0240 Cisplatin plus paclitaxel with and without bevacizumab versus the non-platinum doublet, topotecan plus paclitaxel with and without bevacizumab	III	Stage IVB, recurrent, or persistent cervical cancer	OS and AEs	450	36 months	March 2008	December 2011	This study is not yet open for participant recruitment
GOG-0127U Weekly topotecan in the treatment of persistent or recurrent cervical cancer	II	Persistant or recurrent cervical cancer that failed higher priority treatment protocol	Antitumour activity and safety	60	3 year follow up	Feb 2005	Sep 2006 (primary outcome measure)	Ongoing, not recruiting
GOG-0076EE Weekly topotecan, paclitaxel and cisplatin in the treatment of cervical cancer	II	Advanced, persistent, or recurrent cervical cancer	Anti-tumour activity, Toxicity	66	5 year follow up	-	-	This study is not yet open for participant recruitment
CACA-2008-GSK1 Cisplatin combined with topotecan in advanced, recurrent or persistent cervical cancer	II	Advanced (Stage IVB) recurrent or persistent cervical cancer	Response rates	40	12 months	Feb 2009	Jan 2010	This study is not yet open for participant recruitment

Study name	Phase	Patient population	Primary objectives	Planned number of patients	Trial duration	Start of trial	End of trial	Progress (as reported on htto://clinicaltrial.gov)
GSK 107278 Topotecan, cisplatin and bevacizumab for recurrent / persistent cervical cancer	II	Recurrent or persistent cervical cancer not amenable to curative treatment with surgery and/or rdiotherapy	Progression free survival	30	-	Sep 2007	March 2010	Currently recruiting
GOG-9913 Pelvic radiation therapy with concomitant cisplatin and weekly topotecan in patients with cervical cancer and paraortic nodal metastasis as the only evidence of extrapelvic disease	I	patients with cervical cancer and paraortic nodal metastasis as the only evidence of extrapelvic disease	Safety and tolerability	60	5 year follow up	Sep 2007	Sep 2008 (final data collection date)	Currently recruiting
NCI-V97-1324 Topotecan and paclitaxel in treating patients with recurrent or metastatic cancer of the cervix	II	Recurrent or metastatic cancer of the cervix	RR, TTP, OS, DFS, feasibility, toxicity	25	-	July 1997		This study is ongoing, but not recruiting participants
GOG-0204 Comparison of four combination chemotherapy regimens using cisplatin in treating patients with stage IVB, recurrent, or persistent cancer of the cervix	III	Stage IVB, recurrent, or persistent cancer of the cervix	Survival and reponse, toxicity and QoL	600	48 months follow up	July 2003	Terminated early	Full publication due spring 2009

Data from htto://clinicaltrial.gov

NCI-V97-1324
Topotecan and paclitaxel in treating patients with recurrent or metastatic cancer of the cervix in recorded as being ongoing, but it has been running since 1997 and published in 2004.

Studies using topotecan as a background therapy, but not evaluating topotecan have been excluded.

6.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-

statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

GOG-0179

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

GOG-0179 was conducted in 47 centres in the United States. Patients recruited in GOG-0179 entered an open-label, Phase III, randomised, multi-centre study. Patients were randomised to receive either cisplatin, cisplatin with topotecan or methotrexate, vinblastine, doxorubicin and cisplatin combination (MVAC). The latter treatment was terminated early due to safety concerns and the other two treatment groups remained.

In the cisplatin only treatment arm, patients were administered 50 mg/m^2 IV cisplatin on day 1 and then every three weeks for six courses or until disease progression or unacceptable adverse effects prohibited further therapy. For patients in the topotecan in combination with cisplatin treatment arm, topotecan 0.75 mg/m^2 was infused over 30 minutes on days 1, 2, and 3 followed by cisplatin 50 mg/m^2 IV on day 1; the regimen was repeated every three weeks for six courses or until disease progression or unacceptable adverse effects prohibited further therapy.

6.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

The inclusion and exclusion criteria for the pivotal study, GOG-0179, are presented in Table 2.

Table 2. Inclusion and exclusion criteria for the trial

Inclusion criteria	Exclusion criteria
Women with histologically confirmed, advanced (stage IVB) recurrent or persistent carcinoma of the uterine cervix unsuitable for curative treatment with surgery and/or radiotherapy; Squamous, adenosquamous, adenocarcinoma of the cervix; Measurable disease; GOG performance status (PS) 0 to 2; Recovered from the effects of recent surgery, chemoradiotherapy, or radiotherapy; Free of clinically significant infection	Patients with bilateral hydronephrosis not alleviated by ureteral stents or percutaneous nephrostomy drainage; Absolute neutrophil count ≤ 1,500/L; Platelet count ≤ 100,000/L; Abnormal liver function (bilirubin ≥ 1.5x normal and/or AST/alkaline phosphatase level ≥ 3 x normal

AST: Aspartate aminotransferase

The patient baseline characteristics for the pivotal study, GOG-0179, are presented in Table 3.

Table 3. Patient characteristics at baseline; ITT population

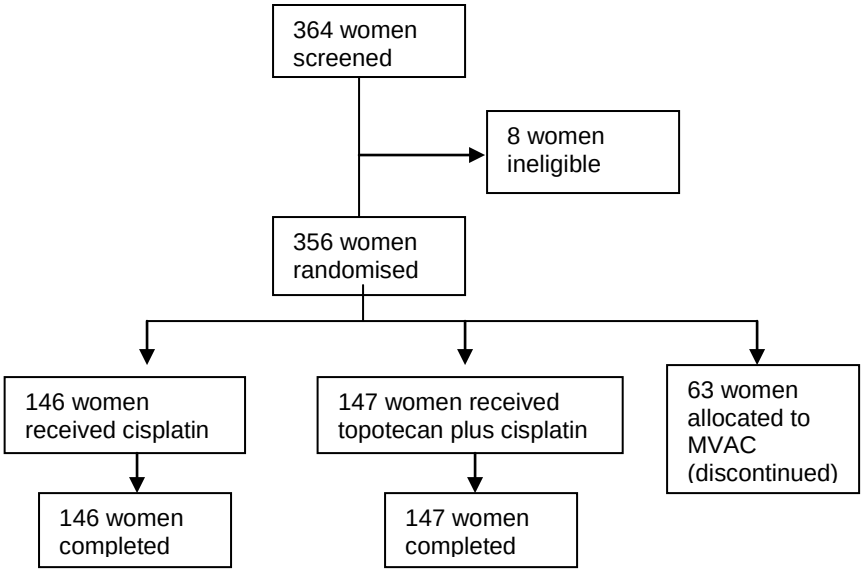
Characteristic	Cisplatin (n=146)	Topotecan plus cisplatin (n=147)
	No pts (%)	No pts (%)
Age, years		
Median	48	46
Range	27-76	22-84
No. Cycles therapy		
Median	3	4
Range	0-7	0-7
Not treated	2	7
Race or ethnicity		
White	108 (74)	105 (71)
Black	23 (16)	29 (20)
Other	15 (10)	13 (9)
Performance status 0	68 (47)	69 (47)
Performance status 1	66 (45)	66 (45)
Performance status 2	12 (8)	12 (8)
Cell type		
Squamous	121 (83)	128 (87)
Adenosquamous	11 (8)	5 (3)
Adenocarcinoma	9 (6)	9 (6)
Mucinous	0	4 (3)
Clear cell	2 (1)	0
Endometrioid	3 (2)	0
Villoglandular	0	1 (1)
Tumour grade		
Tumour grade 1	9 (6)	8 (5)
Tumour grade 2	81 (55)	84 (57)
Tumour grade 3	52 (36)	52 (35)
Stage IVB	16 (11)	14 (10)
Persistent	12 (8)	20 (14)
Recurrent	118 (81)	113 (77)
Prior cisplatin	82 (56)	83 (56)
No prior cisplatin	64 (44)	64 (44)

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 9 overleaf presents the CONSORT flow chart for GOG-0179.

Figure 9. CONSORT flow chart for GOG-0179



MVAC = methotrexate, vinblastine, doxorubicin and cisplatin combination. NB this study group was discontinued.

6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Primary outcome measure: Overall survival (all-cause mortality)

This was defined as the time from randomisation until death in the intent-to-treat (ITT) population, or until date of last contact, for patients who were still alive at this point.

Secondary outcome measures:

- progression-free survival (PFS), defined as the minimum amount of time from randomisation until clinical progression, death, or date of last contact
- response rates (RR)
- toxicities (discussed in Section 4)
- health-related quality of life (HRQoL)

The following definitions were used for RR:

Response rate (RR)	the percentage of all eligible patients responding to treatment; i.e., patients with complete response (CR) or partial response (PR) divided by the total number of patients in each group in the ITT population
Complete response (CR)	complete disappearance of all gross evidence of cancer for at least four weeks
Partial response (PR)	at least a 50% decrease in the cross-product dimensions of each tumour compared to the cross-product dimensions reported on the first cycle of therapy for at least four weeks
Progressive disease (PD)[a]	at least 50% increase in the cross-product dimensions of any tumour compared to the cross-product dimensions reported on the first cycle of therapy and occurring within eight weeks of study entry or the appearance of any new lesion within eight weeks of study entry

a. The GOG definition of PD used in GOG-0179 differs slightly from that of the WHO criteria, i.e. GOG criterion is a 50% or greater increase in the cross-product from any lesion or a new lesion, compared to the WHO criterion, a 25% or greater increase in the cross-product from any lesion or a new lesion.

Health-related quality of life (HRQoL) was measured prospectively and was assessed with the following instruments:

1) The Functional Assessment of Cancer Therapy – Cervix cancer (FACT-Cx): The FACT-Cx is the Functional Assessment of Cancer Therapy – General (FACT-G) plus a cervix cancer-specific subscale.[28] The FACT-G is a 27-item self-reporting QoL measure developed and validated among cancer patients for use in clinical trials.[29] It includes four subscales (physical well-being, functional well-being, social well-being, and emotional well-being). Each scale produces a separate score that can be summed into one total QoL score. The cervix subscale of the FACT consists of 15 items developed by cervical cancer patients and clinicians. Along with the cervix subscale, six items measuring neurotoxicity (NTX) were included to take into account the side effects that may result from the variable doses of cisplatin.
2) The Brief Pain Inventory (BPI): The BPI consists of 14 questions designed to assess pain related to cancer and other diseases.[30]
3) The UNISCALE, a single item visual analogue scale that asks the patient to place an "x" on a 0 to 100 mm scale corresponding to overall QoL.[31]

All enrolled patients were expected to complete QoL assessments at four time points (at baseline, just before the second and fifth chemotherapy cycles, and nine months after randomisation) using FACT-G, FACT-Cx, NTX, Brief Pain Inventory and UNISCALE. Treatment effect on QoL before and after chemotherapy was examined, adjusting for patient age, baseline scores and effects of time. Mean QoL scores over time were summarised by treatment group using descriptive statistics.[12] Missing data were tabulated over time by treatment group and by reason.

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

GOG-0179

The primary hypotheses of GOG-0179 were;

The null hypothesis was that the survival distribution with cisplatin alone equaled the survival distribution with topotecan in combination with cisplatin. An alternative hypothesis was that the survival distribution of cisplatin alone did not equal the survival distribution with topotecan in combination with cisplatin.

Sample size calculations

The median survival for the cisplatin group was anticipated to be 8.5 months using data from a previous GOG study (GOG-0149).[32] A decrease in death rate of 33% (i.e., hazard ratio of topotecan in combination with cisplatin relative to cisplatin = 0.67) was considered to be an important difference to detect in this study. Based on the hypothesised difference, the final analysis was planned after a total of 111 deaths were observed in the cisplatin group. This was expected to yield 82% power and 2.5% overall one-tailed type I error for a pairwise comparison of the experimental arm to cisplatin. Based on the above parameters, the planned sample size was 400 patients, 133 patients in each treatment group, to be recruited into the three treatment arms of the study.

Premature discontinuation and missing data

For time-to-event endpoints, the last date of known contact was used for those patients who had not reached the event at the time of the analysis; such patients were considered censored in the analysis.

No imputation was carried out for missing data in response assessment, safety endpoints, or baseline characteristics.

Follow-up

Withdrawal or study completion:

A completed patient was one who finished six cycles of treatment as defined in the protocol. In the case of withdrawal of a patient, the study conclusion form was completed.

0-2 years following study completion:

All patients were followed until death. All follow-up therapies and toxicities were reported until progression was documented. Patients were monitored every three months for up to two years following study completion or withdrawal and vital status, medical history and physical examination, QoL, disease status, evidence of long term and cancer therapy were documented.

2-5 years following study completion:

Patients were monitored every six months and vital status, medical history and physical examination, disease status, evidence of long term AEs and cancer therapy were documented.

Efficacy analyses

An interim analysis was performed after 56 deaths were observed in the cisplatin arm. This analysis compared the topotecan in combination with cisplatin arm to the cisplatin arm to determine the feasibility of further recruitment. Based on the interim analysis results, it was decided to proceed to complete the study. Since the analysis created multiplicity issues, the significance level was adjusted from 0.05 to 0.044 for the final analysis.

Based on the sample size calculations, the final efficacy analysis was planned to be performed after at least 111 events (deaths) were observed in the cisplatin group. The efficacy data base was locked on 31st October 2003, after 129 events (deaths) had occurred in the cisplatin group. These data were used for the trial efficacy analyses.

Analysis of primary outcome:
The study tested the hypothesis that adding topotecan to cisplatin (a community standard of care) will extend overall survival in patients with stage IVB, recurrent or persistent carcinoma of the cervix compared to cisplatin monotherapy.

Three populations were studied:

1. The principal population was the intention-to-treat (ITT) population. Unusually this consisted of all randomised patients, excluding ineligible patients, and was assessed for subject disposition, demography, baseline characteristics, efficacy, and post study therapy. This is the population referred to in Section 6 of this submission.
2. The randomised population consisted of all randomised patients, including the ineligible subjects. This population was assessed for survival and data are not reported in this submission.
3. The treated population included all patients who were randomised and treated. This population unusually excluded the ineligible patients and was assessed for safety/exposure. Analyses in Section 6.7 are based on this population.

Differences between the treatment groups in the ITT population for overall survival were evaluated using the log-rank test. Kaplan-Meier survival estimates, including median (95% CI), minimum event time, maximum event time, number (%) of events, and number (%) of censored events, were summarised.

Analyses of secondary outcomes:

PFS was summarised in the ITT population for the two treatment arms by Kaplan-Meier method. Differences between the treatment groups in PFS were evaluated using the log rank test.

To be considered assessable for response, patients had to complete their first cycle of protocol therapy and undergo repeat evaluation of their measurable disease before initiating cycle 2; patients who discontinued cycle 1 because of toxicity or who died as a result of complications from their disease (although unassessable for response) were considered assessable for toxicity if interval toxicity measurements were obtained. The response rates for treatment groups in the ITT population were summarised along with binomial two-sided

95% CI. Differences between the treatment groups in response rates were evaluated using the Pearson chi-square test.

QoL scores were summarised and plotted over time by treatment group using descriptive statistics. Compliance rates were tabulated over time by treatment group and reason for non compliance.

The doses and number of cycles of chemotherapy for each patient were recorded.

Exposure to treatment was assessed by treatment group. Therapeutic interventions such as dose reductions and dose delays required to ameliorate toxicities associated with the treatment regimen were summarised. Dosing delays were defined as a delay in dosing ≥ 7 days. Reasons for dose reductions and dose delays were summarised.

Subgroup analyses:

Prospectively planned subgroup analyses of survival in the ITT population were evaluated by:

- prior radiotherapies (no RT, RT without radiosensitiser, RT with cisplatin as a radiosensitiser, RT with radiosensitisers other than cisplatin)
- race (Caucasian vs. black vs. others)
- GOG performance status (PS 0 vs. 1 vs. 2)
- histology (adenocarcinoma vs. squamous cell carcinoma)
- age (<65 years vs. ≥ 65 years)
- time from diagnosis to study entry for patients with recurrent disease (limits were not prospectively defined)

It should be noted that whilst the last subgroup analysis was pre-planned, a cut-off point of 16 months for subgroup partitioning was chosen post-hoc because it was approximately where the survival shift occurred.

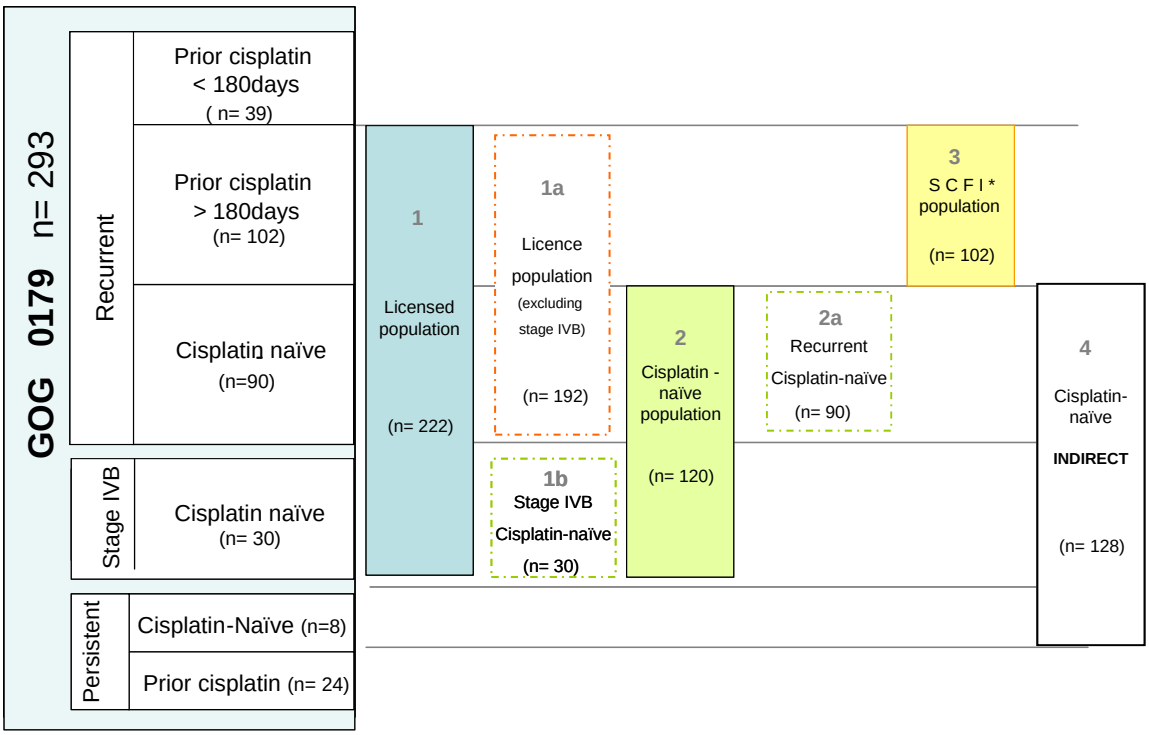
Additional subgroup analyses were undertaken for this submission as the licence for topotecan in combination with cisplatin does not include all patients in the GOG-0179 trial (see Appendix 1). Specifically, the SmPC excludes patients with persistent disease, reflective of the low number of these patients in the GOG-0179 trial. Acknowledging the impact of prior cisplatin on outcomes in patients re-challenged with cisplatin, the SmPC also states that “patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination”. Although the length of the treatment-free interval is not explicit in the SmPC, we have assumed a period of 180 days for this submission; in line with analyses presented in Section 5.1 of the SmPC (see Appendix 1). It should be noted that this 180-day period relates to the period between the last cisplatin dose and the recurrence of disease that resulted in eligibility for GOG-0179; referred to hereafter as the sustained cisplatin-free interval (SCFI). There is some uncertainty regarding the extent of prior exposure to cisplatin in England and Wales. Therefore, we have also analysed two key subgroups within the *Licensed population,* namely those patients who had not received prior cisplatin *(Cisplatin-naïve population),* and those with a sustained cisplatin free interval (*SCFI population*). Further exploratory analysis is undertaken in the economic section to evaluate the impact of removing Stage IVB patients from the licensed population, and from the cisplatin-naïve population:

The sub-groups of interest are summarized below, and illustrated in relation to the GOG-0179 population in Figure 10:

1. *Licensed population, consisting of:*
   - *1a. Licensed population excluding IVB patients*
   - *1b. Stage IVB patients (by definition cisplatin-naïve, as they are newly presenting)*
2. *Cisplatin-naïve population, consisting of:*
   - *2a. Cisplatin-naïve recurrent population excluding Stage IVB patients*
   - *(1b. Stage IVB patients)*
3. *Patients with a sustained cisplatin-free interval (SCFI; >180 days)*

A further subgroup was analysed specifically for an indirect comparison of topotecan in combination with cisplatin versus paclitaxel in combination with cisplatin. The *cisplatin-naïve (for indirect analysis (IND)) population* contains all cisplatin-naïve patients in GOG-0179 for comparison with patients in a second study (GOG-0169).[14] The rationale for this is discussed in Section 7.

Figure 10. Schematic of study population and subgroups analysed in this submission



6.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

GOG-0179

- *How was allocation concealed?*

The study was open-label.

- *What randomisation technique was used?*

The GOG Statistical and Data Center randomly assigned the treatment regimens with equal probability using a fixed-block design; patients were stratified by treating institution only.

- *Was a justification of the sample size provided?*

Yes. The median survival for the cisplatin group was anticipated to be 8.5 months using data from a previous GOG study (GOG-0149).[32] A decrease in death rate of 33% (i.e. hazard ratio of topotecan in combination with cisplatin relative to cisplatin = 0.67) was considered to be an important difference to detect in this study. Based on the hypothesised difference, the final analysis was planned after a total of 111 deaths were observed in the cisplatin group. This was expected to yield 82% power and 2.5% overall one-tailed type I error for a pairwise comparison of the experimental arm to cisplatin. Based on the above parameters, the planned sample size was 400 patients, 133 patients in each treatment group, to be recruited into the three treatment arms of the study.

- *Was follow-up adequate?*

Yes. A completed patient was one who finished six courses of treatment. All patients were followed until death. All follow-up therapies and toxicities were reported until progression was documented.

- *Were the individuals undertaking the outcomes assessment aware of allocation?*

Yes. This was an open-label study.

- *Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.*

This was a parallel group design with three treatment arms.

- *Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?*

There were 47 centres in the United States. The prevalence of prior cisplatin use and the length of the cisplatin-free interval in England and Wales will be the main factors that may influence the efficacy of topotecan in combination with cisplatin versus cisplatin compared with the results from the ITT population in GOG-0179.

- *How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.*

Although GOG-0179 was conducted in the United States, the demographic characteristics of the patients in the study (and the specified subgroups) are likely to be representative of the English and Welsh population for the following reasons:

- They were predominantly (over 70%) Caucasian and over 90% were aged <65 years at study entry, with a median age of 45-50 years across the ITT population and subgroups. This median age is similar to that of the UK patients in the IMS Oncology Analyzer, selected as representative of the licensed indication, who have a median age of 41-50 years (see Appendix 4). Approximately 85% of patients in the ITT population had squamous cell carcinoma, the predominant form of cervical cancer in the UK.[33]

- The majority of patients in all populations (~90%) had a PS of 0 or 1 (the ratio of these was approximately 1:1), i.e. either fully active or ambulatory but restricted in strenuous activity. There is no reason to believe that the eligibility criteria would have selected patients with a better PS than those patients who would be seen in clinical practice in England and Wales. It is noted in the SmPC (see Appendix 1) that accurate assessment of PS at the time therapy is given is important, to ensure that patients have not deteriorated to PS 3.

- *For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?*

Cisplatin: 50 mg/m^2 IV on day 1 and then every three weeks for six courses or until disease progression or unacceptable adverse effects prohibited further therapy.

Topotecan: 0.75 mg/m^2 infused over 30 minutes on days 1, 2, and 3 followed by cisplatin 50 mg/m^2 IV on day 1, the regimen was repeated every 21 days for six courses or until disease progression or unacceptable adverse effects prohibited further therapy.

- Were the study groups comparable?

Yes. See Table 3, Summary of baseline characteristics.

- *Were the statistical analyses used appropriate?*

Yes, see below.

- *Was an intention-to-treat analysis undertaken?*

Primary efficacy analysis of survival data were applied to the ITT population and comparison of survival between regimens in the ITT population was made via Cox proportional-hazards regression in the presence and absence of the prognostic factors (baseline GOG PS, age, and disease stage). Subgroup analyses of survival in the ITT population were evaluated by prior radiotherapies. Progression-free survival was summarised in the ITT population for topotecan in combination with cisplatin and cisplatin alone treatment arms by the Kaplan-Meier method.

- *Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?*

No.

6.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. For each outcome for each included RCT the following information should be provided.

- *The unit of measurement.*
- *The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.*
- *A 95% confidence interval.*
- *The number of patients included in the analysis.*
- *The median follow-up time of analysis.*
- *State whether intention-to-treat was used for the analysis and how data were imputed if necessary.*
- *Discuss and justify definitions of any clinically important differences.*
- *Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.*
- *If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.*
- *Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.*

As a whole, GOG-0179 has documented the consistent efficacy and safety of topotecan. The results are presented in Tables 4 and 5. The results reported here were derived from the clinical study report.[34]

Primary efficacy endpoints

Effect of topotecan on survival

The primary efficacy endpoint for GOG-0179 was overall survival, which was defined as the time from randomisation to death, in the ITT population. Patients treated with topotecan in combination with cisplatin had a longer median survival (9.4 months, 95% CI: 7.9, 11.9 months) than those treated with cisplatin alone (6.5 months, 95% CI: 5.8, 8.8 months; Table 4).

For the topotecan in combination with cisplatin treatment group, the 1- and 2-year estimates of survival probability were 40.4% (95% CI: 32.3%, 48.5%) and 11.9% (95% CI: 5.5%, 18.3%), respectively. The corresponding figures for cisplatin were 28.0% (95% CI: 20.6%, 35.4%) and 7.1% (95% CI: 2.0, 12.2%). Topotecan in combination with cisplatin was statistically superior to cisplatin in OS after adjusting for interim analysis (log-rank p =0.033). The log-rank p-value was significant as it was less than nominal significance level of 0.044 after adjusting for interim analysis. The unadjusted hazard ratio for survival in the topotecan in combination with cisplatin group relative to cisplatin alone was 0.762 (95%CI: 0.593, 0.979; p = 0.0333), favouring the combination arm. This corresponds to a 24% reduction in death rate for the topotecan in combination with cisplatin arm.

Table 4. Overall survival in patients treated with topotecan in combination with cisplatin compared with cisplatin alone (data derived from clinical study report)

Overall survival time (months)	**Cisplatin (n=146)**	**Topotecan/cisplatin (n=147)**
Median	6.5	9.4
95% confidence interval for median survival time	5.8 - 8.8	7.9 - 11.9
Log-rank p-value	0.033*	
Hazard Ratio (95% confidence interval)†	0.762 (0.593, 0.979)	

*Log-rank p-value was significant as it was less than the type 1 error level of 0.044 after adjusting for interim analysis.
†Hazard ratio of overall survival for topotecan in combination with cisplatin group relative to cisplatin alone.

Survival by prior cisplatin radiotherapy among patients with recurrent disease (ITT population)

Among patients with prior cisplatin radiotherapy, median survival was two months longer for those treated with topotecan in combination with cisplatin (median 7.9 months, 95% CI: 5.5, 10.9 months) than those who received cisplatin alone (median 5.9 months, 95% CI: 4.7, 8.8 months; Table 5).

Among patients without prior cisplatin radiotherapy (cisplatin-naïve; Figure 10), the median survival was almost twice as long in patients who received topotecan in combination with cisplatin (median 15.7 months, 95% CI: 11.9, 17.7 months) compared with cisplatin alone (median 8.8 months, 95% CI: 6.4, 11.5 months).

The median survival was longer for both treatment groups in patients without prior cisplatin radiotherapy (cisplatin-naïve), than in patients who had previously received cisplatin radiotherapy.

Table 5. Median survival in recurrent disease ITT subgroup populations in GOG-0179 (data derived from clinical study report)

Overall survival time (months)	Cisplatin (n=72) with prior cisplatin radiotherapy	Topotecan/cisplatin (n=69) with prior cisplatin radiotherapy	Cisplatin (n=46) cisplatin naïve	Topotecan/cisplatin (n=44) cisplatin naïve
Median	5.9	7.9	8.8	15.7
95% CI for median survival time	4.7 - 8.8	5.5 – 10.9	6.4 – 11.5	11.9 – 17.7
Log-rank p-value		0.357		0.005

CI = confidence interval

Secondary efficacy endpoints

Effect of topotecan on progression-free survival

A secondary efficacy endpoint for GOG-0179 was progression-free survival (PFS) in the ITT population which was defined as the time from randomisation until death or relapse. The median PFS was longer among patients who received topotecan in combination with cisplatin compared with those treated with cisplatin alone. The median PFS times were 4.6 months (95% CI: 3.5, 5.7 months) for topotecan in combination with cisplatin and 2.9 months (95% CI: 2.6, 3.5 months) for cisplatin alone. Overall PFS showed an advantage for the topotecan in combination with cisplatin treatment group compared to the cisplatin treatment group (log-rank p= 0.026). The unadjusted hazard ratio for PFS in the topotecan in combination with cisplatin treatment group was 0.761 (95% CI: 0.597, 0.969; p = 0.0270), favouring the combination arm. This corresponds to a 24% reduction in progression or death for topotecan in combination with cisplatin.

Effect of topotecan on response rate

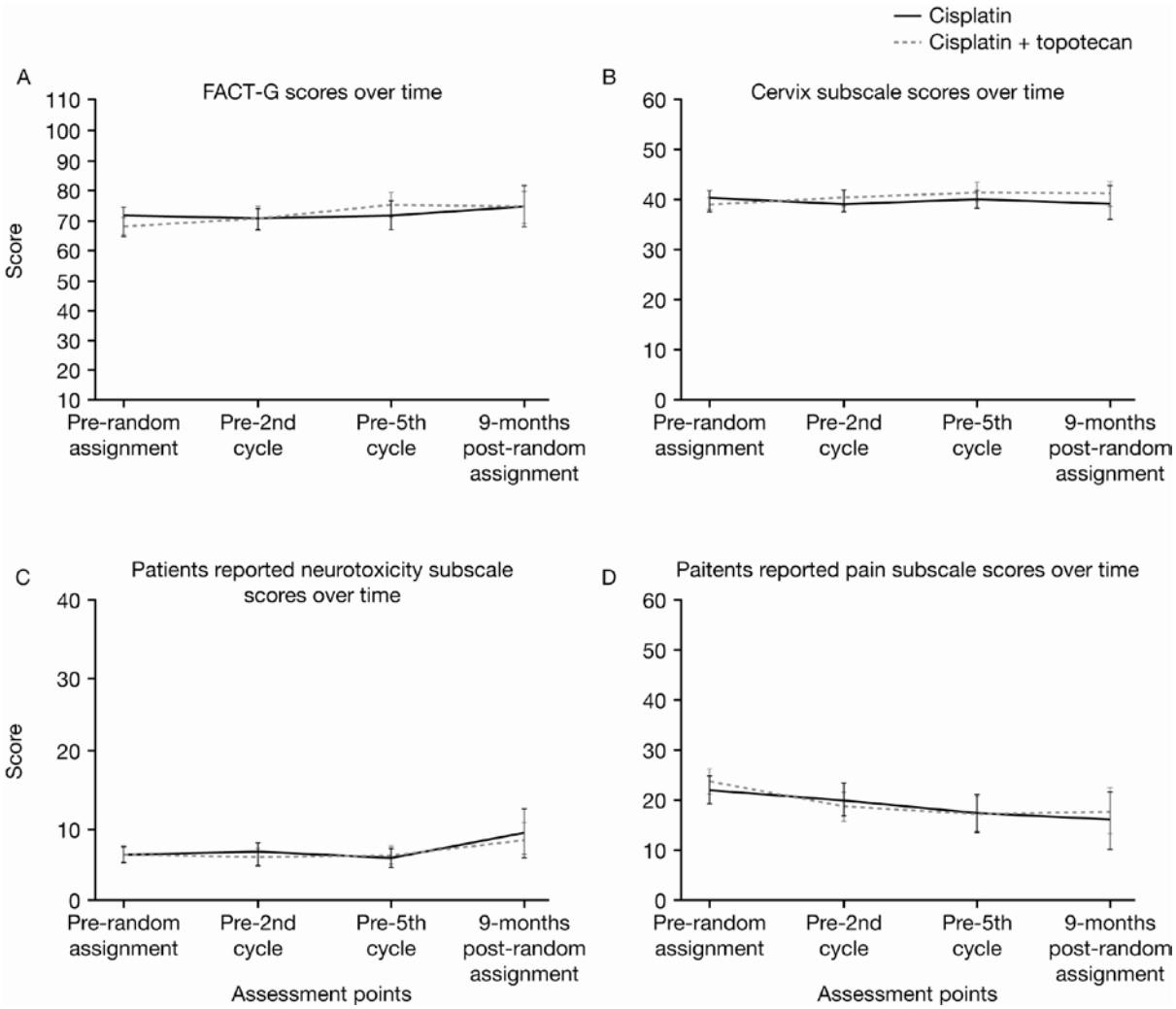
A further secondary efficacy endpoint for GOG-0179 was response rate, which was defined as the number of patients responding to treatment (either CR or PR) divided by the number of patients in each respective treatment group in the ITT population. Response rate results showed an advantage for the topotecan in combination with cisplatin treatment group compared to the cisplatin treatment group (p = 0.0073). The overall response rate for patients treated with cisplatin was 12% (18/146). The overall response rate for patients treated with topotecan in combination with cisplatin was 24% (36/147).

Of the 18 patients who responded to cisplatin therapy, 4 (3%) patients achieved a CR and 14 (10%) patients achieved a PR. In addition, 70 (48%) patients had stable disease. Of the 36 patients who responded to topotecan in combination with cisplatin, 14 (10%) patients achieved a CR and 22 (15%) patients achieved a PR. This was a greater than three-fold increase in CR. In addition, 61 (41%) patients had stable disease.

Effect of topotecan on health-related quality of life

QoL was assessed in GOG-0179 using the Functional Assessment of Cancer Therapy-Cervix Cancer (FACT-Cx), FACT-G, FACT- NTX and Brief Pain Inventory (BPI), all of which are validated instruments. In GOG-0179, there was no statistical evidence suggesting that reported QoL and adverse effects scores changed over time across regimens after adjusting for baseline scores and age at entry. QoL scores for each parameter were similar between treatment groups at baseline. Both treatment groups presented nearly stable FACT-G and Cx subscale scores during the assessment period; however, there was an increasing trend for the NTX score and a declining trend for the BPI score over time for both treatment groups (Figure 11). A secondary report concluded that topotecan added to cisplatin produced no significant reduction in QoL, and this effect remained stable over time.[6]

Figure 11. Mean QoL scores over time by treatment group in the GOG-0179 trial

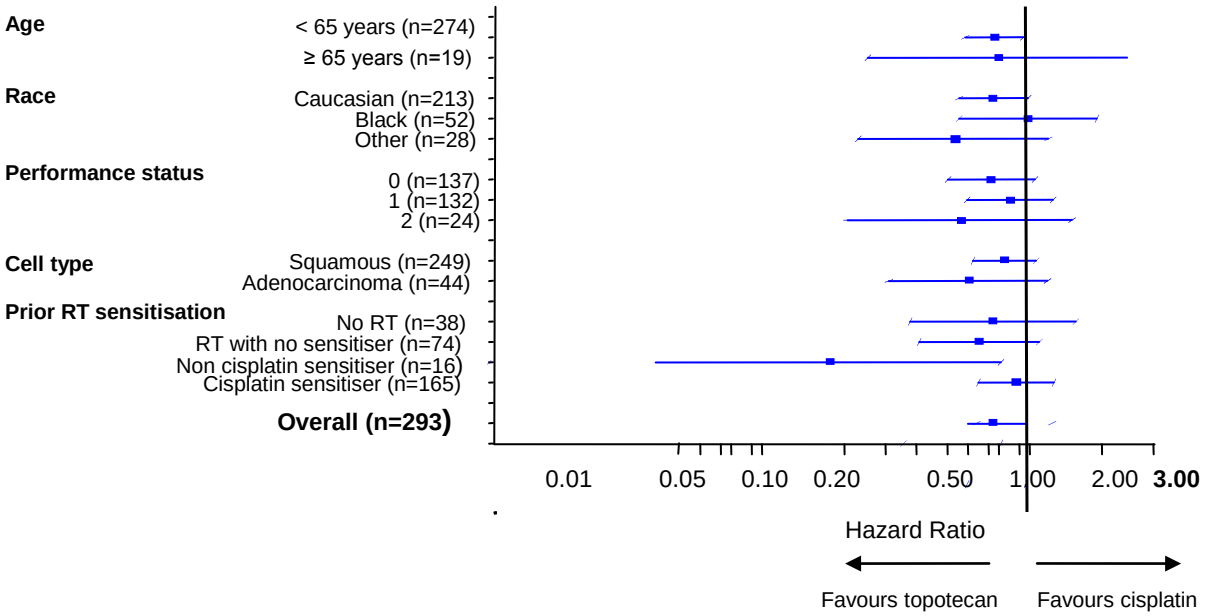


QoL = quality of life; FACT- G = Functional Assessment of Cancer Therapy-General; Cx = Cervix Subscale ; NTX = Neurotoxicity Subscale ; BPI = Brief Pain Inventory.

Results of prospectively planned subgroup analyses for overall survival (ITT population)

The results of the prospectively-planned subgroup analyses are summarised in Figure 12.

Figure 12. Treatment hazard ratios for survival – results of planned subgroup analyses, ITT population *Source: GOG-0179 CSR[34] (with modification)*



For age (< 65yrs), race (Caucasian), PS (0,1) and cell type (squamous cell carcinoma), the 95% CIs for the hazard ratio (HR) indicate that the survival trend favoured the topotecan plus cisplatin group. However, in each analysis, there were too few subjects in the remaining subgroups (i.e. age ≥ 65 years, Black/Other race, PS 2 and adenocarcinoma) to make meaningful comparisons therefore reported results should be viewed with caution.

Regarding the time from diagnosis to study entry analysis, the majority of patients (59%) with recurrent disease were in the <16 month subgroup. Although time from diagnosis to study entry is itself a strong prognostic factor, the 95% CIs for the HRs for both subgroups indicate that the survival trend favoured topotecan plus cisplatin. It should be noted that this 16 month cut-off does not represent a distinct threshold in terms of a patient's potential chemo-sensitivity and therapeutic benefit.

A majority of patients (56%) in both treatment groups had prior cisplatin as a radiosensitiser. The 95% CIs for the hazard ratios for the prior RT with cisplatin as a radiosensitiser and prior RT with no radiosensitiser subgroups indicate a survival advantage for the combination of topotecan plus cisplatin. There were too few patients in the other subgroups (RT with a radiosensitiser other than cisplatin and no RT) to make a meaningful comparison.

An overall survival benefit was maintained across pre-defined subgroups in study GOG-0179 relating to prior radiotherapy, race, age, GOG PS, time from diagnosis to study entry, and histology. However, the margin of benefit from topotecan plus cisplatin was greater in patients who had not been exposed to prior cisplatin.

In the subgroup with stage IVB disease at study entry, the median survival was 9.9 months (95% CI: 4.1, 22.5) in the topotecan/cisplatin arm compared with 7.1 months (95% CI: 5.3, 12.9) in the cisplatin monotherapy arm. The hazard ratio for survival was 0.84 (95% CI: 0.38, 1.87) favouring the topotecan arm. The response rates were 50% and 13% for the topotecan/cisplatin combination and the cisplatin monotherapy arms respectively. Too much should not be read into this as the numbers in each arm are very small (topotecan/cisplatin (n=14); cisplatin monotherapy (n=16)). The median progression free interval also favoured the topotecan/cisplatin combination arm, (median PFS = 5.8 months (1.8, 11.7) vs 2.7 months (1.6, 6.0) for topotecan/cisplatin combination and cisplatin monotherapy arms respectively).

The data for those with stage IVB disease did show a larger margin of difference in efficacy between the two treatment arms, than was seen in recurrent subgroup, but this was not so large as to be able to make a significant difference to the overall efficacy results, especially given the small number of patients in this subpopulation (n=30) compared to the number of patients in the recurrent subpopulation (n=231).

Results of additional subgroups evaluated in the economic analysis

Figure 10 depicted the key subgroups (1-4) that have been analysed for this submission in addition to the GOG-0179 ITT population. Patient characteristics for these subgroups are presented in Table 6 and Table 7. Overall survival data are presented in Table 8.

Discussion of results of subgroups analysed for this submission

The baseline characteristics (in terms of age, race, and histological grade) for the various subgroups are similar. It should be recognised that patients were randomised into the ITT population and these subgroups are *post-hoc* analyses of the data.

There was a slight imbalance in the performance status of the patients in the subgroups analysed, which is not surprising given that randomisation was performed at the ITT population level. The two treatment arms of the ITT population of GOG-0179 had approximately the same percentage of patients with a PS of 0 and 1 (both arms had PS 0:1:2 ratio of 47%:45%:8%). Whilst the cisplatin arms of the sustained-cisplatin free interval (*SCFI) population* and *cisplatin-naïve population* show similar distributions, there are some differences in the topotecan in combination with cisplatin arms. In the topotecan in combination with cisplatin arm of the *SCFI population,* proportionately fewer patients had a PS of 0 (PS 0:1:2, 43%:51%:6%) whilst the converse is seen in the topotecan in combination with cisplatin arm of the *cisplatin-naïve population* (PS 0:1:2, 60%:33%:7%). Although there is a possibility of increased benefit from chemotherapy for those with a better performance status, it is not clear whether this would have any significant impact on the results.

The topotecan in combination with cisplatin arm in the *cisplatin-naïve population* had a median OS of 14.5 months (vs. 8.5 months for cisplatin, HR 0.587, 95% CI: 0.389-0.884), the highest of any subgroup. The topotecan in combination with cisplatin arm in the *SCFI population* had a median OS of 9.9 months (vs. 6.3 months for cisplatin, HR 0.75, 95% CI: 0.492-1.155), the lowest of any subgroup (although not statistically significant). This is likely to reflect the effect of prior cisplatin. However, given the discussion on PS above, the former may be an overestimate of efficacy and the latter an underestimate of efficacy.

In GOG-0179, 61% of patients with recurrent disease had previously received cisplatin as a radiosensitiser. This may be broadly representative of English and Welsh practice, as estimates of prior cisplatin exposure range from 30% and 90% (Appendix 4).

Table 6. Patient characteristics: GOG-0179 key subgroup analyses carried out for this submission

	Licence population				***Cisplatin naïve population***				***Sustained cisplatin-free interval (SCFI) population***				***Cisplatin naïve (for indirect analysis (IND)) population***			
	Cisplatin (n=115)		**Topotecan plus cisplatin (n=107)**		**Cisplatin (n=62)**		**Topotecan plus cisplatin (n=58)**		**Cisplatin (n=53)**		**Topotecan plus Cisplatin (n=49)**		**Cisplatin (n=64)**		**Topotecan plus Cisplatin (n=64)**	
Age (years)																
Mean (standard deviation)	49 (10.2)		49 (11.7)		50 (10.0)		52 (13.3)		47 (10.0)		45 (8.0)		50.4 (10.1)		51.8 (13.1)	
Median (range)	48 (27-76)		46 (29 - 84)		50 (31-76)		53 (29-84)		47 (27-68)		44 (29-65)		50 (31-76)		52.5 (29-84)	
	n	%	N	%	n	%	n	%	n	%	n	%	n	(%)	n	%
≥ 65	8	7%	9	8%	6	10%	8	14%	2	4%	1	2%	7	11%	8	12%
Race																
Caucasian	84	73%	81	76%	44	71%	43	74%	40	76%	38	78%	46	72%	47	73%
Black	21	18%	16	15%	14	23%	9	16%	7	13%	7	14%	14	22%	11	17%
Other	10	9%	10	9%	4	6%	6	10%	6	11%	4	8%	4	6%	6	9%

Table7. Disease characteristics: GOG-0179 key subgroup analyses carried out for this submission

	Licence population				***Cisplatin naïve population***				***Sustained cisplatin-free interval (SCFI) population***				***Cisplatin naïve (for indirect analysis (IND)) population***			
	Cisplatin (n=115)		**Topotecan plus cisplatin (n=107)**		**Cisplatin (n=62)**		**Topotecan plus cisplatin (n=58)**		**Cisplatin (n=53)**		**Topotecan plus Cisplatin (n=49)**		**Cisplatin (n=64)**		**Topotecan plus Cisplatin (n=64)**	
	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%
Performance status (PS)																
0	55	48%	56	52%	30	48%	35	60%	25	47%	21	43%	31	48%	39	61%
1	51	44%	44	41%	29	47%	19	33%	22	42%	25	51%	30	47%	20	31%
2	9	8%	7	7%	3	5%	4	7%	6	11%	3	6%	3	5%	5	8%
Histological grade																
1	7	6%	6	6%	2	3%	4	7%	5	9%	2	4%	2	3%	4	6%
2	64	56%	65	61%	39	63%	34	59%	25	47%	31	63%	41	64%	38	59%
3	42	37%	33	31%	20	32%	18	31%	22	42%	15	31%	20	31%	20	31%
Not graded	2	2%	3	3%	1	2%	2	3%	1	2%	1	2%	1	2%	2	3%
Stage																
IVB	16	14%	14	13%	16	26%	14	24%	0	0%	0	0%	16	25%	14	22%
Recurrent	99	86%	93	87%	46	74	44	76%	53	100%	49	100%	46	72%	44	69%
Persistent	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	2	3%	6	9%
Prior radiotherapy (RT) and cisplatin																
No prior RT	20	17%	18	16%	20	32%	18	31%	0	0%	0	0%	20	31%	18	28%
Prior RT, no prior sensitiser	35	30%	34	30%	35	56%	34	59%	0	0%	0	0%	37	58%	37	58%
Prior cisplatin RT sensitiser	53	46%	49	43%	0	0%	0	0%	53	100%	49	100%	7	11%	9	14%
Prior non-cisplatin RT sensitiser	7	6%	6	5%	7	11%	6	10%	0	0%	0	0%	0	0%	0	0%

Table 8. Overall survival: GOG-0179 key subgroup analyses carried out for this submission

	Licence population		***Cisplatin naïve population***		***Sustained cisplatin-free interval (SCFI) population***		***Cisplatin naïve (for indirect analysis (IND)) population***	
	Cisplatin (n=115)	**Topotecan plus cisplatin (n=107)**	**Cisplatin (n=62)**	**Topotecan plus cisplatin (n=58)**	**Cisplatin (n=53)**	**Topotecan plus Cisplatin (n=49)**	**Cisplatin (n=64)**	**Topotecan plus cisplatin (n= 64)**
Overall survival time (months)								
Mean	9.93	12.95	11.1	15.1	7.95	9.54	11.1	14.4
Median	7.3	11.9	8.5	14.5	6.3	9.9	8.5	12.5
95% CI for median survival time	6.0-9.5	9.4-13.7	6.4-11.1	11.5 - 17.5	4.9-9.5	7.0-12.6	6.5-11.3	9.2-17.4
Log rank p-value	0.0041		0.0098		0.1912		0.0206	
Hazard ratio (95% CI)	0.652 (0.485; 0.875)		0.587 (0.389; 0.884)		0.75 (0.492;1.155)		0.633 (0.428;0.935)	
Minimum	0.3	0.4	1.3	0.4	0.3	0.6	1.3	0.4
Maximum	39	34.4	34	31	17.2	27.1	38.9	34.4
Observed events	100 (87.0%)	81 (75.7%)	55 (89.0%)	40 (69.0%)	45 (84.9%)	41 (83.7%)	57(89.1%)	46 (71.9%)
Censored events	15 (13.0%)	26 (24.3%)	7 (11.0%)	18 (31.0%)	8 (15.1%)	8 (16.3%)	7 (10.9%)	18 (28.1 %)

GOG – 0169 - Paclitaxel plus cisplatin versus cisplatin monotherapy

GOG-0169, a phase III study compared paclitaxel plus cisplatin (n=130) with cisplatin alone (n=134) in patients with stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix.[14] GOG-0169 had a similar design to GOG-0179, although some differences existed in the proportion of patients who had received prior chemoradiation therapy. Data from these two studies, with cisplatin as the common comparator, form the basis of an indirect cost-effectiveness comparison to be presented in Section 6 of this submission.

Methods

Eligible patients with measurable disease, PS 0 to 2, and adequate haematological, hepatic, and renal function received either cisplatin 50 mg/m^2 or paclitaxel 135 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks for six cycles unless disease progression or toxicity prohibited further therapy. Pre-treatment clinical evaluation was repeated before each treatment cycle with the exception of tumour measurements (repeated at least at every other treatment cycle) and QoL assessments (FACT-G, FACT-Cx, NTX and BPI were obtained at baseline and successive cycles, for a total of four). Patients who received paclitaxel were premedicated with dexamethasone, diphenhydramine, and an H_2 receptor antagonist (e.g. cimetidine or ranitidine). A prophylactic antiemetic regimen based on ondansetron or granisetron was administered to all patients, along with adequate IV hydration and electrolyte replacement.

Dose reductions for cisplatin were very similar to those described in GOG-0179. Paclitaxel dose level reductions to 110 mg/m^2 (level 1) or 90 mg/m^2 (level 2) were prescribed for specific adverse effects. A 1-dose-level reduction was required for grade 3 to 4 neutropenic fever or grade 4 thrombocytopenia, and a 2-dose-level reduction was required for grade 2 peripheral neuropathy. Treatment with paclitaxel was discontinued for grade 3 to 4 peripheral neuropathy or hepatotoxicity.

Critical Appraisal

- *How was allocation concealed?*

The study was open-label.

- *What randomisation technique was used?*

Randomization with equal probability to each of the treatment arms was carried out using a block design, which balances the sequence of assigned arms within parent institutions

- *Was a justification of the sample size provided?*

Among women treated with cisplatin alone, it was anticipated that 19% would experience either partial or complete response. It was considered significant if the addition of paclitaxel to cisplatin increased the proportion responding by 15% without undue toxicity. Registering and evaluating 238 women (119 to each treatment arm) provided an 80% chance of detecting this magnitude of effect while the type I error is set at 0.05 for a one-sided test.

- *Was follow-up adequate?*

Yes. The estimated median duration of PFS for women treated with cisplatin was 3.2 months. If patients entered this study at a constant rate over 22 months and the addition of paclitaxel to cisplatin decreased the relative hazard by one-third (50% increase in median PFS to 4.8 months), then there would be a 92% chance of detecting this effect after 12 months of post-accrual follow-up, when the type I error is set at 5% for a one-tail test.[16] The estimated median survival duration for patients treated with cisplatin was 8.0 months. This sample size would permit an 86% chance of detecting a one-third decrease in the relative death rate (50% increase in median survival) after a 12-month post-accrual follow-up period, with the type I error set at 5% for a one-tail test.[15] The anticipated duration of accrual for this study was 22 months, and a 12-month post-accrual follow-up period was planned..

- *Were the individuals undertaking the outcomes assessment aware of allocation?*

Yes. This was an open-label study.

- *Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.*

This was a parallel group design with two treatment arms.

- *Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?*

This study was conducted in the United States. The prevalence of prior cisplatin use and the length of the cisplatin-free interval in England and Wales will be the main factors that may influence the efficacy of paclitaxel in combination with cisplatin versus cisplatin compared with the results from the ITT population in GOG-0169.

- *How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.*

Although GOG-0169 was conducted in the United States, the demographic characteristics of the patients in the study (and the specified subgroups) are likely to be representative of the English and Welsh population for the following reasons:

- They were predominantly (over 65%) Caucasian and over 90% were aged <65 years at study entry, with a median age of 45-50 years across the ITT population and subgroups. This median age is similar to that of the UK patients in the IMS Oncology Analyzer, selected as representative of the licensed indication, who have a median age of 41-50 years (see Appendix 4).

- The majority of patients in all populations (~90%) had a PS of 0 or 1 (the ratio of these was approximately 1:1), i.e. either fully active or ambulatory but restricted in strenuous activity. Around 10% were unable to work.

- *For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?*

Single-agent cisplatin was administered at an intravenous dose of 50 mg/m^2 on day 1 and then every three weeks for six courses or until disease progression or unacceptable adverse effects prohibited further therapy.

Patients assigned to the combination arm (C+P) received paclitaxel at an IV dose 135 mg/m^2 infused over 30 minutes on days 1, 2, and 3 followed by cisplatin 135 mg/m^2 IV as a 24-hour infusion followed immediately by cisplatin at a dose of 50 mg/m^2, the regimen was repeated every 21 days for six courses or until disease progression or unacceptable adverse effects prohibited further therapy.

Were the study groups comparable?

Yes. The groups were well matched with respect to age, time from diagnosis to study, PS, tumour grade, prior radiotherapy, and median number of treatment cycles received on the current study. There were numeric differences between the groups in terms of ethnicity, prior chemoradiation and site of disease. (see Table 9 below). The differences appear to be within the bounds of reasonable variation though and the differences in baseline criteria do not appear to favour one arm over the other. For instance, although the patients in the combination cisplatin/paclitaxel arm appear to have a slightly worse PS and more non-pelvic disease, slightly fewer of them had prior chemoradiation and thus the likelihood of response is probably fairly evenly balanced.

- *Were the statistical analyses used appropriate?*

Yes,

- *Was an intention-to-treat analysis undertaken?*

Among the 264 eligible patients, five patients never received protocol chemotherapy but were included in the intent-to-treat analysis.

- *Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?*

No.

Results

A total of 280 patients were enrolled in the study, 16 patients were ineligible. After randomisation 134 received cisplatin alone and 130 received paclitaxel plus cisplatin. Five patients never received study treatment but were included in the ITT population.

Baseline patient characteristics of the GOG-0169 ITT population are described in Table .9.

Table 9. Patient characteristics, GOG-0169, ITT population[14]

Patient Characteristic	No. of Patients	
	Cisplatin (n=134) n (%)	**Cisplatin plus paclitaxel (n=130) n (%)**
Age, Years		
Median	46.0	48.5
Range	22-84	21-77
Median time from diagnosis to study entry, days	434	436
Performance Status (PS)		
0 (fully active)	64 (48)	59 (45)
1 (restricted physically)	59 (44)	54 (42)
2 (unable to work)	11 (8)	17 (13)
Grade		
1	5 (4)	8 (6)
2	90 (67)	78 (60)
3	38 (28)	42 (32)
Unspecified	1 (<1)	2 (1.5)
Prior radiotherapy	123 (92)	118 (91)
Prior chemoradiation	40 (30)	31 (24)
Race/ethnicity		
White	92 (69)	75 (58)
Black	29 (22)	47 (36)
Hispanic	11 (8)	6 (5)
Asian	1 (<1)	2 (1.5)
Filipino	1 (<1)	0
Site of disease		
Pelvic	66 (49)	52 (40)
Distant	49 (37)	61 (47)
Both	19 (14)	17 (13)
Number of cycles[a]		
Median	4	5
Range	0-11	0-11
No. not treated	4	1

[a] No. of cycles of protocol therapy

Overall, 71 patients had received chemotherapy plus radiation as primary treatment for cervical carcinoma, including 40 (30%) 134 patients in the cisplatin group and 31 (24%) patients in the paclitaxel plus cisplatin group. Cisplatin represented only one of four chemotherapeutic agents (cisplatin, fluorouracil, hydroxyurea, and navelbine) used alone or in combination as a radiation sensitiser.

Age, PS, histological grade and number of cycles were broadly similar for patients in GOG-0169 when compared with those in the *Cisplatin naïve (IND) population* in GOG-0179. As mentioned, the proportion of patients with experience of chemotherapy as a radiosensitiser was different in the two studies. This will be addressed in Section 6.6

A summary of the efficacy outcomes is shown in Table 10.

Table 10. Summary of efficacy outcomes, GOG-0169, ITT population[14]

Outcome	Cisplatin (n=134)	Paclitaxel plus cisplatin (n=130)	p-value
Median overall survival (months)	8.8	9.7	ns
Median PFS survival (months)	2.8	4.8	<0.001

Although there was a significant difference in median PFS, there was no significant difference in median overall survival for patient receiving paclitaxel plus cisplatin versus cisplatin alone.

Objective responses were documented in 19% of patients receiving cisplatin alone versus 36% of patients receiving paclitaxel plus cisplatin (p<0.002). Apparent differences between the two arms in the prior use of chemoradiotherapy were not significant.

Reporting of QoL information declined progressively during the treatment period. Regardless of assigned treatment, Treatment Outcome Index and BPI were stable among completers and worsened among drop-outs. Notably, among those who dropped out of the QoL portion of the study after completing at least one questionnaire, there was a disproportionate number of drop-outs among patients randomly allocated to receive cisplatin alone (50 of 133 patients) versus paclitaxel plus cisplatin (33 of 128 patients; p<0.05). However, among completers or drop-outs, there were no significant differences between treatment arms for any QoL subscale or summary scores. The authors found no evidence that patients receiving the combination therapy experienced worse QoL.

Pooled analysis

6.5 Meta-analysis of topotecan studies

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- *Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.*

- *Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).*

- *Provide an adequate description of the methods of statistical combination and justify their choice.*

- *Undertake sensitivity analysis where appropriate.*

- *Tabulate and/or graphically display the individual and combined results.*

Only one study is available; therefore, meta-analysis has not been performed.

6.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

A systematic review of the literature was performed to identify relevant studies of platinum-based chemotherapies used for the treatment of women with cervical cancer recurrent after radiotherapy or in stage IVB.

Identification of studies

See section 6.3.2 for details of the search performed and inclusion and exclusion criteria.

Methods of meta-analysis

Indirect comparisons were performed using data from GOG-0179 versus GOG-0169 to permit comparison of topotecan in combination with cisplatin versus cisplatin plus paclitaxel via the common comparator of cisplatin monotherapy. Both GOG-0179 and GOG-0169 were conducted in patients with stage IVB, recurrent or persistent carcinoma of the cervix (Table 11), but there were some differences between the respective study populations. Patients with prior chemotherapy were eligible for GOG-0179 but ineligible for GOG-0169 (except when chemotherapy was used for radiation sensitisation). Fewer patients had received chemotherapy as a radiosensitiser in GOG-0169 (27%) than in GOG-0179 (~60%) and these patients were unevenly distributed between treatment arms in GOG-0169. In addition, the proportion of patients receiving cisplatin as a radiosensitiser in GOG-0169 is unknown. For these reasons, there are limitations associated with the indirect meta-analysis.

As described in section 6.2.1, GOG-204 included a head to head comparison of four cisplatin-containing combinations (paclitaxel, vinorelbine, gemcitabine and topotecan). A planned interim analysis recommended early closure of GOG-0204 as all experimental arms were unlikely to demonstrate a significant advantage of any individual combination. For this reason, GOG-0204 did not achieve the inclusion criteria for meta-analysis but is discussed in section 6.2.1.

Table 11 describes the study designs and patient baseline characteristics for the studies included in the indirect comparison. It was not possible to exclude the patients in GOG-0169 with persistent disease or those with a sustained cisplatin-free interval to achieve consistency with the licensed indication for topotecan. However, given the differences in prior treatments described above, it was inappropriate to compare the ITT populations of both studies. It was considered that the most appropriate, least biased comparison would be that between the overall ITT population of GOG-0169 and the cisplatin-naïve population (including stage IVB patients) of GOG-0179 as few patients in the former group had prior exposure to cisplatin. In addition, the median OS for patients treated with cisplatin monotherapy was similar between trials for these populations.

The indirect comparison analysis was performed in Excel using the hazard ratios in the two studies (both of which refer to mean survival time). A further hazard ratio statistic, together with confidence intervals, was generated which was, in effect, the comparison of topotecan in combination with cisplatin and paclitaxel in combination with cisplatin with respect to the median survival time (Table 12).

Table 11. Summary of study designs

Study	Study design	Patient characteristics	Treatment groups (n)	Regimen
GOG-0179	Open-label Phase III RCT	Stage IVB, recurrent or persistent carcinoma of the cervix unsuitable for curative treatment with surgery and/or radiotherapy	Cisplatin monotherapy (146)†	50 mg/m^2 IV cisplatin on day 1 and then every 3 weeks for 6 courses*
			Topotecan in combination with cisplatin (147)†	Topotecan 0.75 mg/m^2 on days 1, 2, and 3 followed by cisplatin 50 mg/m^2 IV on day 1; the regimen was repeated every 3 weeks for 6 courses*
GOG-0169	Phase III RCT	Stage IVB, recurrent or persistent carcinoma of the cervix	Cisplatin monotherapy (134)	50 mg/m^2 IV cisplatin on day 1 and then every 3 weeks for 6 courses*
			Paclitaxel (130)	50 mg/m^2 IV cisplatin plus 135 mg/m^2 paclitaxel on day 1 and then every 3 weeks for 6 courses*

* Or until disease progression or unacceptable adverse effects prohibited further therapy
†The cisplatin-naïve population was considered in the meta-analysis

Results of the meta-analysis

Table 12 presents the results of the meta-analysis. The calculated hazard ratio of 0.72, favours topotecan in combination with cisplatin but does not reach statistical

significance (95% CI 0.46 to 1.15). A non-significant trend for OS was also reported in GOG-0204 (see section 6.2.1).

Table 12. Results of indirect comparison between GOG-0179 (cisplatin-naïve population) and GOG-0169 (ITT population) (data derived from clinical study report)

Primary endpoint data					
Study	Regimen	n	Hazard ratio	Lower CI	Upper CI
179	Cisplatin	64	0.63	0.43	0.94
	Topotecan in combination with cisplatin	64			
169	Cisplatin	134	0.87	0.68	1.11
	Paclitaxel in combination with cisplatin	130			
Generate the standard error of the hazard ratio					
Study	S.E.				
179	0.20				
169	0.13				
Find the hazard ratio of the compared trials					
179+169	0.72				
Then find the standard errors of these hazard ratios					
179+169	0.24				
And finally calculate the confidence intervals of the hazard ratio					
	Lower CI	Upper CI			
179+169	0.46	1.15			
Hazard ratio 0.72 (0.46, 1.15)					

CI: Confidence interval; PFS: progression-free survival: SE: standard error

6.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials. Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

Summary of safety

The safety of topotecan 0.75 mg/m^2 plus 50 mg/m^2 cisplatin was assessed as part of study GOG-0179. Topotecan in combination with cisplatin was found to have a toxicity profile that was predictable and consistent with the established individual toxicity profiles of the two cytotoxic agents. The results of GOG-0179 are supported by the GSK-CRT-234, where topotecan in combination with cisplatin was demonstrated to be safe and well tolerated in the evaluable population (n=32). In addition, GOG-0204, a head to head comparison of four cisplatin-containing

combinations (paclitaxel, vinorelbine, gemcitabine and topotecan), showed similar toxicities for all four regimens, except for less marrow suppression for gemcitabine in combination with cisplatin and more alopecia for paclitaxel in combination with cisplatin.

Haematological toxicities in GOG-0179 were more common and more severe among patients treated with topotecan in combination with cisplatin, including neutropenia, leukopenia, and decreased haemoglobin. The incidence of severe thrombocytopenia was low in both treatment groups. Generally, while the sequelae of neutropenia can be both life-threatening and treatment-limiting, in the GOG-0179 study most cases of neutropenia were uncomplicated and resolved in time for the next cycle of therapy.

The haematological toxicities with topotecan in combination with cisplatin were well managed with interventions for haematological toxicity, dose delays and dose reductions and did not lead to increased SAEs, withdrawals, deaths or a reduction in HRQoL when compared to the cisplatin treatment group.

The non-haematological safety profiles of the two groups were similar.

Topotecan and cisplatin have non-overlapping toxicities. The established principal toxicities associated with topotecan are haematological, particularly neutropenia, whereas cisplatin is associated with dose-limiting, cumulative nephrotoxicity and neurotoxicity.

Methodology

For the treated population, haematological and non-haematological toxicities were evaluated. Interventions for haematological toxicities, dose delays, and dose reductions were summarised. Serious adverse events (SAEs), deaths, and withdrawals were summarised by treatment group. Haematological and non-haematological laboratory assessments were also summarised. Prior medical history and concomitant medication were not captured at screening or during the course of the study. In the event of an AE or SAE the relevant history would be recorded and reported. Reports of AEs did not record the considered relationship to study medication, but all reports of SAEs did.

Haematological and non-haematological toxicities were expressed as the worst common toxicity criteria grade experienced by the patient for the study. The toxicity grading was assigned using the common toxicity criteria (CTC) version 2.0. In addition to the 21 major categories from the CTC version 2.0, four- toxicity items specific to haematological toxicity were recorded after each cycle of therapy. The laboratory assessment of haematological toxicities examined levels of: white blood cells (WBC), neutrophils/granulocytes, platelets, and haemoglobin (anaemia).

Serious adverse events were summarised separately. In general all grade 4 (except haematological) and grade 5 AEs were categorised as SAEs. Patient withdrawals from the study due to adverse events were summarised. Patient deaths were classified by time and cause of death.

Results

Exposure

Exposure data are summarised in Table 13. The treated population that was assessed for safety and exposure included all patients randomly assigned to treatment with cisplatin or topotecan in combination with cisplatin who were treated, excluding the ineligible patients and the untreated patients. Eleven patients in total were not treated. Three of these patients were in the cisplatin treatment group, one because of an administration error and the other two patients had 'other disease' reported as reason for non-treatment. Seven patients in the topotecan in combination with cisplatin group were not treated; four died prior to receiving treatment and the other three refused treatment.

Table 13. Exposure to study drugs in GOG-0179, treated population

Parameter	Cisplatin	Topotecan plus cisplatin
No. of patients	144	140
Starting dose	50 mg/m^2/day on day 1 every 21 days	Topotecan: 0.75 mg/m^2/day on day 1, 2, and 3 every 21 days Cisplatin: 50 mg/m^2/day on day 1 every 21 days
No. of cycles at target dose (%)	549/550 (99)	567/628 (90)
Median no. of cycles (range)	3 (1 to 12)	4 (1 to 20)

Source: GOG-0179 CSR

Haematological toxicity

For topotecan in combination with cisplatin, the principal haematological adverse events were leukopenia and neutropenia. The overall incidence of haematological toxicities by CTC grade is shown in Table 14. Consistent with the established toxicity profile for topotecan when administered over five consecutive days and cisplatin monotherapy, the incidence of grade 3 and 4 neutropenia and grade 3 and 4 leukopenia was substantially higher in the combination treatment arm.

Table 14. Number (%) of patients with haematological toxicity by worst CTC grade, Treated population

Haematological toxicity	Cisplatin (n=144)		Topotecan plus cisplatin (n=140)	
	n	%	n	%
Leukopenia				
Grade 1 / 2	42	29	35	25
Grade 3 / 4	1	1	93	66
ANC-AGC (neutropenia)				
Grade 1 / 2	26	18	22	16
Grade 3 / 4	2	1	103	74
Thrombocytopenia				
Grade 1 / 2	16	11	58	41
Grade 3 / 4	5	3	46	33
Haemoglobin				
Grade 1 / 2	97	67	75	54
Grade 3 / 4	33	23	56	40

Note: toxicity is based on the patient's worst grade for the study; percentages are based on the available laboratory data for each patient.
Abbreviations: CTC = common toxicity criteria, ANC/AGC = absolute neutrophil count/absolute granulocyte count.
Source: GOG-0179 CSR

Febrile neutropenia

The incidence of febrile neutropenia was not directly measured, rather it was classified as a subset of the infection category. However, there were at least 22 dose reductions (relating to 15 patients) in the topotecan in combination with cisplatin group that were due to febrile neutropenia.

Despite this identification issue, the publication of GOG-0179[3] assumes that all grade 3 and 4 infections reported were febrile neutropenia; i.e. occurring in 17.7% of patients treated with topotecan in combination with cisplatin versus 7.5% of those who received cisplatin.

Two patients withdrew from the study due to febrile neutropenia; one patient in the cisplatin treatment group withdrew due to a grade 4 SAE of febrile neutropenia (this patient also had a SAE of deep vein thrombosis) and one patient in the topotecan in combination with cisplatin group withdrew from the study due to the AE febrile neutropenia.

Interventions for haematological toxicities

More patients receiving topotecan in combination with cisplatin required interventions for haematological toxicity (Table 15).

Table 15. Summary of therapeutic interventions

Treatment	n	G-CSF (neutropenia)[a]	Platelet transfusion (TCP)[a]	RBC transfusion (anaemia)[a]	Erythropoietin (anaemia)[a]
Cisplatin	144	5 (3.5%)	1 (0.7%)	49 (34.0%)	38 (26.4%)
Topotecan plus cisplatin	140	37 (26.4%)	16 (11.4%)	68 (48.6%)	51 (36.4%)

[a]Most likely reasons for these interventions; TCP: thrombocytopenia
Source: GOG-0179 CSR

Non-haematological toxicity

Non-haematological toxicities were tabulated for all patients in the treated population. Toxicity was expressed as the worst grade experienced by the patient for the study as determined by the investigator. The non-haematological toxicities reported by over 25% of patients are presented in Table 16.

Table 16. Number (%) of patients with reported non-haematological toxicities for all cycles, regardless of attribution, treated population

CTC Category[a]	CTC Grade (n, %)							
	Cisplatin (n = 144)				Topotecan plus cisplatin (n = 140)			
	1	2	3	4+ [b]	1	2	3	4+ [b]
Constitutional	32 (22)	40 (28)	17 (12)	0 (0)	28 (20)	57 (41)	11 (8)	0 (0)
Other gastrointestinal	39 (27)	26 (18)	12 (8)	3 (2)	32 (23)	36 (26)	16 (11)	4 (3)
Other pain	16 (11)	33 (23)	18 (13)	5 (3)	17 (12)	34 (24)	28 (20)	3 (2)
Nausea	36 (25)	30 (21)	13 (9)	0 (0)	29 (21)	28 (20)	18 (13)	2 (1)
Dermatological	19 (13)	10 (7)	0 (0)	0 (0)	22 (16)	44 (31)	1 (1)	0 (0)
Vomiting	13 (9)	27 (19)	13 (9)	0 (0)	16 (11)	18 (13)	20 (14)	2 (1)
Metabolic laboratory	17 (12)	12 (8)	14 (10)	1 (1)	22 (16)	13 (9)	13 (9)	7 (5)
Genitourinary	20 (14)	15 (10)	7 (5)	7 (5)	16 (11)	17 (12)	9 (6)	9 (6)
Other neurological	26 (18)	8 (6)	7 (5)	2 (1)	29 (21)	16 (11)	3 (2)	1 (1)
Infection / febrile neutropenia	0 (0)	15 (10)	11 (8)	0 (0)	1 (1)	12 (9)	21 (15)	5 (4)

[a]Patients may have had more than one non-haematological toxicity. A patient was only counted once, by the worst CTC grade experienced.
[b]Grade 4+ includes both grade 4 and 5 toxicities.
Source: GOG-0179 CSR

In general, the incidence of non-haematological toxicities between the two treatment groups was comparable. The four most frequently reported non-haematological toxicities were the same for patients who were treated with topotecan in combination with cisplatin or cisplatin. These were: constitutional (69% and 62%, respectively), other gastrointestinal symptoms (63% and 56%), other pain (59% and 50%), and nausea (both 55%).

Several specific non-haematological toxicities that are associated with these two regimens were evaluated. The incidence of gastrointestinal-related, genitourinary toxicities, and neuropathy was similar between the two treatment groups.

Deaths and serious adverse events (SAEs)

Most deaths in both treatment groups were due to disease; 116 (81%) of the patients in the cisplatin group and 100 (71%) in the topotecan in combination with cisplatin group. In addition, 8% and 5% respectively, of deaths had cause of death reported as other, unknown or missing. Deaths occurred within 30 days of day 1 of the last dosing cycle of study drug in 11 (8%) patients treated with topotecan in combination with cisplatin and 10 (7%) patients treated with cisplatin. Four patients (3%) in the topotecan in combination with cisplatin group died within 30 days due to treatment-related causes, compared with none in the cisplatin group. However in two out of the four cases the investigator considered that the cause of death was not treatment related but may have been aggravated by treatment.

SAEs were reported to GOG using the following rules: any deaths, grade 2, 3, or 4 unknown toxicities based on information in the package insert or literature, and known grade 4 non-haematological toxicities included in the package insert or literature. There were only three grade 5 AEs in the ITT population (these were in the topotecan in combination with cisplatin arm: one related to haemorrhage and two pulmonary-related) and none of these occurred within the Licence population.

SAEs occurred in 10% (15/144) of patients treated with cisplatin and 14% (20/140) of those treated with topotecan in combination with cisplatin. The SAEs with the highest per-patient incidence rate were genitourinary/renal (3%, 4/144) among patients treated with cisplatin and cardiovascular (2%, 3/140), allergy/immunology (2%, 3/140), and haemorrhage (2%, 3/140) in the topotecan in combination with cisplatin group.

Treatment withdrawal

Adverse events

Fifteen patients (10%) treated with cisplatin were withdrawn for adverse events, as were 15 patients (11%) treated with topotecan in combination with cisplatin. The pattern of events leading to withdrawal was similar in each group (elevated creatinine, haematological toxicity).

Serious adverse events

Three patients (2%) who were treated with cisplatin were withdrawn for SAEs. Two patients (1%) treated with topotecan in combination with cisplatin were withdrawn due to SAEs.

Dose delays

More patients treated with topotecan in combination with cisplatin (56%, 78/140) experienced dose delays of 7 days or more compared with patients treated with cisplatin (18%, 26/144). Treatment delays occurred in 8% (34/406) of cisplatin monotherapy cycles and in 38% (187/488) of topotecan in combination with cisplatin cycles. The primary reason for delay in both treatments was haematological toxicity, these were more common with topotecan in combination with cisplatin (118/488 cycles, 24%) than with cisplatin alone (11/406 cycles, 3%).

Dose reductions

Cycles of study medication with reason for dose reduction and by study drug reduced are presented in Table 17.

Table 17. Number (%) of cycles of study medication with dose reductions by reason for reduction (treated population)

Reason for dose reduction	Cisplatin		Topotecan plus cisplatin			
	Total cycles >1 (n = 406)		Topotecan Total cycles >1 (n = 488)		Cisplatin Total cycles >1 (n = 488)	
	n	%	n	%	n	%
Haematological	1	0.25	12	2.46	0	0.00
Gastrointestinal	0	0.00	8	1.64	4	0.82
Neurological / otological	0	0.00	1	0.20	2	0.41
Renal	0	0.00	0	0.00	3	0.61
Hepatic	0	0.00	2	0.41	0	0.00
Other	0	0.00	22 [a]	4.51	0	0.00
Missing	0	0.00	1	0.20	0	0.00
Unknown	0	0.00	4	0.82	0	0.00
All reductions	1	0.25	50	10.25	9	1.84

[a.] All 22 dose reductions classified as 'other' were due to febrile neutropenia.

Among patients treated with cisplatin, one (<1%) had a dose reduction. Among patients treated with topotecan in combination with cisplatin, 24 (17%) had dose reductions of topotecan and five (4%) had dose reductions of cisplatin.

In conclusion, the topotecan in combination with cisplatin group had more frequent and severe haematological toxicities than the cisplatin treatment group. However, these were well managed with interventions for haematological toxicity, dose delays, and dose reductions. The additional haematological toxicity observed in the topotecan in combination with cisplatin group did not lead to increased serious adverse events, withdrawals, deaths or a reduction in HRQoL when compared to the cisplatin treatment group. The non-haematological safety profile between the two treatment groups was similar.

6.8 Non-RCT evidence

6.8.1 Summary of methodology of relevant non-RCTs

Recent report on post-marketing exposure to topotecan from the latest Periodic Safety Update Report (PSUR – May 2008 to November 2008) confirmed that the benefit/risk profile of topotecan (powder for infusion) for relapsed small cell lung carcinoma, relapsed ovarian carcinoma, and, in combination with cisplatin, for carcinoma of the cervix, continues to be favourable.[35]

6.8.2 Critical appraisal of relevant non-RCTs

N/A

6.8.3 Results of relevant non-RCTs

N/A

6.9 Interpretation of clinical evidence

6.9.1 Relevance of the evidence base to the decision problem

Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical

The key evidence presented to support the use of topotecan in this setting is the GOG-0179 study, a Phase III, randomized, controlled clinical trial of topotecan in combination with cisplatin, compared with cisplatin monotherapy. The population covered by the licensed indication for topotecan (those with recurrent disease who were either cisplatin-naïve, or who had a sustained treatment free interval prior to recurrence, and those newly presenting with Stage IVB disease) constitutes 75% of the GOG-0179 population, and patients received topotecan (0.75mg/m^2 on day 1,2 and 3) along with cisplatin (50 mg/m^2/day on day 1) every 21 days. Therefore, the key evidence base provides information highly relevant to the decision problem. Some other key decision areas from the decision problem are discussed below in section 6.9.2.

As discussed in previous sections, the evidence base supporting the use of other alternative interventions available for the target population is limited. Available data come from study GOG-0169, comparing a paclitaxel/cisplatin combination and cisplatin monotherapy, as well as a recent published abstract from study GOG-0204, which compares a range of combination treatments including topotecan/cisplatin with paclitaxel/cisplatin. The lack of robust comparative evidence might explain the considerable variation in current clinical practice when treating the population of women with recurrent and stage IVB cervical carcinoma. These patients have few therapeutic options available and there is a demonstrable need for new active treatments with randomised, controlled evidence of improved outcomes in this setting.

Therefore, it is very relevant to clinical practice that study GOG-0179 is the only trial showing a significant advantage in overall survival when compared with standard monotherapy with cisplatin in this population. In addition GOG-0179 is only the second GOG study in cervical cancer to include quality of life measures in a large scale, randomized chemotherapy trial.

The objectives of recurrent and/or advanced stage IVB cervical cancer treatment include improving overall survival and progression-free survival whilst maintaining an acceptable toxicity profile and maintaining or improving patients' quality of life. The combination of topotecan plus cisplatin has been shown to provide a statistically significant benefit in overall survival and PFS compared with cisplatin alone. In addition quality of life during treatment did not significantly differ from quality of life at baseline. It should be noted that despite the increase toxicity seen in patients receiving topotecan and cisplatin, there were no between regimen differences in quality of life scores during the treatment period of up to 9 months after randomization.

Although recurrent or advanced Stage IVB cervical cancer is essentially an incurable disease, the majority of patients in this population are likely to be either fully active or ambulatory, but restricted in strenuous activity; therefore, extension of life and maintenance of quality of life in these patients is both desirable and clearly worthwhile.

The toxicity profile for topotecan is typical of cytotoxic chemotherapy. Haematological events are the principal dose-limiting toxicity but are noncumulative with limited clinical sequelae. Non-haematological toxicities are predominantly mild to moderate and self-limiting. In the studies evaluating topotecan, most serious events could be managed through reductions or delays in dosing and/or other supportive measures; there was a reduction in the incidence of haematological events with each successive cycle reflecting the effectiveness of these measures. Such procedures are commonly used in clinical practice for the management of chemotherapy-related toxicities, and therefore physicians will be familiar with this approach.

6.9.2 Factors that may influence applicability of study results to routine clinical practice

Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

Topotecan in combination with cisplatin versus cisplatin monotherapy – External validity of reported results from direct comparison

GOG-0179 is the pivotal trial examining topotecan in combination with cisplatin (n=147) versus cisplatin (n=146) in cervical cancer. It enrolled patients with stage IVB, recurrent or persistent disease. The open-label design of the GOG-0179 study (and of GOG-0169) may be perceived as a limitation; however, the primary end-point in this study was overall survival, the measurement of which is unlikely to be affected by the open-label design. In addition, considering the advanced stage of the disease, blinding would have required participants in the placebo arm to receive placebo IV injections for three days in each cycle. Such a procedure can be considered as an unnecessary additional burden for these patients given the nature of the outcomes evaluated.

GOG-0179 was conducted independently of GSK by the Gynecologic Oncology Group (GOG). The trial was well conducted, in accordance with FDA regulations for the conduct of clinical trials. In addition, the GOG, which is sponsored by the National Cancer Institute (NCI), conducts clinical studies in accordance with the NCI Standard Operating Procedures, which are submitted to the FDA and are updated annually. These procedures include the principles of Good Clinical Practice (GCP), full approval of Ethics Committees or Institutional Review Boards, and adherence to the Declaration of Helsinki. The assessment of efficacy in study GOG-0179 fully complies with the Committee for Medicinal Products for Human use (CHMP) guidelines.

Reflecting the low number of patients with persistent disease enrolled in the trial (n=32), the licence for topotecan in combination with cisplatin is specific to patients with “carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease”. Acknowledging the impact of prior cisplatin on the relative efficacy of the combination versus cisplatin, the SmPC also states that “patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination” and presents data from an analysis of patients with recurrence within 180 days versus more than 180 days after administration of cisplatin as a radiosensitiser.

The study was designed with adequate power to test the primary hypothesis that the topotecan plus cisplatin combination regimen would offer a survival advantage when compared with cisplatin alone in patients with incurable cervical cancer. The study was not powered to allow for the subgroup analyses of overall survival that have been performed for this submission. Nevertheless, these analyses are considered to be of importance in the evaluation of effectiveness of topotecan plus cisplatin in this patient group. Despite the smaller sample sizes, the p-values for three out of the four key subgroup analyses of OS were less than 0.05, which is suggestive of adequate power. It is important to note that the treatment difference in the 'licensed' population was highly significant (p=0.004) and larger than that for the ITT population (median survival difference 4.6 months and 2.9 months, respectively).

As the licence relates to only a sub-population of those enrolled in GOG-0179, a subgroup (termed the *Licensed population*) which excludes patients with persistent disease and also those patients without a sustained cisplatin-free interval (SCFI) was analysed for this submission. The duration of the 'sustained treatment-free interval' was assumed to be 180 days, consistent with the above data presented in the SmPC.

Patients receiving cisplatin as radiosensitiser

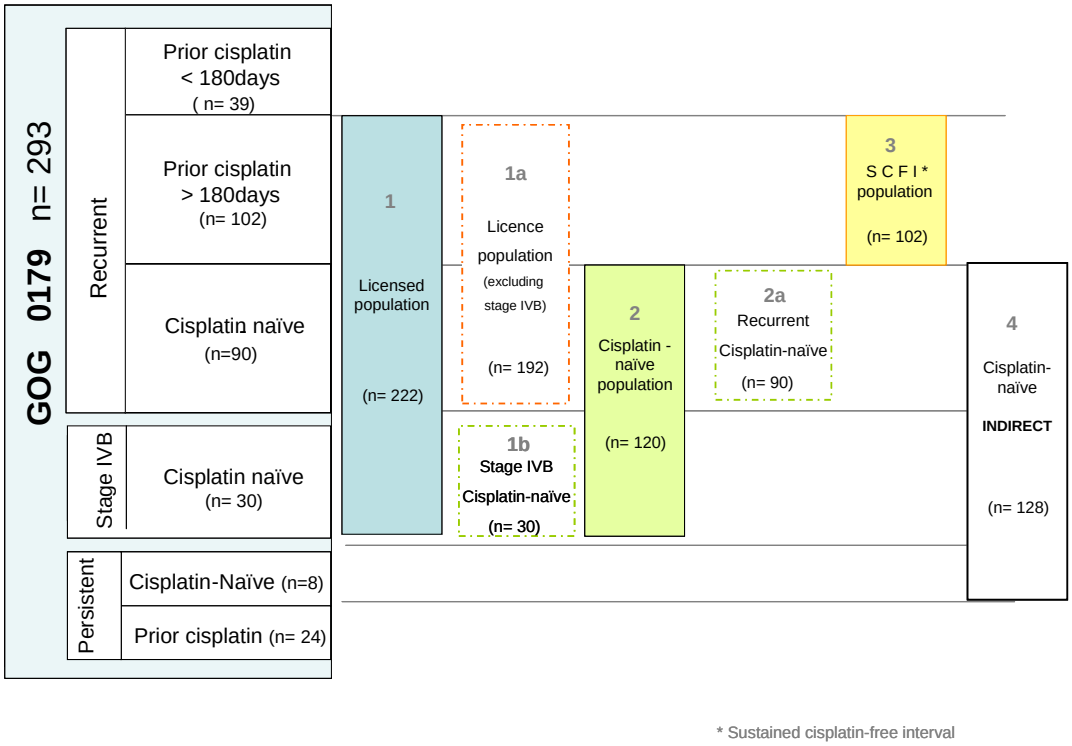
In GOG-0179, 61% of patients in ITT population received cisplatin as a radiosensitiser. Within the licensed population 46% and 43% of patients received cisplatin as radiosensitiser in the cisplatin arm and the cisplatin plus topotecan arm respectively. Whilst it is acknowledged that the practice of radiosensitisation varies between practitioners, there is an increasing shift towards a wider use of brachytherapy in this population. Thus, it can be argued that the proportion of patients receiving cisplatin radiosensitiser in GOG-0179 is aligned with current clinical practice in the UK.

Discontinuation of therapy

In study GOG 0179, major reasons for dose reduction/delay in topotecan/cisplatin combination arm included haematological toxicity and febrile neutropenia. Elevated creatinine and haematological toxicity were the main events leading to withdrawal (see section 6.7).

In current UK clinical practice, haematological toxicity, febrile neutropenia and renal impairment are the most common events leading to dose reduction/delay and even discontinuation of treatment. Discussion with clinical experts suggests that unless treatment is discontinued early due to toxicity or disease progression, patients usually receive six cycles of treatment.[8]

Figure 11. Schematic of study population and subgroups



Analysis of results reported for the key subgroups analysed within the licensed population

Licensed population (n=222):

Although GOG-0179 was conducted in the United States, the demographic characteristics of the patients in the study (and the specified subgroups) are likely to be representative of the English and Welsh population for the following reasons:

The patients in the licensed population were predominantly (over 70%) Caucasian and over 90% were aged <65 years at study entry, with a median age of 48 and 46 in the cisplatin and cisplatin in combination with topotecan respectively. This median age is similar to that of the UK patients in the IMS Oncology Analyzer dataset, selected as representative of the licensed indication, who have a median age of 41-50 years (see Appendix 4). Approximately 90% of patients had PS 0 or 1. There is no reason to believe that the eligibility criteria would have selected patients with a better PS than those patients who would be seen in clinical practice in England and Wales.

The majority of patients (approximately 80%) had previously received radiotherapy, either alone (30%) or in combination with cisplatin (more than 40%). It is likely that due to the expansion of brachytherapy, in future more patients will be exposed to radiotherapy in combination cisplatin as radiosensitiser.

The overall median survival in the licensed population is 11.9 and 7.3 months for cisplatin plus topotecan versus cisplatin alone respectively.

Cisplatin naïve population (n= 120):

This group included patients with recurrent disease (no prior cisplatin) and newly diagnosed stage IV B disease. Other baseline characteristics (age, race and PS) were similar to those discussed above under licensed population.

It is important to note that none of these patients received cisplatin in the past but nearly 70% received radiotherapy either alone or in combination with non cisplatin radiosensitiser. Therefore the overall survival benefit is greater in this group than for those patients previously exposed to cisplatin (median overall survival for topotecan plus cisplatin was 14.5 compared to 8.5 month in cisplatin group).

As reported in the European Public Assessment Report (EPAR)[1] for topotecan the median overall survival of cisplatin naïve patients (n=90) excluding stage IVB was 15.7 months and 8.8 months for cisplatin plus topotecan versus cisplatin alone respectively. The median overall survival of patients with stage IVB disease (n=30) was 9.9 and 7.1 months respectively. Due to improved screening and education, there has been a decline in the incidence of stage IVB disease and these patients represent only a small proportion of metastatic cervical cancer patients. This fact is reflected in the study GOG0179, where only 30 patients had newly diagnosed stage IVB disease. Historically, patients with stage IVB disease have very poor prognosis due to advanced metastatic disease at the time of diagnosis and possibly aggressive disease.[8]

Sustained cisplatin-free interval (SCFI) population (n=102):

This group included patients who had recurrence following cisplatin chemo radiotherapy but with a sustained cisplatin free interval of >180 days. The baseline characteristics (age, race and PS) were similar to those discussed above under licensed population. The median overall survival for cisplatin plus topotecan versus cisplatin alone was 9.9 and 6.3 months respectively. Due to expansion and uptake of brachytherapy in England and Wales, it is likely that the number of patients who have previously received cisplatin as a radiosensitiser will increase in the future.

Topotecan plus cisplatin versus paclitaxel plus cisplatin –External validity of reported results from indirect comparison

Both GOG-0179 and GOG-0169 were conducted in patients with stage IVB, recurrent or persistent carcinoma of the cervix, but there were some differences between the respective study populations. Patients with prior chemotherapy were eligible for GOG-0179 but ineligible for GOG-0169 (except when chemotherapy was used for radiation sensitisation). Fewer patients had received chemotherapy as a radiosensitiser (e.g. either cisplatin or carboplatin) in GOG-0169 (27%) than in GOG-0179 (~60%) and these patients were unevenly distributed between treatment arms in GOG-0169. In addition, the proportion of patients receiving cisplatin as a radiosensitiser in GOG-0169 was not reported.

As patient level data were not available for GOG-0169, it was not possible to construct a population equivalent to the *Licence population* in GOG-0179 and, given the differences in prior treatments described above, a comparison based on the ITT populations of both studies was not considered appropriate. It was therefore considered most appropriate to compare the overall *ITT population of GOG-0169* with the *Cisplatin naïve (IND) population* of GOG-0179, as both groups have either no or low levels of exposure to prior cisplatin. This approach is supported by the fact

that the median OS for patients treated with cisplatin monotherapy was similar between trials for these populations. An indirect comparison of topotecan in combination with cisplatin and paclitaxel in combination with cisplatin was therefore performed using cisplatin monotherapy as a common comparator. The calculated hazard ratio of 0.72 favours topotecan in combination with cisplatin but does not reach statistical significance (95% CI 0.46 to 1.15). The limitations of this methodology should be taken into consideration when interpreting the results. A non-significant trend for OS favouring the combination of cisplatin plus paclitaxel was also reported in GOG-0204 (see below).

Baseline characteristics (GOG-0179 and GOG-1069)

The baseline characteristics (in terms of age, race and histological grade) for the various subgroups and the ITT population are similar (see section Tables 3, 6 and 7). However, it should be recognised that the key subgroup analyses included in this submission were conducted *post-hoc*.

Although GOG-0179 was conducted in the United States, the demographic characteristics of the patients in the study (and the specified subgroups) are likely to be representative of the English and Welsh population for the following reasons:

- They were predominantly (over 70%) Caucasian and over 90% were aged <65 years at study entry, with a median age of 45-50 years across the ITT population and subgroups. This median age is similar to that of the UK patients in the IMS Oncology Analyzer, selected as representative of the licensed indication, who have a median age of 41-50 years (see Appendix 4). Approximately 85% of patients in the ITT population had squamous cell carcinoma, the predominant form of cervical cancer in the UK.[33]

- The majority of patients in all populations (~90%) had a PS of 0 or 1 (the ratio of these was approximately 1:1), i.e. either fully active or ambulatory but some restricted in strenuous activity. There is no reason to believe that the eligibility criteria would have selected patients with a better PS than those patients who would be seen in clinical practice in England and Wales. It is noted in the SmPC (see Appendix 1) that accurate assessment of PS at the time therapy is given is important, to ensure that patients have not deteriorated to PS 3.

GOG-0169 was also performed in the United States and compared cisplatin with paclitaxel in combination with cisplatin in patients with stage IVB, recurrent or persistent squamous cell carcinoma of the cervix. The ITT population of GOG-0169 (n=264) had a marginally higher median age of 46 and 48.5 years in the cisplatin and paclitaxel plus cisplatin arms respectively when compared with IMS data. The majority (nearly 90%) had PS 0 or 1, and the ratio of these was approximately 1:1. The majority of patients were Caucasian (69% in the cisplatin arm and 58% in the paclitaxel plus cisplatin arm).

Relevance of adverse events and safety of cisplatin plus topotecan in routine clinical practice:

The SmPC describes those patient types suitable for treatment with topotecan. This will exclude the following patients:

- Have a history of severe hypersensitivity to the active substance or to any of the excipients

- Are breast feeding

- Already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/l and/or a platelet count of ≤ 100 x 10^9/l.

In clinical practice most patients in whom treatment with topotecan is contraindicated are normally identified by the physician through a routine history review.

Administration of topotecan in combination with cisplatin requires three consecutive visits for administration every 21 days, compared with a single visit per 21 day cycle when using single agent cisplatin. Routine biochemistry, haematology, renal and liver function tests are required for all treatment regimens involving cisplatin. No additional tests are required for use of topotecan plus cisplatin over those required for cisplatin alone.

Haematological toxicity is more frequent and more severe with topotecan in combination with cisplatin than cisplatin alone.[34] However, haematological toxicities with topotecan plus cisplatin treatment were well-managed in clinical trials with interventions, dose delays, and dose reductions. The non-haematological safety profile of the two treatment groups was similar.[34] The risks associated with these toxicities are considered to be lower than the risks associated with this lethal disease, and therefore justify the decision to offer this treatment option to patients.

Importantly, the topotecan plus cisplatin combination regimen produced no significant reduction in health related quality of life compared to cisplatin, and this effect remained stable over time, despite a higher level of haematological toxicity.[6] The combination of topotecan plus cisplatin provides a rational and effective new treatment for patients with stage IVB or recurrent cervical cancer, for whom few effective options are currently available, and for whom no other therapy has been shown to prolong overall survival when compared with cisplatin alone.

<u>Relevance of GOG-204 (as per data from abstract and conference presentation)</u>

GOG-0204 study was a head to head comparison of four cisplatin-containing combinations (paclitaxel, vinorelbine, gemcitabine and topotecan).[4] A planned interim analysis recommended early closure of GOG-0204 as all experimental arms were unlikely to demonstrate a significant advantage compared to paclitaxel plus cisplatin. For this reason, GOG-0204 did not achieve the inclusion criteria for meta-analysis (section 6.6). However, given that GOG-0204 includes a direct comparison of topotecan and paclitaxel, both in combination with cisplatin, this trial is discussed below.

Approximately 70% of patients had previously received cisplatin as a radiosensitiser in GOG-0204. This is consistent with the expansion of brachytherapy, sensitised with cisplatin, as a standard of care for first-line cervical cancer treatment. As discussed above, one of the limitations of the GOG-0204 trial was that it was closed early as all experimental arms were unlikely to demonstrate a significant advantage of any individual combination. An additional limitation of this trial is that the majority of patients (55% in paclitaxel arm, 53% in topotecan arm) were of PS 0, with no patients of PS 2 included and this status is not fully representative of the overall patient population.

With these methodological limitations in mind, the HR for overall survival for topotecan in combination with cisplatin versus paclitaxel in combination with cisplatin in GOG-0204 was 1.268 (Var[ln(HR)]: 0.021), a non-significant trend. The corresponding HR for overall survival data for vinorelbine in combination with cisplatin versus paclitaxel in combination with cisplatin was 1.147 (Var[ln(HR)]: 0.026). The HR for overall survival data for gemcitabine in combination with cisplatin versus paclitaxel in combination with cisplatin was 1.322 (Var[ln(HR)]: 0.025). GOG-0204 also demonstrated a non-significant trend for QoL, response rate and PFS in favour of paclitaxel in combination with cisplatin.

7 Cost effectiveness

7.1 Published cost effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in Appendix 3, section 9.3.

A systematic review of the published literature was performed to identify relevant studies of the cost effectiveness of topotecan and platinum-based single and combination chemotherapy regimens in recurrent and stage IVB carcinoma of the cervix. The details of the systematic literature search is provided in Appendix 3.

Based on the inclusion and exclusion criteria shown in the first- and second-pass checklist (Appendix 2), no relevant published studies were identified.

7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

No relevant cost-effectiveness studies were identified in the search.

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the Institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

Overview

Studies which investigate the treatment of recurrent or stage IV of cervical cancer are identified in section 6.2.1. The pivotal topotecan trial is GOG-0179[3] which compared treatment with topotecan plus cisplatin with treatment with cisplatin monotherapy. This study is the main source for the economic evaluation as it is the only completed topotecan trial and furthermore GSK have access to the individual patient data from

the study. These data are used to make a direct comparison with cisplatin, the standard comparator in the UK (see section 1.2.3). This analysis is considered the primary analysis in the evaluation.

A second pivotal RCT was identified in section 6.2.1, GOG-0169,[14] which compares treatment with paclitaxel and cisplatin versus treatment with cisplatin monotherapy. This study is used in the evaluation to provide an indirect comparison with paclitaxel/cisplatin combination and the topotecan/cisplatin results from the GOG-0179 study. There are, however, limitations to the analysis, discussed in section 7.2.6.5 and therefore the analysis is offered as an attempt to utilise all available study data and provide some preliminary insight into the potential comparisons between topotecan/cisplatin and other cisplatin combinations, in the context of a paucity of other RCT data.

Finally, the latest Gynecologic Oncology Group trial, GOG-0204,[4] in which four combinations of cisplatin (with paclitaxel, topotecan, vinorelbine and gemcitabine) were compared, recently reported initial results. The trial was stopped early when it became evident that no statistical difference in OS would be observed between treatments. Hazard ratios are presented that numerically favour the reference treatment, cisplatin plus paclitaxel, over each of the three combinations, but none of these ratios was statistically significant. The HR between the paclitaxel and topotecan-based arms is used in a sensitivity analysis of the cost-effectiveness model to assess the effect of using this alternative source of clinical data.

Indication

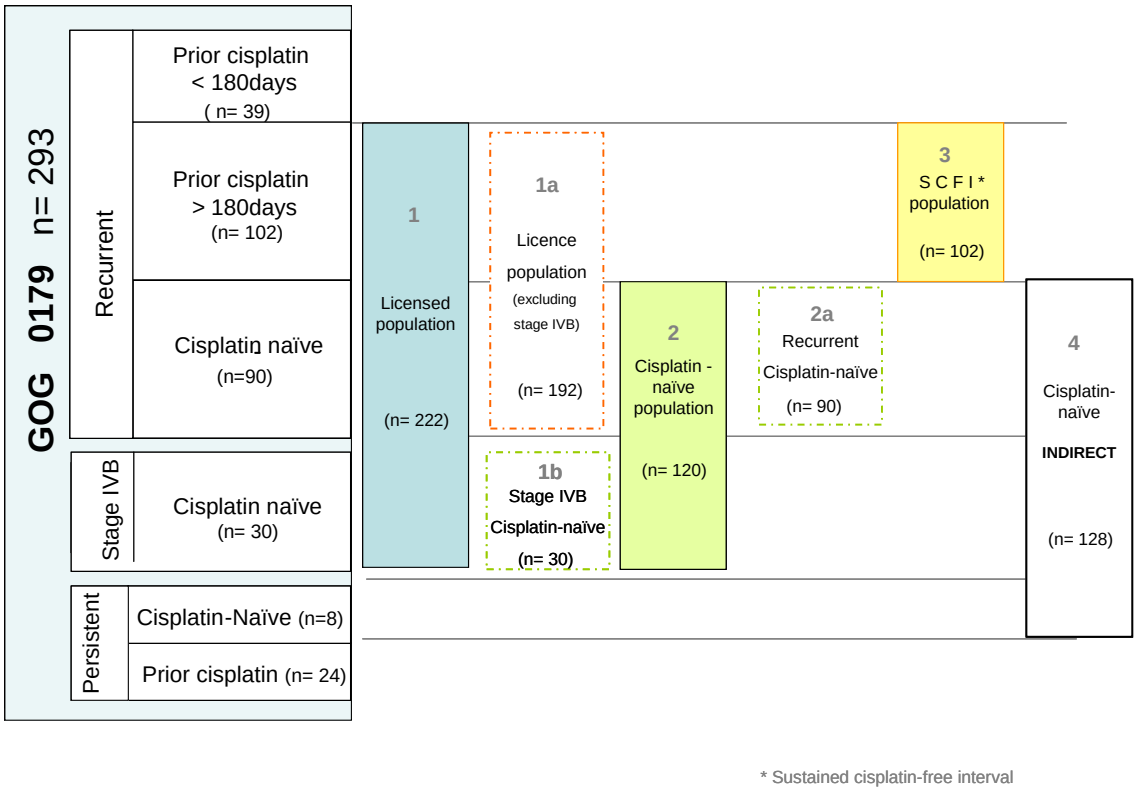
The indication for topotecan in the economic evaluation is topotecan in combination with cisplatin for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination. This population is referred to hereafter as the “licensed population” and is shown in Figure 13 (number 1).

Direct comparison with cisplatin

The direct comparison with cisplatin is considered the primary analysis in the submission. In order to reflect the licensed population, the analysis excludes patients with persistent disease (32 patients in the trial, 11% of the ITT population) and also those patients without a sustained cisplatin-free interval (SFCI), (39 patients, 13% of the ITT population). The indicated population consists of several subgroups which are shown in Figure 7.1, and summarised below:

1. *Licensed population, consisting of:*
   - *1a. Licensed population excluding stage IVB patients*
   - *1b. Stage IVB patients (by definition cisplatin naïve, as they are newly presenting)*
2. *Cisplatin-naïve population, consisting of:*
   - *2a. Cisplatin-naïve recurrent population*
   - *(1b. Stage IVB patients)*
3. *Patients with a sustained cisplatin-free interval (SCFI; >180 days)*

Figure 13. Schematic of study population and subgroups of interest



Indirect comparison with paclitaxel

Patient-level data were not available for GOG-0169 and therefore there were limitations in the populations that could be examined in the comparison. It was not possible to exclude the patients in GOG-0169 with persistent disease or those with a sustained cisplatin-free interval to achieve consistency with the licensed indication for topotecan. It was considered that the most appropriate, least potentially biased comparison would be that between the overall ITT population of GOG-0169 and the cisplatin-naïve (IND) population of GOG-0179 including persistent patients (group number 4 in Figure 13, as few patients in the former group had prior exposure to cisplatin.

<u>Dose, frequency and duration of use</u>

The SmPC states that the recommended initial dose of topotecan is 0.75 mg/m^2/day administered as 30 minute intravenous infusion daily on days 1, 2 and 3. In the direct comparison with cisplatin, trial-based patient level data are used for the analysis and so the exact dosing observed in the trial is available. In the indirect comparison with paclitaxel, the SmPC dose is assumed. The effect of this assumption is likely to be conservative as the topotecan usage-associated with the observed efficacy is likely to include dose reductions (described in section 7.2.9.1) whereas the SmPC dose assumes full dosing.

Concomitant medication

Throughout treatment topotecan patients receive cisplatin. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day following the topotecan dose. This treatment schedule is repeated every 21 days for 6 courses or until progressive disease.

If in the trial, patients discontinued treatment with cisplatin then they are also removed from active treatment with topotecan as topotecan is not licensed for monotherapy.

7.2.1.1 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- *the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)*
- *the robustness and plausibility of the endpoint on which the rule is based*
- *whether the 'response' criteria defined in the rule can be reasonably achieved*
- *the appropriateness and robustness of the time at which response is measured*
- *whether the rule can be incorporated into routine clinical practice*
- *whether the rule is likely to predict those patients for whom the technology is particularly cost effective*
- *issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

A treatment continuation rule is specified in the SmPC which states that topotecan should not be re-administered unless the neutrophil count is more than or equal to 1.5 x 10^9/l, the platelet count is more than or equal to 100 x 10^9/l, and the haemoglobin level is more than or equal to 9g/dl (after transfusion if necessary).

The application of this rule is inherent to the primary analysis as it is trial based and thus patients are treated in accordance with a protocol based on the SmPC. Costs of testing for these conditions are included in the model. These tests are currently part of routine clinical practice and would be easily incorporated when adding treatment with topotecan to cisplatin. The introduction of topotecan into the NHS would therefore be achievable with minimal changes to current processes.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Direct comparison with cisplatin

Licensed population

The patient population included in the economic evaluation is women with carcinoma of the cervix recurrent after radiotherapy and patients with stage IVB disease. This population broadly reflects the patients selected for study GOG-0179, the pivotal clinical trial, which is the primary evidence base supporting the combination of topotecan and cisplatin in this setting, with the following exceptions; patients with persistent disease (32 patients, 11% of the ITT population) and patients without a sustained cisplatin-free interval, 39 patients, 13% of the ITT population. Since this study was used as the basis of a regulatory submission the GOG granted GSK full access to the individual patient level data from the trial and thus have been able to select for analysis only those patients that reflect the licensed indication. This is then reflected in the trial-based analysis that has been developed to support the evaluation.

The patients from GOG-0179 are then split into subgroups to allow analysis of relevant sub populations, described in section 7.2.2.2.

Indirect comparison with paclitaxel

Both GOG-0179 and GOG-0169 were conducted in patients with stage IVB, recurrent or persistent carcinoma of the cervix, but there were some differences between the respective study populations. Patients with prior chemotherapy were ineligible for GOG-0169 but eligible for GOG-0179. Fewer patients had received prior cisplatin in GOG-0169 (27%) than in GOG-0179 (~60%), and these patients were unevenly distributed between groups in GOG-0169 (24% in the paclitaxel plus cisplatin arm and 30% in the cisplatin monotherapy arm). In GOG-0169, the proportion of courses with cisplatin as a radiosensitiser as opposed to three other agents, was not reported; whilst 56% of patients in GOG-0179 had received prior radiosensitisation with cisplatin.

It was not possible to exclude the patients in GOG-0169 with persistent disease or those with a sustained cisplatin-free interval to achieve consistency with the licensed indication for topotecan. However, given the differences in prior treatments described above, it was thought inappropriate to compare the ITT populations of both studies. It was considered that the most appropriate, least biased comparison would be that between the overall ITT population of GOG-0169 and the cisplatin-naïve (IND) population of GOG-0179 (Figure 13) since patients in the former group had prior exposure to cisplatin. In addition, the median OS for patients treated with cisplatin monotherapy was similar between trials for these populations (section 6). It was therefore concluded reasonable to compare topotecan plus cisplatin and paclitaxel plus cisplatin indirectly using cisplatin monotherapy as a common comparator.

We wish to emphasise that this indirect comparison is a secondary analysis and the limitations of this methodology should be considered when interpreting the results.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Direct comparison with cisplatin

Analysis was performed on four subgroups of the *licensed population*, defined below (numbering corresponds with labels in Figure 13):

1a) Licensed population excluding stage IVB patients

As cost-effectiveness of the intervention may differ between stage IVB patients and the remainder of the licensed population, a subgroup analysis for the licensed population excluding stage IVB patients is included. From the GOG-0179 trial this constitutes a population of 201 patients (69% of the ITT population).

2) Cisplatin-naïve population

At baseline, these patients have not had previous exposure to cisplatin and are considered cisplatin-naïve.

2a) Recurrent cisplatin-naïve patients (non stage IVB)

At the point of entry to the study, patients in this subgroup have had no previous exposure to cisplatin. Study GOG-0179 included 60 patients (21% of the ITT population) who had not received prior cisplatin chemo-radiotherapy and were not stage IVB.

3) Sustained cisplatin-free interval (SCFI) patients

The SmPC states that “patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination”. This acknowledges the impact of prior cisplatin on outcomes in patients re-challenged with cisplatin. Although the length of the treatment-free interval is not explicit in the SmPC, we have assumed a period of 180 days for this submission, in line with analyses presented in Section 5.1 of the SmPC. It should be noted that this 180-day period relates to the period between the last cisplatin dose and the recurrence of disease that resulted in eligibility for entry to GOG-0179. Study GOG-0179 included 102 patients (57% of the total population) with a SCFI of at least 180 days.

These subgroups were analysed by running the direct comparison analysis, selecting only the patients with the baseline characteristics of each subgroup.

Subgroup analysis is not performed on the stage IVB patients (labelled 1b in in figure 13). This was because the small number of patients in this group (n=30) meant that methodology for handelling censoring was not possible, so the uncertainty in the analysis would be too great to infer reasonable conclusion in these patients.

Indirect comparison with paclitaxel

GSK does not have access to the individual patient data from GOG-0169 and therefore, as described in section 6.6, the cisplatin-naïve subgroup from the GOG-0179 study was used as the comparator arm in this analysis. No other subgroups are considered here.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

We are aware of no obvious patient subgroups that have not been considered.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the model on the first day they receive therapy., i.e. at the point of entry to trial GOG-0179 as described in section 6.3.1. In the trial-based primary analysis, patients exit at the point they exit the trial, either on censoring from the trial, on death or after 36 months. Patients in the indirect comparison model exit on mortality or after 18 months.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

Cisplatin

Cisplatin is currently the standard of care in the UK and internationally for recurrent and stage IV cervical cancer. This is supported by a recent IMS analysis which examines the treatment regimes of cervical cancer patients between Q3 2004 and Q3 2008 (Table 18, Appendix 4). The analysis shows that the majority of patients (39%) received cisplatin with the second most common regime being a carboplatin and paclitaxel combination (18%). The combination of paclitaxel and cisplatin used in the secondary analysis and the comparator in trial GOG-0169, is used by only 4% of patients. The analysis demonstrates the need for NICE guidance in the treatment of recurrent or stage IV cervical cancer. There are many unlicensed treatment combinations being used without any evidence base supporting their efficacy in this area. The frequent use of cisplatin monotherapy in the UK adds further weight to the choice of this comparator for the primary analysis in this evaluation.

Table 18. IMS data on treatment regimes for topotecan targeted population in cervical cancer. (Q3 2004 to Q3 2008)

Next line of therapy	Number of patients	Percentage of patients
5-fluorouracil	1	2
5-fluorouracil/cisplatin	1	2
5-fluorouracil/mitomycin C	1	2
Bleomycin/cisplatin/folinic acid/methotrexate	2	4
Carboplatin	4	7
Carboplatin/epirubicin	1	2
Carboplatin/Etoposide	1	2
Carboplatin/gemcitabine	1	2
Carboplatin/ifosfamide	1	2
Carboplatin/paclitaxel	10	18
Cisplatin	22	39
Cisplatin/Etoposide	1	2
Cisplatin/ifosfamide	1	2
Cisplatin/methotrexate	2	4
Cisplatin/paclitaxel	2	4
Cisplatin/topotecan	1	2
Docetaxel/gemcitabine	2	4
Mitoxantrone/paclitaxel	1	2
Topotecan	2	4
Total	57	100

Paclitaxel plus cisplatin

A secondary analysis is presented which indirectly compares cisplatin and topotecan with cisplatin and paclitaxel. Whilst the IMS data presented in Table 18 suggests that the use of this combination is scarce in the UK clinical practice, this regime has been studied in two RCTs, GOG-0169 and GOG-0204. Given the range of different treatment options presented, this combination is the only one which has data from which we can model. The results from this analysis will serve to provide an approximate indication of the performance of topotecan versus a platinum-based combination regimen. A topotecan/cisplatin regime however, is the only *licensed* combination in cervical cancer that has shown an overall survival benefit.

Other platinum-based combinations

It is acknowledged that a significant minority of patients receive the carboplatin/paclitaxel combination (18% from IMS data), for which there are no usable data from which conclusions can be made. Furthermore, other platinum-based combinations, including cisplatin plus gemcitabine, cisplatin plus vinorelbine and carboplatin combinations are inconsistently used in clinical practice, and have

the same issue regarding availability of data. These combinations are therefore excluded from the economic analysis.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective is that of the NHS and Personal Social Services.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

Direct comparison with cisplatin

The time horizon chosen for the licensed population analysis is 36 months. The analysis is based on the GOG-0179 study in which the last known deaths occurred at approximately 31 and 34 months in the topotecan plus cisplatin and cisplatin arms respectively. The probability of survival to this point was 0.05 for patients treated with topotecan plus cisplatin and 0.017 for patients treated with cisplatin. Thirty six months reflects the follow-up period of the study.

The last known deaths in the *SCFI population* occurred after approximately 17 months in both treatment arms. The time horizon for this subgroup was therefore set to 18 months. The probability of survival at this point was 0.04 for patients treated with cisplatin and 0.08 for patients treated with topotecan plus cisplatin.

These time horizons are considered appropriate as the majority of patients in all treatment arms had died and thus most of the costs and outcomes for the cohort had been incurred.

Indirect comparison with paclitaxel

Only 24 months of follow-up data were available for GOG-0169. Therefore, although the direct analysis for GOG-0179 is conducted with 36 months of data, only data for the first 24 months are considered in the indirect analysis, for consistency with the GOG-0169 data.

7.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 Please provide the following.

- *A description of the model type.*
- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*
- *A list of all variables that includes their value, range (distribution) and source.*
- *A separate list of all assumptions and a justification for each assumption.*

Description of the model type

Reason for modelling

The main analysis in this submission is the direct comparison with cisplatin, which is performed as a trial-based analysis and does not require an economic model. The trial-based analysis is described in section 7.2.6.9, and is justified in Appendix 6. .

No clinical data were available at the time of analysis to support a generalised, modelled comparison of topotecan plus cisplatin against a range of other cisplatin-containing regimens. Moreover, there was no evidence for a significant increase in overall survival over cisplatin alone of any combination regimen except topotecan plus cisplatin. Paclitaxel plus cisplatin had shown a significant improvement in progression-free survival, but not overall survival.

An indirect, modelled comparison between topotecan plus cisplatin vs. paclitaxel plus cisplatin is possible, since each combination had been studied compared to cisplatin alone in separate trials. The only available evidence of the efficacy of a combination of paclitaxel plus cisplatin is the reported trial results from GOG-0169. In order to compare these two combination regimens, the results of trial GOG-0169 and GOG-0179 are modelled in a cost-effectiveness analysis, using cisplatin as the common comparator. This is presented as secondary, supplementary evidence to the primary cost-effectiveness analysis and may also be representative of the comparison of topotecan plus cisplatin versus carboplatin plus paclitaxel, identified as the second most frequently used combination in the UK in the IMS analysis (see Figure 14) .

Initial results are available from trial GOG-204, in which four combinations of cisplatin (with paclitaxel, topotecan, vinorelbine and gemcitabine) were compared.[4] The trial was stopped early when it became evident that no statistical difference in OS would be observed between treatments. Hazard ratios are presented that numerically favour the reference treatment, cisplatin plus paclitaxel, over each of the three combinations, but none of these ratios was statistically significant. The HR between

the paclitaxel and topotecan-based arms is used in a sensitivity analysis of the cost-effectiveness model to assess the effect of using this alternative source of clinical data.

Model methods

Patient-level data were not available for GOG-0169 and so there were some limitations to the analyses that could be undertaken. Both GOG-0179 and GOG-0169 were conducted in patients presenting with stage IVB, recurrent or persistent carcinoma of the cervix, but there were some differences between the respective study populations. Patients with prior chemotherapy were ineligible for GOG-0169 but eligible for GOG-0179. Fewer patients had received prior chemotherapy as a radiosensitiser in GOG-0169 (27%) than in GOG-0179 (~60%), and these patients were unevenly distributed between groups in GOG-0169 (24% in the paclitaxel plus cisplatin arm and 30% in the cisplatin monotherapy arm). In GOG-0169, the proportion of courses with cisplatin as a radiosensitiser as opposed to three other agents, was not reported; whilst 56% of patients in GOG-0179 had received prior radiosensitisation with cisplatin.

It was not possible to exclude the patients in GOG-0169 with persistent disease or those with a sustained cisplatin-free interval to achieve consistency with the licensed indication for topotecan. However, given the differences in prior treatments described above, it was thought inappropriate to compare the ITT populations of both studies. It was considered that the most appropriate, least biased comparison would be that between the overall ITT population of GOG-0169 and the cisplatin-naïve population (including stage IVB patients) of GOG-0179 as few patients in the former group had prior exposure to cisplatin. In addition, the median OS for patients treated with cisplatin monotherapy was similar between trials for these populations. It was therefore concluded reasonable to compare topotecan plus cisplatin and paclitaxel plus cisplatin indirectly using cisplatin monotherapy as a common comparator. The limitations of this methodology should be considered when interpreting the results.

Only 24 months of follow-up data were available for GOG-0169. Therefore, although the direct analysis for GOG-0179 was conducted with 36 months of data, only data for the first 24 months were considered in the indirect analysis, for consistency with the GOG-0169 data. Mean OS was calculated for the topotecan plus cisplatin and paclitaxel plus cisplatin treatment groups as the area under the OS curve to 24 months.

We describe in section 6.6 the calculation of the overall survival HR between paclitaxel plus cisplatin and cisplatin (0.87, 95% CI 0.68-1.11). This hazard ratio was applied to the observed OS for cisplatin from the GOG-0179 to estimate the OS for paclitaxel plus cisplatin for the indirect comparison with topotecan plus cisplatin. Survival was unadjusted as it was not feasible to apply quality adjustments to the available aggregate-level GOG-0169 data in the same manner as QALYs were calculated at the patient-level in the direct analysis.

Mean costs for each comparator were estimated by following the costing algorithms developed for the direct analysis (see Table 25), insofar as this was possible. As patient-level data were not available for GOG-0169, summary statistics of costs per cycle were applied to the mean number of chemotherapy cycles. Adverse events were costed at a prevalence level.

Inputs to this model are described here in Table 19.

Table 19. Variables used in the economic evaluations

Variable	Value	Distribution	Source
Efficacy			
Survival hazard ratio (paclitaxel plus cisplatin vs cisplatin)	0.87	95% CI (0.68 – 1.11)	Study GOG-0169
Mean number of cycles			
Cisplatin monotherapy	4.23		Calculated from data of all patients in the cisplatin monotherapy arm of the *cisplatin-naïve (IND) population* of GOG-0179. Note: the median number of cycles in GOG-0169 was 4 (range 0-11).
Topotecan plus cisplatin	5.125		Calculated from data of all patients in the topotecan plus cisplatin arm of the *cisplatin-naïve (IND) population* of GOG-0179
Paclitaxel plus cisplatin	5.125		Assumed to equal that for topotecan plus cisplatin as mean data were not reported for GOG-0169. Note: the median number of cycles in GOG-0169 was 5 (range 0-11).
Adverse events			
Percentage of patients incurring AEs			
Topotecan+cisplatin (cisplatin-naïve population)			
Anaemia, Grade 3	26.5%		Study GOG-0179
Anaemia, Grade 4	3.1%		Study GOG-0179
Neutropenia, Grade 3	60.9%		Study GOG-0179
Neutropenia, Grade 4	43.8%		Study GOG-0179
Thrombocytopenia, Grade 3	17.2%		Study GOG-0179
Thrombocytopenia, Grade 4	6.3%		Study GOG-0179
Cisplatin (cisplatin-naïve population)			
Anaemia, Grade 3	20.3%		Study GOG-0179
Anaemia, Grade 4	3.1%		Study GOG-0179
Neutropenia, Grade 3	4.7%		Study GOG-0179
Neutropenia, Grade 4	0.0%		Study GOG-0179
Thrombocytopenia, Grade 3	3.1%		Study GOG-0179
Thrombocytopenia, Grade 4	0.0%		Study GOG-0179
Paclitaxel + cisplatin			
Anaemia, Grade 3	22.5%		Study GOG-0169
Anaemia, Grade 4	5.4%		Study GOG-0169
Neutropenia, Grade 3	20.9%		Study GOG-0169
Neutropenia, Grade 4	45.7%		Study GOG-0169
Thrombocytopenia, Grade 3	1.6%		Study GOG-0169
Thrombocytopenia, Grade 4	2.3%		Study GOG-0169
Chemotherapy drug dose (assuming no dose modification)			
Treatment dose (mg/m^2)			
Topotecan	0.75		Study GOG-0179
Cisplatin	50		Study GOG-0179

Variable	Value	Distribution	Source
Paclitaxel	135		
Dose per IV administration (mg) (assuming surface area of 1.7m^2)			
Topotecan	1.275		Study GOG-0179
Cisplatin	85		Study GOG-0179
Paclitaxel	229.5		Study GOG-0169
IV administrations per cycle			
Topotecan	3		Study GOG-0179
Cisplatin	1		Study GOG-0179
Paclitaxel	1		Study GOG-0169
Chemotherapy drug cost			
Unit cost			
Topotecan 1mg/3ml vial	£97.65		BNF
Topotecan 4mg/5ml vial	£290.62		BNF
Cisplatin 1mg/ml 10ml vial	£5.85		BNF
Cisplatin 1mg/ml 50ml vial	£24.50*		BNF
Cisplatin 1mg/ml 100ml vial	£50.22		BNF
Cost per cycle (including wastage)			
Topotecan	£488.25		BNF/ Study GOG-0179
Cisplatin	£50.74		BNF/ Study GOG-0179
Topotecan dose modification effect on cost			
0.75 mg/m^2 per day	£488.25		BNF/ Study GOG-0179
0.60 mg/m^2 per day	£390.60		BNF/ Study GOG-0179
0.50 mg/m^2 per day	£292.95		BNF/ Study GOG-0179
0.45 mg/m^2 per day	£292.95		BNF/ Study GOG-0179
0.30 mg/m^2 per day	£292.95		BNF/ Study GOG-0179
Paclitaxel (generic) 6mg/mL (by vial presentation)			
5 ml	£106.69		BNF
16.7 ml	£319.77		BNF
25 ml	£532.95		BNF
50 ml	£959.31		BNF
Taxol® (paclitaxel) 6mg/mL *(by vial presentation)*			
5 ml	£116.05		BNF
16.7 ml	£347.82		BNF
25 ml	£521.73		BNF
50 ml	£1,043.46		BNF
Pharmacy and administration costs			
Medical oncology day case	£286.25*		HRG M98: Chemotherapy with a Female Reproductive System Primary Diagnosis
Topotecan outpatient visit	£51		Hind (2005); Tappenden (2007)
Pre- and post-treatment medication costs			
Pre-treatment cycle cost			
Dexamethasone	£1.27		BNF
Granisetron	£25.79		BNF
Post-treatment cycle cost			
Domperidone	£1.81		BNF
Follow-up costs+			
CT scan	£94.04		National Schedule Reference costs (2006)

Variable	Value	Distribution	Source
MRI scan	£25,215*		National Schedule Reference costs (2006)
Blood test	£3.10*		National Schedule Reference costs (2006). Cost per specimen.
Visit	£127.11*		National Schedule Reference costs (2006). 370F – Adult first attendance, follow-up / Medical Oncology [Attendance without Treatment] : Face to Face Total Attendances
Adverse Event Costs			
Anaemia - Grade 3, single intervention	£410.25*		HRG SO5 Red Blood Cell Disorders, age >69 or with complication - Day case, mean
Anaemia - Grade 4	£1,239*		HRG SO5 Red Blood Cell Disorders, age >69 or with complication - Inpatient
Thrombocytopenia or neutropenia - Grade 3	£430.92*		HRG SO7 other haematological or splenic disorders age >69 or with complications - Day case, mean
Thrombocytopenia or neutropenia - Grade 4	£1842.53*		HRG SO7 other haematological or splenic disorders age >69 or with complications - Inpatient

Sources: BNF,[2] Study GOG-0179,[3] National Schedule Reference costs[36]
* Inflated to 07/08 prices using PSSRU HCHS pay and price index inflator of 1.033

7.2.6.2 Why was this particular type of model used?

The analysis supporting the indirect comparison with paclitaxel is restricted by the lack of available individual patient level data from the trial. As a trial-based analysis was not possible, a modelled approximation was performed.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure of the model was limited by the availability of summary data only from the GOG-0169 trial. Therefore, the course of the disease could only be represented by mean overall survival calculated for the topotecan plus cisplatin and paclitaxel plus cisplatin treatment groups as the area under the OS curve to 24 months. Details of this calculation are given in section 7.2.7.2.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

Clinical studies GOG-0179 and GOG-0169 were the primary source for the development of the model structure.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

No, the model has unavoidable shortcomings. It cannot determine the progression-free survival periods for each treatment arm, due to these not being reported for the GOG-0169 study. We are therefore unable to determine the changes in quality of life as the disease progresses and are thus unable to produce a cost-utility analysis unless a single utility value were applied to all survivors regardless of health status. As this would be a crude approximation, outcomes from the model are presented as cost per life-year gained.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

N/A

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

No. The model is not a cycle driven analysis and so half-cycle correction is possible or relevant.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The model has been developed to approximate a trial-based analysis and so is not extrapolated beyond the trial period. The model does however extrapolate beyond the last observed deaths in each treatment arm, which occur several months before the end of the follow up period. Thus we assume that the survival rates observed at the time of final observed death remain constant (i.e. no further deaths) up to the modelled endpoint in both treatment arms

b) Non-model-based economic evaluations

7.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

The main evaluation in the submission is the trial-based direct comparison between topotecan and topotecan plus cisplatin. This is based on the GOG-0179 trial in which data on clinical efficacy, safety and quality of life were recorded but no economic outcomes such as costs and resource use for treatment of adverse events were reported. These were supplemented with external data primarily the NHS National Reference Costs (2006/7),[36] PSSRU (2008),[37] and BNF (2009).[2]

7.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

GOG-0179 was a phase III trial, which demonstrated that the combination of topotecan plus cisplatin provides a clinically meaningful and statistically significant increase in overall survival beyond that achieved with cisplatin alone (9.4 months vs. 6.5 months; HR 0.76, p=0.033, ITT population) in patients with histologically confirmed stage IVB, recurrent or persistent carcinoma of the cervix that is not considered amenable to curative surgery or radiotherapeutic intervention.

Quality of life was recorded using the FACT-G instrument and was shown not to be adversely affected among patients receiving topotecan plus cisplatin, as compared to those who received single-agent cisplatin. An overall survival benefit was maintained across pre-defined subgroups in study GOG-0179 relating to prior radiotherapy, race, age, GOG PS, time from diagnosis to study entry, and histology. However, the margin of benefit from topotecan plus cisplatin was greater in patients who had not been exposed to prior cisplatin.

Additional subgroup analyses were undertaken for this submission as a). the GOG-0179 trial includes patients outside the licensed indication for topotecan plus cisplatin, and b). the licensed indication includes patients for whom, because of their

clinical background, topotecan in combination with cisplatin may be more or less cost effective when compared with single agent cisplatin. These sub-groups are defined in section 7.2.2.

Baseline characteristics were broadly similar across the key subgroups (1, 2 and 3). The OS hazard ratios were 0.59 (p= 0.010), 0.65 (p= 0.004), and 0.75 (p= 0.191) for the cisplatin naïve, licensed and the SCFI populations, respectively.

GOG-0179 was chosen for this analysis as it is the only available trial which compares topotecan plus cisplatin with cisplatin.

7.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Data were not complete for all patient included in the trial. Missing data were imputed as last observation carried forward for surviving patients.

Resource utilisation during trial follow-up was derived from individual patient data. However, observations for many patients were censored, so that subsequent resource utilisation and costs were unknown. To avoid bias due to censoring we estimated mean costs using the "without cost histories" variant of the standard method described by Lin et al (1997).[38] In this variant of Lin's method, the trial follow-up period is divided into several intervals (the present study used 36 intervals each of one month). The mean total cost per patient is estimated as the sum over the intervals of the Kaplan-Meier estimator of the probability of dying in an interval multiplied by the mean total costs of those who die in that interval.

7.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

In the direct analysis, costing was performed at patient level. However, the trial protocol of GOG-0179 had made no specific arrangements to record resource utilisation prospectively to facilitate the population of an economic evaluation. Therefore, the costing was carried out retrospectively from an NHS perspective. The costs considered included acquisition costs of study drug (based on actual cycles and dosage administered), pre- and post-treatment medications, as well as costs of healthcare resource utilisation for pharmacy preparation, treatment administration, monitoring and management of adverse events. Unit costs were assigned to those resource items that could be directly deduced from the trial case record forms, such as study drug and concomitant medication, while other items of resource consumption required assumptions. Resource utilisation contingent on clinical events was based on the expert opinion of oncologists with experience of working in the UK. Unit costs were derived primarily from the NHS National Reference Costs 2006/7.

7.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

The model does not extrapolate beyond the trial follow up period. The model does, however, extrapolate beyond the last observed deaths in each treatment arm, which

occur several months before the end of the follow up period and thus we assume that the survival rates observed at the time of final observed death remain constant (i.e. no further deaths) up to modelled endpoint in both treatment arms

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Direct comparison with cisplatin

The primary objective and measure of disease progression in the GOG-0179 study was overall survival. The baseline risk of mortality, represented by the cisplatin treatment arm, was estimated using the Kaplan-Meier method (section 6.3.5).

Indirect comparison with paclitaxel

The baseline measure of disease progression in the indirect comparison is mean OS, calculated for the topotecan plus cisplatin (the reference arm) and paclitaxel plus cisplatin treatment groups as the area under the OS curve to 24 months.

7.2.7.2 How were the relative risks of disease progression estimated?

Direct comparison with cisplatin

This is a trial-based analysis and so the relative risk of disease progression is fully reflected by the survival outcomes of patients on both treatment arms. The relative risk of survival was calculated using the Kaplan-Meier method.

Indirect comparison with paclitaxel

Baseline and survival results for paclitaxel are taken from the published study report of the GOG-0169 trial. To perform the indirect comparison, mean survival is required for all treatment groups under consideration. The publication provided only median survival, survival curves and overall numbers of events. From the survival curves and drawing on the methods suggested by Parmar et al (1998),[39] we deduced the survival probability for each month (and therefore the overall mean survival) and calculated the hazard ratio between paclitaxel plus cisplatin and cisplatin (0.87, 95% CI 0.68-1.11). This hazard ratio was applied to the observed OS for cisplatin from the GOG-0179 to estimate the OS for paclitaxel plus cisplatin for the indirect comparison with topotecan plus cisplatin. (Figures 14 and 15).

Survival was unadjusted as it was not feasible to apply quality adjustments to the available aggregate-level GOG-0169 data in the same manner as QALYs were calculated at the patient-level in the direct analysis.

Figure 14. Estimated overall survival curves deduced from Kaplan-Meier curves

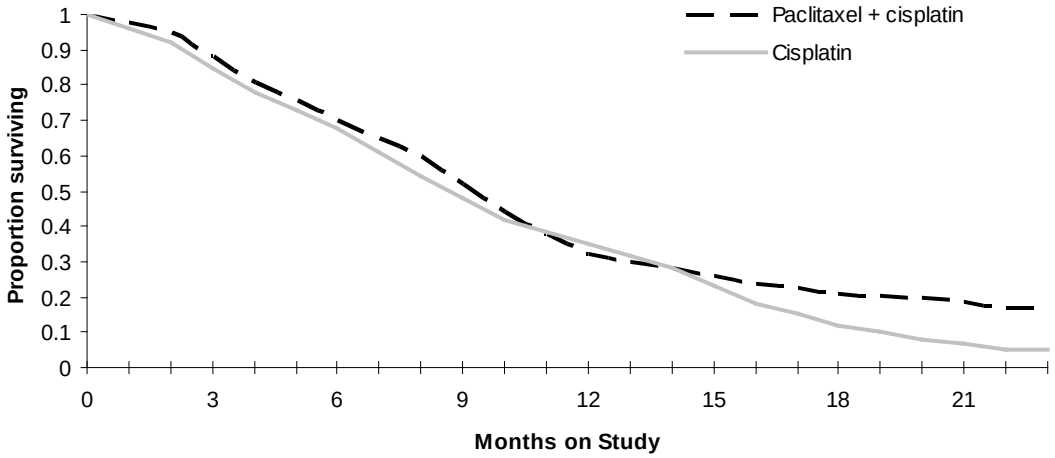
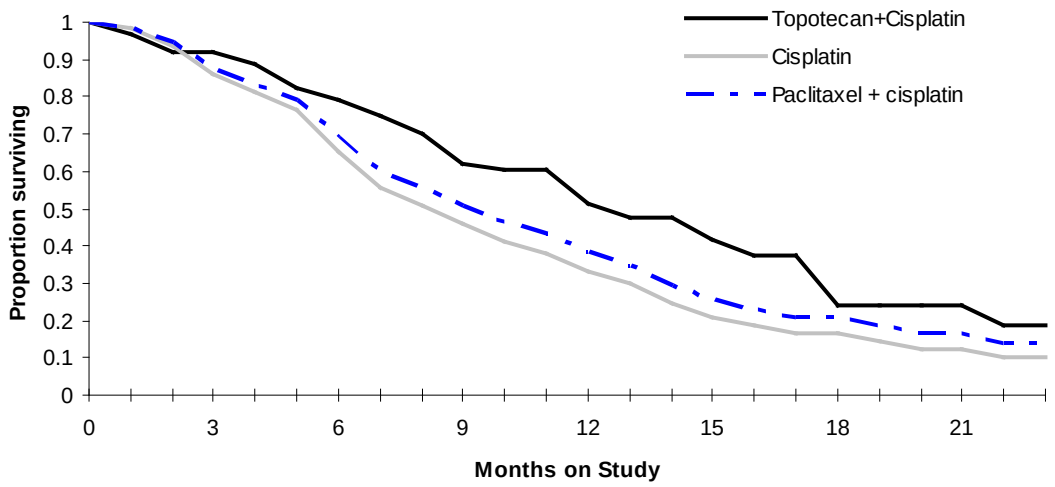


Figure 15. Estimated overall survival curves for all three comparators



7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No.

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Direct comparison with cisplatin

Adverse events associated with both treatment arms were included in the evaluation. Datasets relating to adverse events were available for GOG-0179:

- Adverse event (AE) data
- Serious AE (SAE) data
- Laboratory reports relating to haematological events
- Intervention reports relating to haematological events (G-CSF, platelet transfusions, red blood cell transfusions, erythropoietin)
- Dose reduction data (note: these data were used to identify instances of febrile neutropenia in order to apply utility decrements)

The AE dataset recorded whether each patient had experienced a certain AE during the trial but not the frequency or the timing of that event. Therefore, the laboratory and intervention reports were used to calculate the frequency and timing of AEs (and the grade of each), avoiding double counting of the events reported as SAEs. The SAE dataset recorded the cycle of treatment within which each specific SAE occurred.

In sensitivity analysis an alternative set of utility values based on breast cancer patients (see section 7.2.8) is used in which a change in utility score is driven by a change in health state. (The base case analysis uses utility scores recorded at fixed 4 intervals and is not driven by health state)

Indirect comparison with paclitaxel

Accurate modelling of adverse events was difficult in the indirect analysis as patient-level data (and therefore number of AEs) were not available for GOG-0169. Grade 3 and 4 AEs were therefore modelled according to their observed prevalence rates as reported for GOG-0169 and the cisplatin-naïve (IND) population of GOG-0179. Cisplatin monotherapy rates were based on prevalence data from the cisplatin-naïve (IND) population from GOG-0179 rather than the GOG-0169 ITT population, for consistency with the direct analysis.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

No expert opinion on clinical parameters was sought.

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

N/A.

7.2.8 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects are expressed in terms of QALYs.

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

In the base case analysis, the trial based utility estimates mapped from the FACT-G scores recorded in the study population are used. Quality of life scores were recorded at fixed time points in the trial (see section 7.2.8.3) and thus reflect patients' perceptions at these discrete points only.

A sensitivity analysis is performed in which a tariff of utility values is assigned to health states derived from reported clinical outcomes. These values include utility increments from the starting value for patients who respond and decrements for patients suffering progression or adverse events (see Table 23). This alternative method does not rely upon patients' reporting of quality of life at the time of study visits.

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

- *State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.*
- *Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.*
- *Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.*

- *How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?*

- *Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.*

- *Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.*

Base case

The base case analysis utilises patient-level utility estimates derived from the Functional Assessment of Cancer Therapy - General (FACT-G) data collected in study GOG-0179. These data are then mapped to utility values using an algorithm recently developed by researchers at the School of Public Health, University of Illinois at Chicago.[40] The attraction of this method lay in the use of QoL data prospectively collected in the same trial as the clinical data.

The algorithm uses four items from the FACT-G (energy, feeling ill, ability to work and ability to enjoy life) and was developed and validated in samples of 1433 individuals with cancers of various types, and HIV/AIDS over a range of severity of illness. Item response theory was used to collapse response categories and ordinary least squares regression with the constant constrained to one was used to estimate the algorithm.

The algorithm was reported as performing well in predicting mean utilities (mean absolute difference < 0.03, P <0.05) for most subgroups defined by ECOG-PS and Short Form-36 physical functioning scores, and responses to the FACT-G overall quality of life item. The authors do note however that the algorithm over-predicted utility for poor health. This finding may limit the applicability of the algorithm to the GOG-0179 population.

The protocol specified four observations during the course of the trial: prior to randomisation, prior to cycle 2, prior to cycle 5 and 9 months after randomisation. For each patient, the utility score calculated by the algorithm was applied from the date of observation until the sooner of the next observation or death. Table 20 shows summary statistics of the utility values generated by the algorithm for the licensed population. Missing data were imputed as last observation carried forward for surviving patients.

Table 20. Summary values for FACT-G-based utility weights (*licensed population*)

Treatment group	Time period	Mean utility value (std. deviation)	Min.	Max.
Cisplatin	Prior to randomisation	0.79 (0.11)	0.46	1
	Prior to cycle 2	0.73 (0.21)	0	1
	Prior to cycle 5	0.58 (0.34)	0	1
	9 months after randomisation	0.33 (0.39)	0	1
Topotecan plus cisplatin	Prior to randomisation	0.79 (0.11)	0.52	1
	Prior to cycle 2	0.72 (0.22)	0	1
	Prior to cycle 5	0.66 (0.30)	0	1
	9 months after randomisation	0.45 (0.40)	0	1

The method of Lin et al (1997)[38] originally developed for costing, was adapted to estimate quality-adjusted survival while accounting for censored observations (Personal communication: Professor Alistair McGuire, London School of Economics). The adaptation was made to account for the fact that it is not known what proportion of patients survive during the final (36th) interval of the partition, due to censoring. To estimate the mean quality-adjusted survival in this interval in the absence of actual survival data, the observed quality-adjusted survival of the last patient(s) who died, multiplied by the probability of survival at the end of the study, was applied to the censored observations. This minor adaptation was required to apply Lin's method to quality-adjusted survival.

Sensitivity analysis: alternative utility values

Because there was some doubt as to whether the algorithm used to map FACT-G scores to utility values was applicable to the GOG-0179 population, with the results of mapping suggesting a ceiling effect, alternative sets of utility values were sought. A systematic literature search in MEDLINE and HEED was conducted for publications presenting utility data for patients with cervical cancer. The full review is not reproduced here, for reasons of brevity, but details can be found in Appendix 5. In summary, 541 potentially relevant titles and abstracts were identified, of which 36 were selected for full-text review and 18 yielded relevant data that were extracted. Most of these articles evaluated the impact of HPV vaccination, or/and cervical screening. Utility data according to FIGO staging of cervical cancer were presented in six publications: Kulasingam 2008,[41] Goldie 2004,[42] Mandelblatt 2002,[43] Kim 2002,[44] Ginsberg 2007[45] and Dasbach 2008.[46] It was feasible to group the reported utility values according to the following classifications: stage I/local; stage II/III/regional and stage IV/distant. The values presented in each article were compared with the calculated mean utility values across articles, and the former were ranked according to proximity to the latter. Hence, a low ranking value represents a utility value that is close to the calculated mean. Table 21 presents the results of this analysis.

The utility values presented in Kulasingam 2008[41] are consistently closer to the calculated mean values, for each stage of cervical cancer. This implies that a mean utility value of approximately 0.67 would be appropriate for the starting population of GOG-0179, a value that is somewhat lower than the 0.79 implied by the FACT-G algorithm.

Unfortunately, none of the above studies contained utilities describing the health states encountered during the course of the trial-based analysis, notably response, stable disease, progression and various degrees of haematological toxicity.

Therefore, they would be of no value to determine the utility changes associated with treatment outcomes, or to differentiate treatments according to quality as well as quantity of survival. Further literature searching (non-systematic) was performed to investigate other gynaecological (including breast) cancers in advanced stages that reported utility values according to outcomes. Three potentially useful studies were identified: Ortega 1997[47], Launois et al 1996[48] and Brown & Hutton 1998.[49] Ortega elicited TTO utilities of 40 Canadian volunteers for advanced (stage III/IV) ovarian cancer states. The other two studies each elicited utilities for advanced metastatic breast cancer from nurses using standard gamble. Summary utility estimates from the three studies are shown in Table 22.

Table 21. Ranking of literature utility values according to proximity to mean

Study	**Stage I/local**	**Stage II/III/regional**	**Stage IV/distant**	**Overall**
Kulasingam 2008[41]				
Utility value	0.76	0.67	0.67	-
Rank	1.5	1.5	2	5
Goldie 2004[42]				
Utility value	0.65	0.56	0.48	-
Rank	4	4.5	4	12.5
Mandelblatt 2002[43]				
Utility value	0.9	0.7	0.5	-
Rank	5	3	1	9
Kim 2002[44]				
Utility value	0.68	0.56	0.48	-
Rank	3	4.5	4	11.5
Ginsberg et al. 2007[45]				
Utility value	0.915	0.913	0.881	-
Rank	6	6	6	18
Dasbach et al. 2008[46]				
Utility value	0.76	0.67	0.48	-
Rank	1.5	1.5	4	7
Mean utility value	0.76*	0.68†	0.58†	-

*Mean calculated from values presented in all of the above studies, and values from Sanders 2003;[50] Goldie 2001;[51] Szucs 2008[52]
†Mean calculated from the above six studies only.

Table 22. Gynaecological cancer utility values from literature

Reference	**Ortega 1997[47]**	**Launois 1996[48]**	**Brown 1998[49]**
Setting	Stage III/IV ovarian cancer	Metastatic breast cancer, second-line chemotherapy	Metastatic breast cancer, second-line chemotherapy
Respondents	40 healthy female volunteers, Canada	20 nurses, France	25-30 nurses from each of US, Germany, Italy, Netherlands, Spain, UK
1st line response	0.68	-	-
Start 2nd line	0.53	0.86	0.64
2nd line response	-	0.81	0.81
2nd line stable	-	0.75	0.65
2nd line progression	0.42	0.65	0.39
Febrile neutropenia without hospitalisation	-	0.66	0.56
Febrile neutropenia with hospitalisation	-	0.47	0.30
Terminal	-	0.25	0.16

Brown 1998[49] analysed more states than did Ortega 1997[47] and of the above three studies involved the largest number of respondents, a sample of approximately 160 nurses who rated health state scenarios describing second-line chemotherapy of metastatic breast cancer.

According to expert oncologist opinion (personal communication, Dr Paul Symonds, between 27 February 2006 and 30 January 2009), patients on first-line chemotherapy for metastatic breast cancer have a life expectancy of 20-22 months, but those who need second-line therapy survive only about 8 or 9 months, a comparable survival time to stage IV cervical cancer cases. The expert stated it would therefore be reasonable to use the Brown 1998 study as a proxy in the absence of cervical cancer data. Moreover, the starting utility value of 0.64 is close to the value of 0.67 reported by Kulasingam 2008[41] for patients with stage II-IV cervical cancer. The utility values from Brown 1998[49] were therefore selected for use in the sensitivity analysis.

Clinical events occurring in GOG-0179 were assigned to the health states described as shown in Table 23. Patient records were scanned for each of these events and the relevant utility was applied to the time interval between that event and the recording of the next event. The exceptions to this are the utilities relating to AEs. These were applied for week-long intervals only, in line with clinician opinion of 5-7 days' hospitalisation, after which the previous utility was reapplied. AE utilities were not used once a patient's disease had progressed as the AE utilities are higher than the utility for progressive disease. If a patient experienced two AE health states at the same time, the lowest value was applied to that time period.

Table 23. Utility assumptions for sensitivity analysis (after Brown 1998)[49]

Health state	Value	Proxy for event in GOG-0179
Start	0.64	Randomisation
Response	0.81	Defined in trial (see Section 3.3.1)
Stable	0.65	Not used (assumed start utility encompasses this)
Progression	0.39	Defined in trial
Febrile neutropenia without hospitalisation	0.56	Dose reduction for febrile neutropenia relating to a Grade 3 event
Febrile neutropenia with hospitalisation	0.30	Dose reduction for febrile neutropenia relating to a Grade 4 event
Thrombocytopenia with platelet transfusion	0.42[a]	Grade 3 or 4 thrombocytopenia with platelet transfusion
Terminal	0.16	Last week of life

Source: All values from Brown 1998,[49] except [a]thrombocytopenia with platelet transfusion which was considered similar in clinical severity to febrile neutropenia with hospitalisation.[8]

Brown & Hutton, 1998[49] highlights the impact of febrile neutropenia and thrombocytopenia on utility. There were significant difficulties in determining numbers of cases of the former AE in GOG-0179, as laboratory reports used to calculate the number of cases of neutropenia did not specify whether this condition was accompanied by fever. Available data detailing the number of cases of febrile neutropenia resulting in dose reductions were reconciled with laboratory reports to deduce when these events occurred. Therefore, decreases in utility were only applied to those cases of grade 3 or 4 febrile neutropenia resulting in dose reductions. It is believed that this is a conservative assumption for topotecan, as all dose reductions for febrile neutropenia occurred in the topotecan plus cisplatin arm (11/107 patients in the topotecan plus cisplatin arm of the licensed population, five in the cisplatin-naïve population, six in the SCFI population). In contrast, the GOG assumed that all reports of infection were due to febrile neutropenia and therefore reported that 7.5% of patients receiving cisplatin experienced grade 3 or 4 febrile neutropenia (versus 17.7% of patients receiving topotecan plus cisplatin). Oncologist expert opinion suggested that thrombocytopenia requiring a platelet transfusion was the only AE that would have an impact on patients' HRQoL comparable to that of febrile neutropenia. Therefore, the utility decrement for febrile neutropenia was also assigned to thrombocytopenia with platelet transfusion, but not to other haematological toxicities. This was assumed for patients with both grade 3 and 4 toxicity accompanied by platelet infusion.

An investigative analysis has been performed to examine the potential effect of weighting the end of life QALYs gained by patients on treatment with topotecan plus cisplatin. This anlysis has been performed in response to the new NICE guidance to Appraisal Committees on appraising end of life medicines. Detail of the methodology used and the results of this analysis are presented in Appendix 7.

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see section 6.2.11).

No.

7.2.8.5 Were any health effects excluded from the analysis. If so, why were they excluded?

No.

7.2.9 Resource identification, measurement and valuation

For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible. These resources should be valued using the prices relevant to the NHS and PSS. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

Chemotherapy

The cost of each chemotherapy regimen was calculated using the unit prices from the British National Formulary (January 2009).[2] For all chemotherapy, a mean body surface area of 1.7 m^2 was assumed as neither surface area nor height/weight data were available for individual patients. This is in line with body surface area assumptions in recent technology appraisals in ovarian cancer[53] (second line and beyond) and advanced breast cancer.[54]

The standard regimens for topotecan and cisplatin in GOG-0179 (and the SmPC for topotecan) and paclitaxel in GOG-0169 are shown in Table 24 and relate to a cycle length of 21 days. Both treatments are given as IV infusions and the same regimen of cisplatin is assumed whether given in combination with topotecan or as monotherapy.

Table 24. Chemotherapy drug dosage (assuming no dose modification)

Drug	Treatment dose (mg/m^2)	Dose per IV administration (mg)[a]	IV administrations per cycle	Total dose per cycle (mg)
Topotecan	0.75	1.275	3	3.825
Cisplatin	50	85	1	85
Paclitaxel	135	229.5	1	229.5

[a] Assuming surface area of $1.7m^2$

Topotecan is available in two vial sizes: 1mg and 4mg. Hence the number of vials required per cycle per patient will depend on the assumptions made regarding utilisation of vial contents and wastage. While the SmPC states that vials should be discarded 24 hours after opening, communication from pharmacists suggests that practice ranges from using remaining drug to make up to three days' worth of treatment for one patient to discarding unused vial contents immediately after opening.

Three scenarios were analysed, with the base case assuming some re-use (approximately midrange) and alternative scenarios assuming minimum wastage and maximum wastage (no re-use) in sensitivity analyses. These scenarios all assume that vials of topotecan are not shared between patients. They are also all consistent with the topotecan SmPC which states that if reconstitution and dilution are performed under strict aseptic conditions the product should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored at 2-8 °C after the first puncture of the vial. This approach does not appear to contravene the NHS Multiple Use of Injections policy because topotecan is licensed, within the limitations described above, for multiple uses.

No sensitivity analysis around cisplatin vial utilisation was performed. As maximum wastage is assumed for cisplatin, this is likely to be conservative for topotecan as the number of cycles of topotecan plus cisplatin is likely to be greater than the number of cycles of cisplatin alone.

In the indirect comparison, the price of *generic* paclitaxel was used as the base case whilst a sensitivity analysis was performed using 50% of the price of branded paclitaxel, given possible future price volatility.

The costs of the standard doses of chemotherapy are given in Table 25.

Table 25. Chemotherapy drug cost assumptions

Drug	Dose per cycle (mg)*	Vial presentation	Unit cost	Costs per cycle (by alternative utilisation scenarios for topotecan)					
				Minimal wastage[a,b]		Base case (midrange)[c]		Maximum wastage (no re-use)[a,d]	
				No. of vials	Cost per cycle	No. of vials	Cost per cycle	No. of vials	Cost per cycle
Topotecan	3.825	1mg/3ml	£97.65	4	£390.60	5	£488.25	6	£585.90
		4mg/5ml	£290.62	0	-	0	-	0	-
					£390.60		£488.25		£585.90
Cisplatin 1mg/ml	85	10ml	£5.85			0	0		
		50ml	£25.37			2	£50.74		
		100 ml	£50.22			0	-		
							£50.74		
Paclitaxel (generic) 6mg/mL	229.5	5ml	£106.69			1	£106.69		
		16.7ml	£319.77			2	£639.54		
		25ml	£532.95			0			
		50ml	£959.31			0			
							£746.23		
Paclitaxel (Taxol®) 6mg/mL	229.5	5ml	£116.05			1	£106.69		
		16.7ml	£347.82			2	£695.64		
		25ml	£521.73			0			
		50ml	£1,043.46			0			
							£811.69		

Source of unit costs: BNF[2] *Assumes mean body surface area of 1.7 m^2

[a]. Applicable only to topotecan
[b]. Retain unused vial contents in aseptic conditions and redeploy within 24 hours
[c]. Midrange practice (between re-using any drug left in the vial within 24 hrs to discarding all remaining drug)
[d]. Discard all unused contents after preparation of each daily infusion i.e. no re-use.

Dose modifications were taken into account for each patient. The protocol-specified levels and criteria for dose reductions of each regimen due to toxicity are shown in Table 26 below:

Table 26. Dose reduction for each regimen due to toxicity.

Dose Level	Dose (mg/m^2)
Topotecan (regimen II)	
Initial	0.75
-1	0.60
-2	0.45
Cisplatin (regimen I and II)	
Initial	50
-1	37.5
-2	25

Dose modification for haematological toxicity

For cisplatin, no reduction was made in the dose for any degree of haematological toxicity.

For topotecan, provision was made for the following dose modifications:

- Grade 4 thrombocytopenia required a 1-level dose reduction.
- Neutropenic fever required a 1-level dose reduction. Those hospitalised for fever with either grade 3 or 4 neutropenia could be treated with granulocyte colony stimulating factor (G-CSF) 5 μg/kg/day during the episode.
- If febrile neutropenia occurred despite a 1-level dose reduction, then patients received G-CSF. At least 2 days must have elapsed between last dose of G-CSF and initiation of another treatment cycle.
- If febrile neutropenia occurred despite the use of G-CSF, then the patient received a second dose reduction. If a dose reduction below the lowest dose described above was required a, a dose reduction of 20% may have taken place after consulting the Study Chair.
- Anaemia was not an indication for dose reduction but data on transfusions and use of erythropoietin were collected.

Dose modification for non-haematological toxicity

For cisplatin, provision was made to adjust or withhold the dose according to the following criteria:

- Renal toxicity: Persistent elevation of serum creatinine ≥ 2.0 mg/dL: dose interruption.
- Peripheral neuropathy grade 3 or 4: dose interruption; persistent grade 2: 2-dose level reduction.
- Ototoxicity: tinnitus and symptomatic hearing loss: a 2-dose level reduction. Cessation on further worsening.

- Gastrointestinal toxicity: 2 or more successive episodes of grade 4 nausea and vomiting: 1-level dose reduction.
- Supportive care: particular attention was paid to adequate control of nausea and vomiting, including use of 5-HT_3 antagonists, and treatment of severe non-haemolytic anaemia after several cycles of therapy. The patient was transfused as needed without interruption of therapy. Platelet transfusions were also required. G-CSF for neutropenia was not required for patients receiving single-agent cisplatin unless reduced drug doses were associated with grade 3 or 4 neutropenia and fever.

For topotecan, provision was made to adjust or withhold the dose according to the following criteria:

- Peripheral neuropathy grade 2: 2-dose level reduction; grade 3 or 4: dose interruption. .
- Gastrointestinal toxicity grade 3: 1-level dose reduction; grade 4: dose interruption.
- Hepatic toxicity grade 2: 1-level dose reduction; grade 3 and 4: dose interruption.

The overall effect of dose modification on topotecan costs is shown in Table 27 below.

Table 27 Effects of dose modification on topotecan costs

Dose (mg/m^2) per day	Minimal wastage[a]		Base case[b] (midrange)		Maximum wastage (no re-use)[c]	
	Number of 1mg vials per cycle	Cost per cycle	Number of 1mg vials per cycle	Cost per cycle	Total number of 1 mg vials	Cost per cycle
0.75	4	£390.60	5	£488.25	6	£585.90
0.60	4	£390.60	4	£390.60	4	£390.60
0.50	3	£292.95	3	£292.95	3	£292.95
0.45	3	£292.95	3	£292.95	3	£292.95
0.30	2	£195.30	3	£292.95	3	£292.95

Assumes mean body surface area of 1.7 m^2

[a]. Retain unused vial contents in aseptic conditions and redeploy within 24 hours
[b]. Midrange practice (between re-using any drug left in the vial within 24 hrs to discarding all remaining drug)
[c]. Discard all unused contents after preparation of each daily infusion (i.e. no re-use).

Pharmacy and administration costs

Costs related to hospitalisation and chemotherapy administration were taken predominantly from the NHS National Reference Costs (2006/7),[36] PSSRU (2008),[37]

and the BNF (2009).[2] National Reference Costs are inflated to 2007/8 prices using the Hospital & Community Health Services inflator from the PSSRU.

The administration of cisplatin requires a pre- and post-treatment hydration of two hours with at least one litre of 0.45-0.9% saline. Therefore, administration of cisplatin, with or without topotecan, involves day case attendance. The day case cost is incurred only on day one of each cycle.

The cost of a medical oncology day case was estimated at £277 (based on HRG M98: Chemotherapy with a Female Reproductive System Primary Diagnosis). This was assumed to cover the cost of the drug administration, any nursing time and pharmacy costs.

Topotecan is administered over 3 consecutive days. In addition to the day case on day 1, out-patient visits are required for infusions on days 2 and 3.Each of these two out-patient visits was costed as £51, including £28 for one hour of nursing time plus £23 to cover pharmacy time to prepare a simple IV infusion (based on pharmacy cost estimates from the Christie Hospital as detailed in two recent HTA reports)[55,56] at each of these visits.

In GOG-0169, administration of 135mg/m^2 paclitaxel occurred over 24 hours. However, based on a clinician's opinion that this dose of paclitaxel is normally administered over 3 hours. It was assumed that administration of paclitaxel plus cisplatin requires attendance as day case.

Pre- and post-treatment medication

As cisplatin commonly causes severe renal toxicities as well as nausea and vomiting, anti-emetics and steroids are routinely used pre- and post-treatment to ameliorate the adverse effects.

Pre-treatment medication in the trial consisted of granisetron (1mg orally or IV) with dexamethasone (20mg orally or IV) administered 30 minutes prior to cisplatin. Based on a clinician's opinion, pre-treatment with 3mg IV of granisetron and with 8mg IV of dexamethasone was assumed for costing purposes (delivered on day one prior to cisplatin and also on days 2 and 3 for patients receiving topotecan plus cisplatin).

As anti-emetics may not be routinely given for treatment with topotecan, a one-way sensitivity analysis was carried out examining the impact of giving pre-treatment on day one only for patients receiving topotecan plus cisplatin.

Post-treatment medication in the trial consisted of ondansetron 8mg every 8 hours or metoclopramide 40mg twice daily (bid) for 3-4 days post-treatment. Based on a clinician's opinion a regimen of domperidone 20mg 4 times daily (qds) was assumed as more representative of UK practice and this was applied for 5 days for both treatment regimens.[57]

It was assumed that the pre-and post-treatment medications used in have equal efficacy in ameliorating adverse events to those used in GOG-0179 and that practice is similar whether cisplatin is delivered on a weekly or 3-weekly schedule. No additional costs were included for administration or pharmacy for these medications as it is assumed that these costs will be included in the costs relating to the chemotherapy. The costs of the pre- and post-treatment medications can be found in Table 28.

Based on a clinician's opinion[57] of UK practice, it was assumed that patients who receive paclitaxel plus cisplatin would receive granisetron (3mg IV) with dexamethasone (20mg IV) as pre-treatment medication, and oral dexamethasone 2mg three times a day (tds) for 3 days and domperidone 20mg four times a day (qds) for 5 days as post-treatment medication as described in Table 28.

Follow-up management

The costs of resources likely to be used in routine follow-up were included in the analysis. Schedules were based on clinician opinion and are shown in Table 29.

Costing for non-haematological adverse events

It was assumed that the majority of non-haematological AEs would not require interventions and, therefore, these were not costed. Each patient's dataset was reviewed for SAEs. All serious adverse events classified as 'Disease Related' were assumed to occur equally across both arms and therefore were not costed. All 'Treatment Related' events were costed; events classified as 'Unknown' or 'Other' were not costed as relationship to treatment was unknown.

Likely clinical interventions were inferred by discussion with three oncologists (two from GSK and a non-GSK oncologist). Where there was a conflict of opinion, the worst case assumption was chosen for each of the events as a conservative basis for costing. Unit costs for SAEs were taken from the NHS Reference Costs and are shown in Table 30

Costing for haematological adverse events

Grade 3 and 4 episodes of neutropenia, thrombocytopenia and anaemia were described by UK clinical expert opinion as being the key drivers of AE-related costs.

In most clinical trials, all hospitalisations would normally be categorised as SAEs, yet there appeared to be fewer SAEs than expected on this basis (the rules governing SAE reporting for GOG-0179 are given in section 6.7). The GOG-0179 dataset provided no information on whether patients were hospitalised for specific AEs. Therefore, it was assumed that all grade 4 haematological toxicities resulted in hospital admission (i.e. inpatient stays) and these were assigned the costs in Table 31

For grade 3 haematological events, the number of interventions (G-CSF, platelet transfusions, red blood cell transfusions, erythropoietin) influenced the costs as described in the algorithm in Table 30. If several AEs occurred at the same time then only the most expensive was costed. For example, if a single laboratory report shows that a patient experienced grade 3 anaemia (for which the intervention data show they received a red blood cell transfusion) and also grade 4 thrombocyctopenia, then only the £1,783 cost for the latter would apply.

Where usage of G-CSF was reported, it was not possible to determine which of the protocol-mandated reasons (secondary prophylaxis or post-event treatment) was applicable. However, the extent of usage of G-CSF in GOG-0179 as mandated by the protocol (see section 6.7) was considered to be reasonably consistent with its place in UK practice. Therefore, G-CSF usage was assumed to be covered adequately within HRG S07.
The incidence of febrile neutropenia was not specifically collected as an AE but was collected as a subset of 'infection', which was classified as a non-haematological

toxicity. The methods described above, whilst not specifically costing episodes of febrile neutropenia, include calculation of the costs involved in these events by utilising the laboratory reports of neutropenia (which do not specify whether fever was concurrent) and intervention data.

The serious adverse event dataset for haematological events was reconciled with the AE dataset, laboratory reports and intervention reports to ensure that all SAEs had been accounted for under the above process for AEs.

Table 28. Pre- and post-treatment cost assumptions

Pre-treatment	Formulation	Presentation	Size	Unit cost	Total Dose	Total cost
Cisplatin and topotecan plus cisplatin						
Pre-treatment						
Dexamethasone[54]	IV	2ml vial (4mg/ml)	1	£1.27	8mg	£1.27
Granisetron[55]	IV	3ml vial (1mg/ml)	1	£25.79	3mg	£25.79
Subtotal						£27.06
Post treatment						
Domperidone[56]	Oral (tablets)	10mg	30	£1.86	20mg qds for 5 days	£2.48
Subtotal						£2.48
Cisplatin and paclitaxel plus cisplatin						
Pre-treatment						
Dexamethasone[54]	IV	1mL vial (4mg/ml)	1	£0.83	20mg	£4.15
Granisetron[55]	IV	3mL vial (1mg/ml)	1	£25.79	3mg	£25.79
Subtotal						£29.94
Post treatment						
Domperidone[56]	Oral (tablets)	10mg	30	£1.86	20mg qds for 5 days	£2.48
Dexamethasone[54]	Oral (tablets)	2mg	20	£2.41	2mg tid for 3 days	£1.08
Subtotal						£3.56

qds = 4 times a day

Table 29. Follow-up management schedules and costs

Resource Item	Cost	Source	Resource use in relation to cycles in UK clinical practice		
			Prior to 1st cycle	Prior to 4th cycle[a]	Prior to all other cycles[b]
CT scan	£94.04[c]	National Schedule Reference costs (2006)	YES	YES	NO
MRI scan	£252.15[c]	National Schedule Reference costs (2006)	YES	NO	NO
Blood test	£3.10[c]	National Schedule Reference costs (2006). Cost per specimen.	YES	YES	YES
Visit	£127.11[c]	National Schedule Reference costs (2006). 370F – Adult first attendance, follow-up / Medical Oncology [Attendance without Treatment] : Face to Face Total Attendances	YES	NO	NO
Visit	£10.33[c]	National Schedule Reference costs (2006). 370N; Medical Oncology [Attendance without Treatment]: Non-Face to Face Total Contacts	NO	YES	YES

[a] Costs applied in economic evaluation after 3rd cycle
[b] Costs applied in economic evaluation after all cycles other than 3rd cycle
[c] Inflated to 07/08 prices using PSSRU HCHS pay and price index inflator of 1.033

Table 30. List of serious adverse events costed

Serious Adverse Event	Number of patients	HRG description	HRG code	HRG Cost
Rash, Shortness of breath	1	No cost	n/a	£0
Hypersensitivity reaction	1	Dermatology : Face to Face Total Attendances	330F	£110.57[a]
Small bowel obstruction (SBO)	2	Other Gastrointestinal or Metabolic Disorders	P13	£764.70[a]
Small bowel obstruction (SBO), Pleural effusion	2	Other Gastrointestinal or Metabolic Disorders	P13	£764.70[a]
Gastrointestinal, Nausea, Small bowel obstruction (SBO)	4	Other Gastrointestinal or Metabolic Disorders	P13	£764.70[a]
Nausea and vomiting	2	Other Gastrointestinal or Metabolic Disorders	P13	£764.70[a]
Nausea, vomiting, dehydration	1	Other Gastrointestinal or Metabolic Disorders	P13	£764.70[a]
Creatinine high – Renal failure	1	Acute Renal Failure <70 w/o cc £	L50	£1593.48[a]
Creatinine high	2	Acute Renal Failure <70 w/o cc	L50	£1593.48[a]
Renal failure, BUN and Creatinine high	5	Acute Renal Failure <70 w/o cc	L50	£1593.48[a]
Syncopal episode.	5	Acute Renal Failure <70 w/o cc	L50	£1593.48[a]
Hepatic, gamma glutlamyl transferase (GGT)	1	no cost	n/a	£0
Disabling weakness	2	no cost	n/a	£0

[a] Inflated to 07/08 prices using PSSRU HCHS pay and price index inflator of 1.033

Table 31. Adverse event cost assumptions

Adverse event	Circumstances of AE	Relevant HRG code	Specific value taken from HRG code	Unit cost
Anaemia / neutropenia / thrombocytopenia	Grade 1 or 2 with or without interventions	None applied	None applied	£0
	Grade 3, no intervention	None applied	None applied	£0
Anaemia	Grade 3, single intervention	HRG SO5 Red Blood Cell Disorders, age >69 or with complication	Day case, mean	£410.25[a]
	Grade 3, two interventions	HRG SO5 Red Blood Cell Disorders, age >69 or with complication	Day case, upper value	£519.79[a]
	Grade 3, >2 interventions. All Grade 4	HRG SO5 Red Blood Cell Disorders, age >69 or with complication	Inpatient	£1280.37[a]
Thrombocytopenia or neutropenia	Grade 3, single intervention	HRG SO7 other haematological or splenic disorders age >69 or with complications	Day case, mean	£430.92[a]
	Grade 3, two interventions	HRG SO7 other haematological or splenic disorders age >69 or with complications	Day case, upper value	£518.76[a]
	Grade 3, >2 interventions. All Grade 4	HRG SO7 other haematological or splenic disorders age >69 or with complications	Inpatient	£1842.53[a]

Source: Department of Health.[36] Interventions are G-CSF, platelet transfusions, red blood cell transfusions, erythropoietin

[a] Inflated to 07/08 prices using PSSRU HCHS pay and price index inflator of 1.033

7.2.9.2 How were the resources measured?

Resource utilisation was based on the clinical events that were observed during the trial and then supplemented with data from external sources. The events in the trial that triggered resource use were; treatment dosing (including wastage); disease progression; death and adverse events

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes. The resource use was measured using the individual patient level data from the trial.

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Yes. The model covers the follow-up period of the trial from which the resource use is observed.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

Resources were values using standard UK sources of the NHS National Reference Costs (2006/7),[36] PSSRU (2008),[37] and the BNF (2009).[2]

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The unit cost by vial size for topotecan, cisplatin and paclitaxel are shown in Table 32. The discount arrangements for branded Paclitaxel are not publicly available and are individually and locally negotiated. An assumption of 50% discount has therefore been made in sensitivity analysis.

Table 32. Intervention unit costs used in the analyses.

Intervention	Unit cost
Topotecan 1mg/3ml vial	£97.65
Topotecan 4mg/5ml vial	£290.62
Cisplatin 1mg/ml 10ml vial	£5.85
Cisplatin 1mg/ml 50ml vial	£24.50
Cisplatin 1mg/ml 100ml vial	£50.22
Paclitaxel (generic) 6mg/mL 5ml vial	£106.69
Paclitaxel (generic) 6mg/mL 16.7ml vial	£319.77
Paclitaxel (Taxol®) 6mg/mL 5ml vial	£116.05
Paclitaxel (Taxol®) 6mg/mL 16.7ml vial	£347.82

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values

No additional infrastructure is required.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes.

7.2.9.9 Were resource values indexed to the current price year?

Yes. 2006/7 NHS reference costs were inflated to 07/08 prices using PSSRU HCHS pay and price index inflator of 1.033.

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

All assumptions and justifications are laid out in section 7.2.9.1.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes. All costs and health benefits are discounted at an annual rate of 3.5%.

7.2.11 Sensitivity analysis

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The primary analysis in this evaluation is a trial based analysis, making a direct comparison between treatment with cisplatin and cisplatin plus topotecan. The structure and methodology of a trial based analysis ensures that there is high internal validity and the trial randomisation principle is preserved. Whilst there are limitations to a trial based analysis, in particular its generalisability to other situations, the analysis is structurally highly valid. No structural sensitivities have therefore been investigated.

7.2.11.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

<u>Direct comparison with cisplatin</u>

Sensitivity analyses were carried out to test the effects of alternative assumptions regarding the source of utility values, wastage and the utilisation of pre-treatment medication for topotecan plus cisplatin. Separate CEACs were generated for the two methods of estimating utilities. The scenarios and assumptions tested and the rationale are listed in Table 33

Table 33. Sensitivity analyses for comparison of topotecan plus cisplatin with cisplatin

Scenario or alternative assumption	Rationale	Base case parameter input	Alternative parameter input
Wastage assumption for opened vials of topotecan	Effective cost of topotecan is affected by hospital pharmacy policy	Midrange of wastage of contents of opened topotecan vials	Minimal wastage and maximal (i.e. no re-use of contents of opened topotecan vials) wastage
Pre-treatment medications	The GOG-0179 protocol only suggested use of anti-emetic medication for cisplatin treatment. However, opinion from a UK oncologisti suggested that anti-emetic treatment may also be given on days 2 and 3 for the topotecan plus cisplatin regimen.	Pre-treatment medication given on days 1-3 of topotecan administration	Pre-treatment medication given on day 1 only of topotecan administration
Utility values	Availability of alternative literature-based breast cancer source of utilities and uncertainty regarding applicability of the trial-based FACT-G utilities.	Trial utility values	Breast cancer utility values extracted from the literature

Indirect comparison with paclitaxel

Deterministic sensitivity analysis was performed on the price of paclitaxel, which was considered *a priori* to be a factor likely to affect the conclusions, in view of the availability of unbranded, generic paclitaxel and possible future price volatility.

Investigation into the high level preliminary results from GOG-0204

New evidence has been recently presented from study GOG-204[4] which included a head to head comparison between cisplatin and topotecan versus cisplatin and paclitaxel. However, there is very limited information currently available in the public domain. Nevertheless, given the relevance of the data, this submission attempts to conduct a separate sensitivity analysis of the available data from this study.

Study GOG-0204 was terminated early due to the likelihood that there would be no significant difference demonstrated between the treatment arms. However, initial results show that there is a trend towards superiority in the paclitaxel arm of trial with a non statistically significant hazard ratio of 1.255 in favour of paclitaxel.

The indirect comparison model is used in this analysis with the paclitaxel overall survival arm generated from the topotecan arm, using the hazard ratio described above.

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Yes. In trial-based cost-effectiveness analyses, sampling uncertainty is present in estimates of mean costs and effects. To propagate this uncertainty into the calculated ICERs, bootstrap estimates of incremental costs and effects were generated and presented as scatter plots (with 1000 samples, each sampling the whole of the appropriate population with replacement). The resulting probabilistic estimates of the ICER were presented as cost-effectiveness acceptability curves.

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

N/A.

7.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

N/A.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The following measures were taken to quality assure the economic analysis;

- Professor Alistair McGuire provided extensive guidance on the selected economic methodology and particular aspects of its implementation, including the analysis of costs and quality-adjusted survival in the presence of censored and missing data.
- The initial SAS programs for the trial-based analysis and the algorithm for converting SAS bootstrap output to Excel and calculation of ICERs and CEACs were independently checked and run by two external parties.
- The indirect comparison model, the method to calculate the hazard ratio based on the survival curves available on paper only for the GOG-0169 was checked and validated by Professor Alistair McGuire.
- Diagnostics were performed on the final results to explore the source of the difference between the ICERs obtained by deterministic analysis and as the mean of the bootstrapped data. No errors were detected and an explanation for the non-comparability was provided by Professor Alistair McGuire.

7.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves including a representation of the cost-effectiveness acceptability frontier
- scatterplots on cost-effectiveness quadrants
- a tabulation of the mean results (costs, QALYs, ICERs) the probability that the treatment is cost-effectiveness a thresholds of £20,000-£30,000 per QALY gained and the error probability.

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

Direct comparison with cisplatin

Deterministic cost-effectiveness results for the *licensed population* are shown in Table 34. Probabilistic sensitivity analysis (PSA) results are displayed as a scatterplot of bootstrap results in Figure 16 and a cost-effectiveness acceptability curve (CEAC) in Figure 17. The results show that the *licensed population* is cost effective at an acceptability threshold of £20,000 with an ICER of £17,974/QALY. PSA analysis shows that on more than 50% of occasions the ICER was below £20,000/QALY and on 88% of occasions was under £30,000/QALY.

Table 34. Deterministic cost-effectiveness results for the licensed population

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Topotecan + Cisplatin	£6,074	0.83 (1.12)	£4,122	0.23 (0.27)	£17,974 (£15,091)
Cisplatin	£1,952	0.60 (0.84)			

**All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years*

Figure 16. Scatter plot of bootstrap results: *Licensed population*

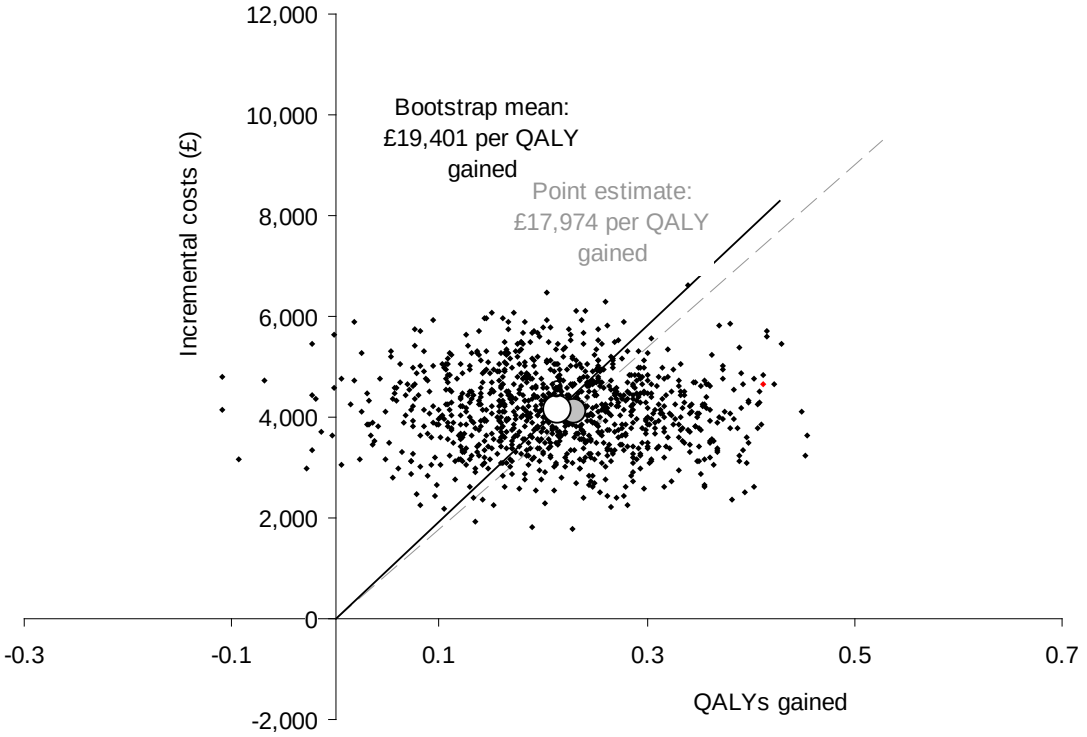
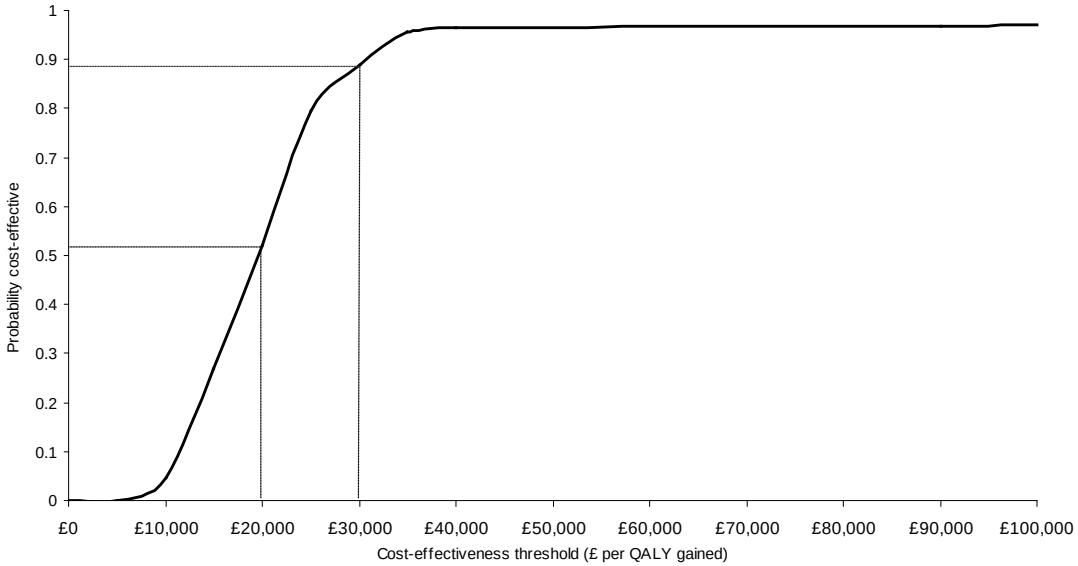


Figure 17. Cost-effectiveness acceptability curve: *Licensed population*



Indirect comparison with paclitaxel

The mean total costs based on mean number of cycles administered are given in Table 35.

Table 35. Mean costs per patient

Mean values	Cisplatin	Topotecan plus cisplatin	Paclitaxel plus Cisplatin
Number of cycles	4.230	5.125	5.125
Chemotherapy costs	£215	£2,762	£4,084
Administration costs	£1,308	£2,107	£1,584
Pre-treatment medication costs	£114	£416	£153
Post-treatment medication costs	£10	£13	£18
Follow-up costs	£591	£604	£604
Adverse event costs	£157	£1,408	£1,142
Total cost per patient	**£2,395**	**£7,310**	**£7,587**

In the base case analysis the comparators in ascending order of costs were: 1: cisplatin, 2: topotecan plus cisplatin and 3: paclitaxel plus cisplatin. The indirect CEA results are shown in Table 36. The ICER for topotecan plus cisplatin vs. cisplatin was £19,964 per life year gained. Paclitaxel plus cisplatin, which was associated with greater costs and worse survival than topotecan plus cisplatin, was strictly dominated.

Table 36. Cost effectiveness results for the indirect comparison with paclitaxel.

	Mean cost per patient	Incremental cost	Mean life years	Incremental life years	ICER: cost per life years gained
Cisplatin	£2,395		0.87		
Topotecan + cisplatin	£7,310	-£4,915	1.12	0.25	£19,964 (vs. Cisplatin)
Paclitaxel + cisplatin	£7,587	£277	0.94	-0.17	Dominated (by Topotecan +Cisplatin)

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

1a) Licensed population excluding stage IVB patients

Deterministic cost-effectiveness results for the licensed population excluding stage IVB are shown in Table 37. PSA results are displayed as a scatterplot of bootstrap results in Figure 18 and a CEAC in Figure 19. The results show that the *licensed population excluding stage IVB* is cost effective at an acceptability threshold of

£20,000/QALY, with an ICER of £18,991 /QALY. PSA analysis shows that on 45% of occasions the ICER was below £20,000 and on 92% of occasions was under £30,000/QALY.

Table 37. Deterministic cost-effectiveness results for the licensed population excluding stage IVB patients

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Topotecan + Cisplatin	£6,889	0.81 (1.14)	£4,938	0.26 (0.31)	£18,991 (£15,691)
Cisplatin	£1,951	0.55 (0.83)			

**All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years*

Figure 18. Scatter plot of bootstrap results: *licensed population* excluding stage IVB patients

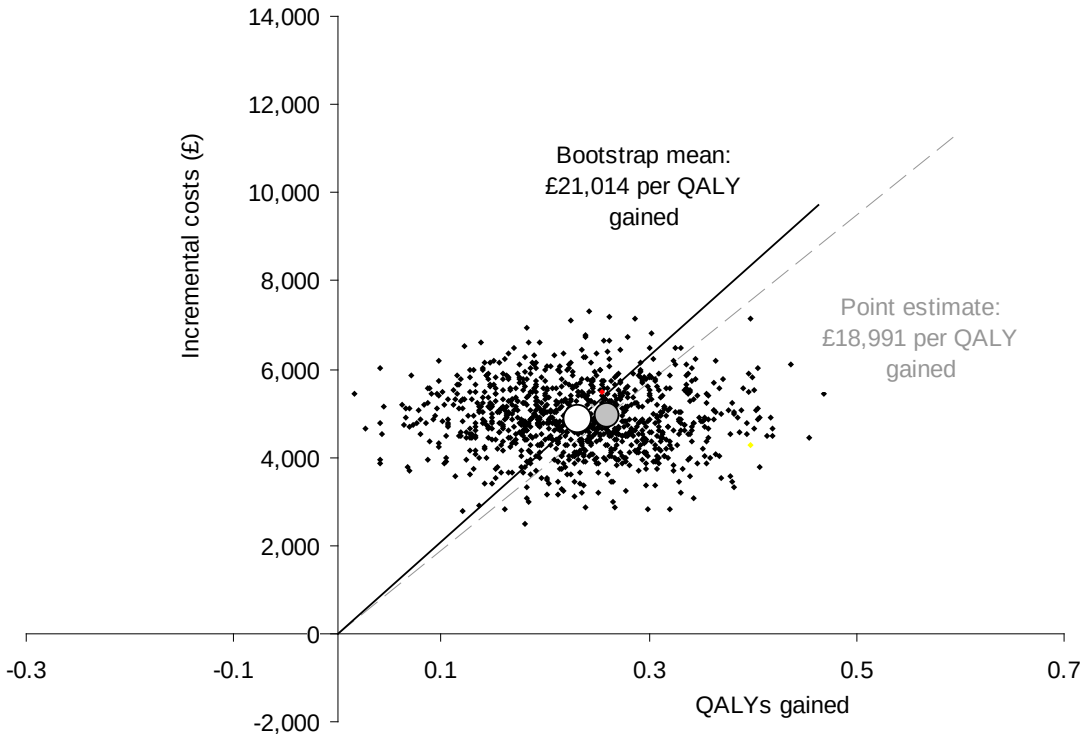
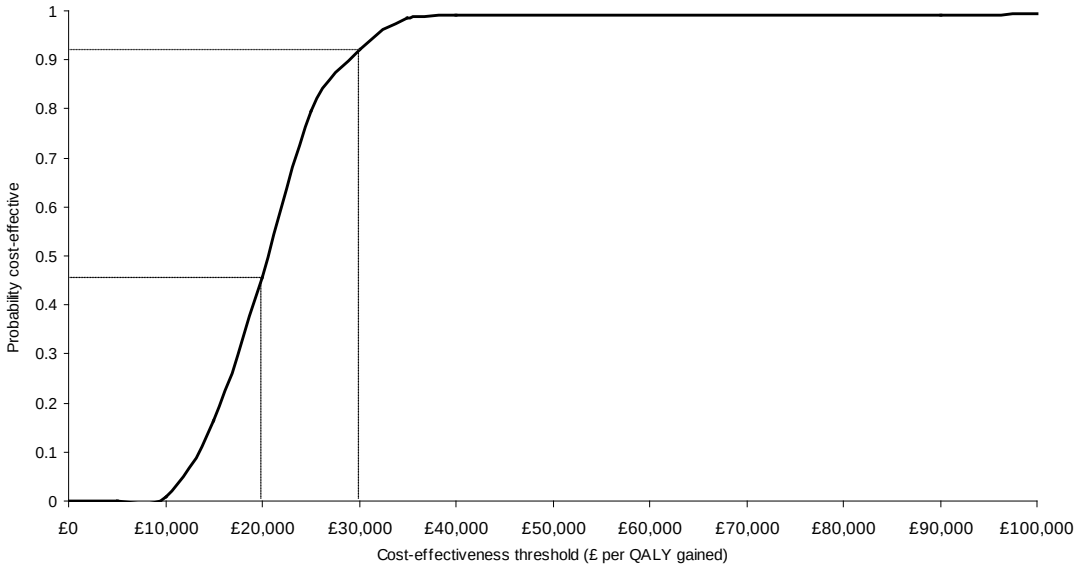


Figure 19. Cost-effectiveness acceptability curve: *Licensed population* excluding stage IVB patients



2. Cisplatin-naïve including stage IVB patients

Deterministic cost-effectiveness results for the stage IVB population are shown in Table 38. PSA results are displayed as a scatterplot of bootstrap results in Figure 20 and a CEAC in Figure 21. The results show that the cisplatin-naïve population is cost effective at an acceptability threshold of £20,000/QALY with an ICER of £10,928/QALY. PSA analysis shows that on 89% of occasions the ICER was below £20,000 and on 98% of occasions was under £30,000/QALY.

Table 38 Deterministic cost-effectiveness results for cisplatin-naïve including stage IVB patients (comparison with cisplatin)

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Topotecan + Cisplatin	£5,522	0.98 (1.30)	£3,521	0.32 (0.37)	£10,928 (£9,564)
Cisplatin	£2,001	0.66 (0.93)			

**All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years*

Figure 20. Scatter plot of bootstrap results: Cisplatin-naïve patient including stage IVB patients (compared with cisplatin)

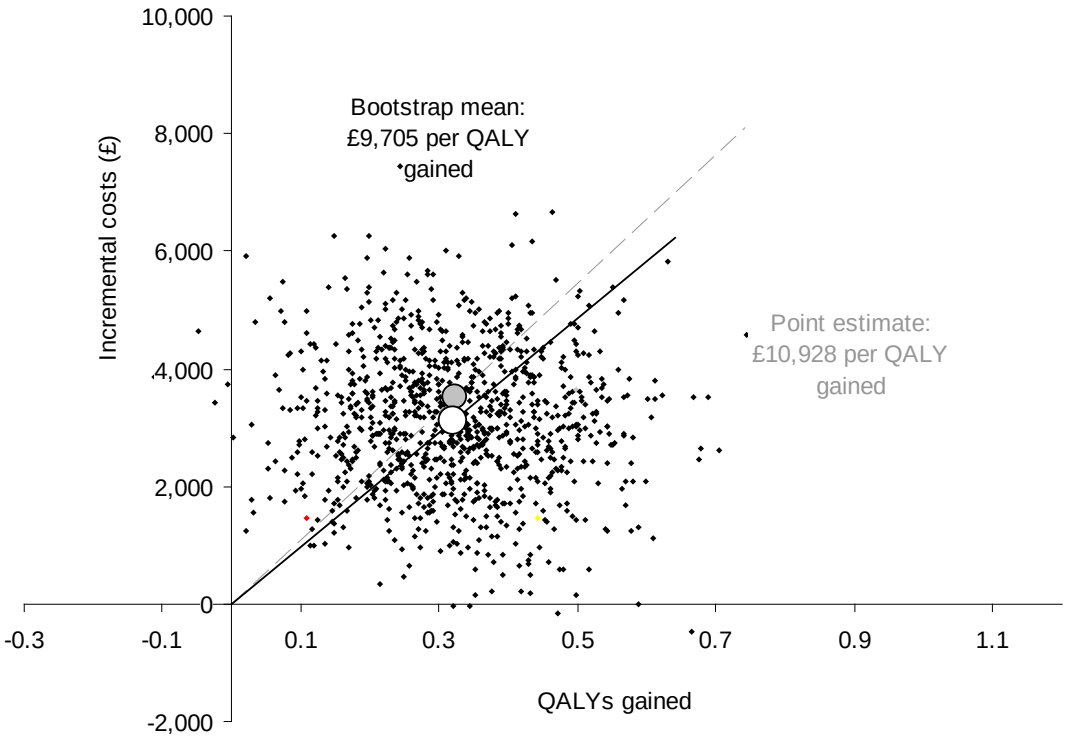
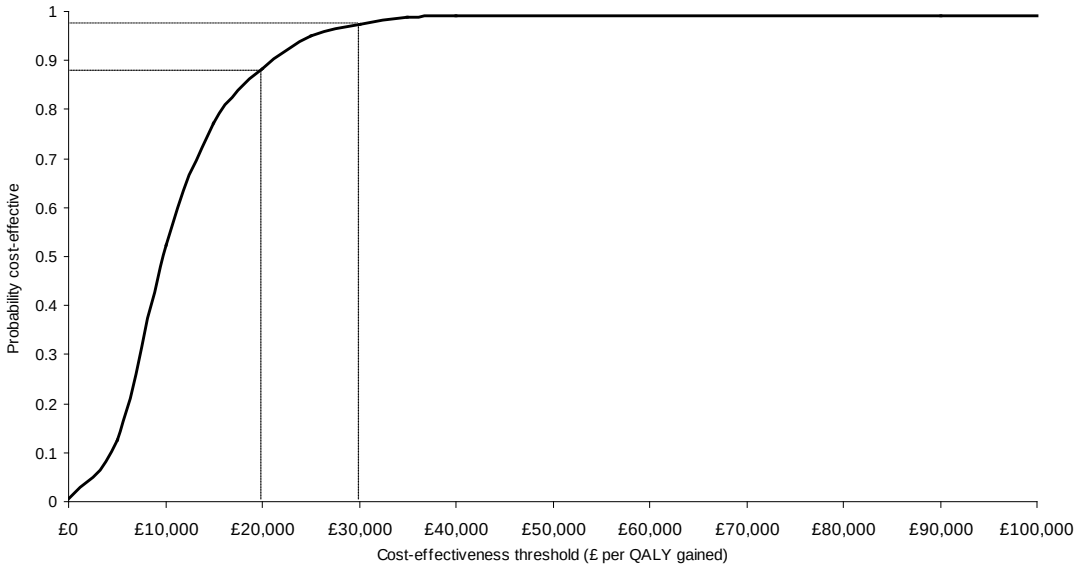


Figure 21. Cost-effectiveness acceptability curve: Cisplatin-naïve patients including stage IVB patients (compared with cisplatin)



2a) Cisplatin-naïve population (excluding stage IVB patients)

Deterministic cost-effectiveness results for the cisplatin-naïve population (excluding stage IVB patients) are shown in Table 39. PSA results are displayed as a scatterplot of bootstrap results in Figure 22 and a CEAC in Figure 23. The results show that the cisplatin-naïve population excluding stage IVB patients is cost effective at an acceptability threshold of £20,000/QALY with an ICER of £8,662/QALY. PSA analysis shows that on more than 98% of occasions the ICER was below £20,000/QALY and on 99% of occasions was under £30,000/QALY.

Table 39. Deterministic cost-effectiveness results for the cisplatin-naïve population excluding stage IVB patients (comparison with cisplatin)

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Topotecan + Cisplatin	£5,923	1.05 (1.39)	£3,954	0.46 (0.47)	£8,662 (£8,450)
Cisplatin	£1,968	0.59 (0.93)			

**All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years*

Figure 22. Scatter plot of bootstrap results: Cisplatin-naïve population (excluding stage IVB patients)

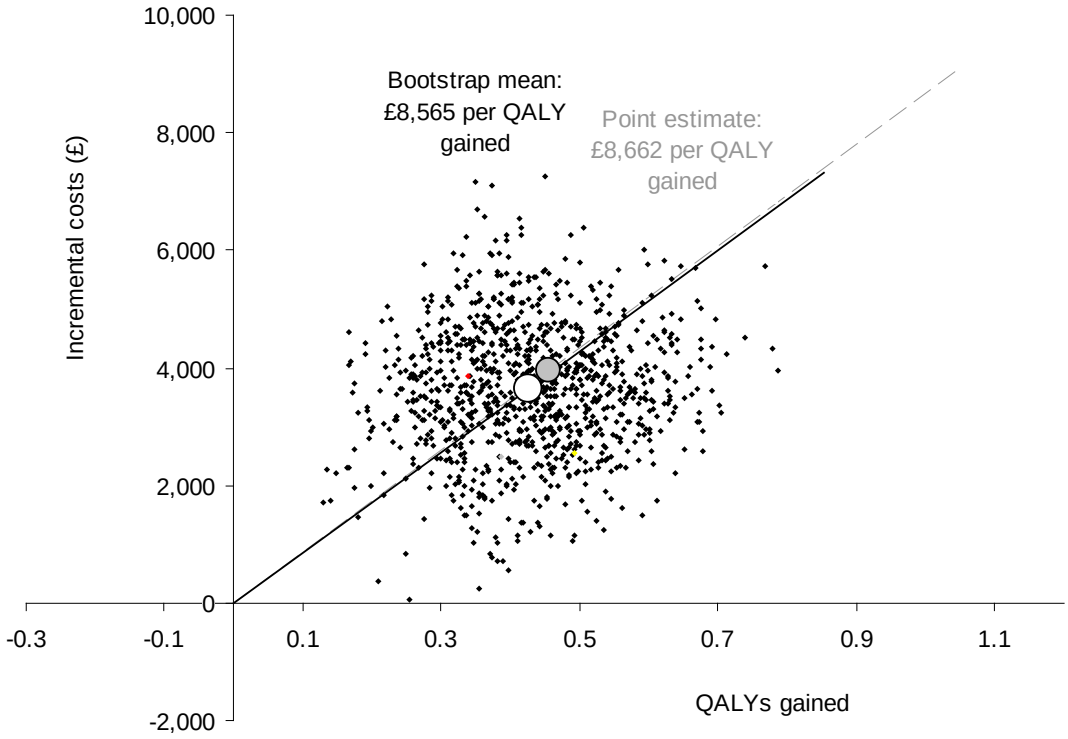
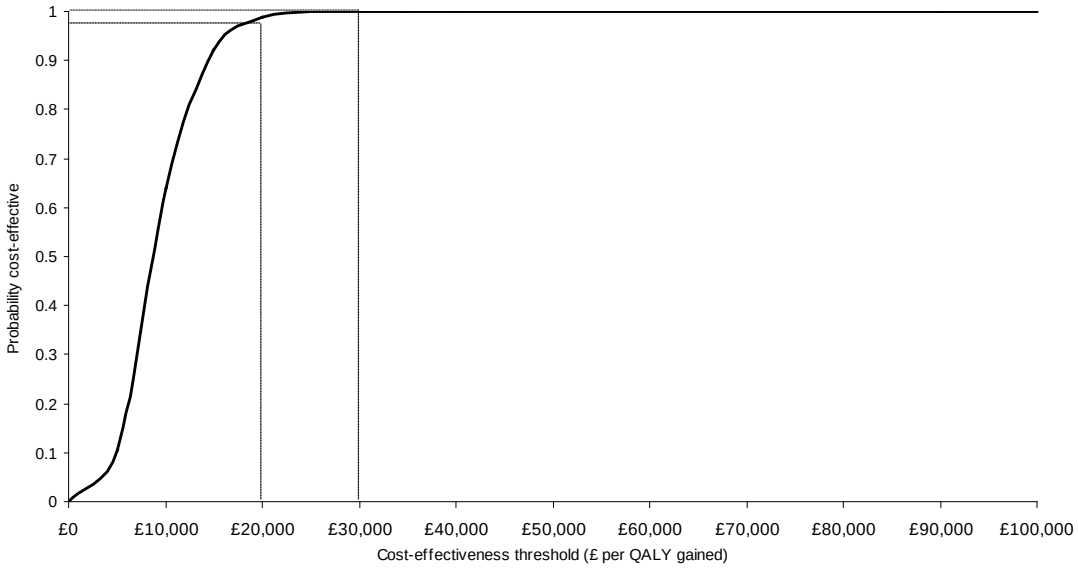


Figure 23. Cost-effectiveness acceptability curve: Cisplatin-naïve population (excluding stage IVB patients)



3) SCFI patients

Deterministic cost-effectiveness results for the SCFI population are shown in Table 40. PSA results are displayed as a scatter plot of bootstrap results in Figure 24 and a CEAC in Figure 25. The results show that the SCFI population has an ICER slightly over the £30,000/QALY cost effectiveness threshold with an ICER of £32,463/QALY. PSA analysis shows however that on more than 55% of occasions the ICER was below £30,000 and on 31% of occasions was under £20,000.

Table 40. Deterministic cost-effectiveness results for the SCFI patients (comparison with cisplatin)

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Topotecan + Cisplatin	£5,855	0.67 (0.98)	£4,145	0.13 (0.20)	£32,463 (£20,757)
Cisplatin	£1,710	0.55 (0.87)			

**All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years*

Figure 24. Scatter plot of bootstrap results: SCFI patients

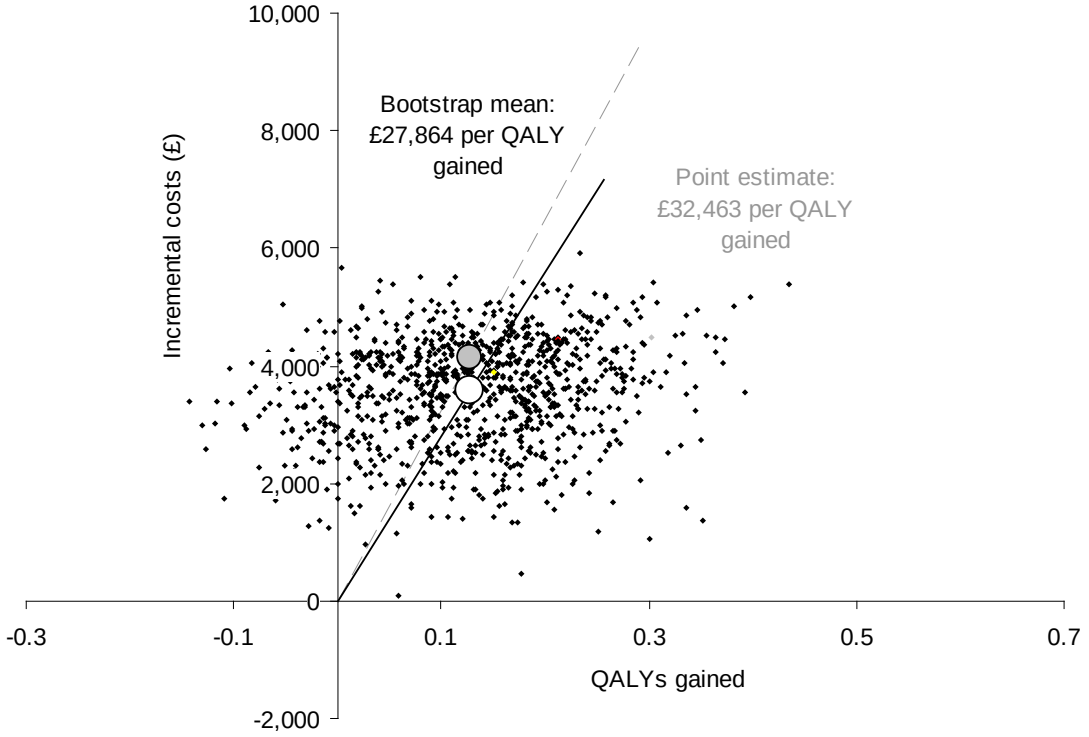
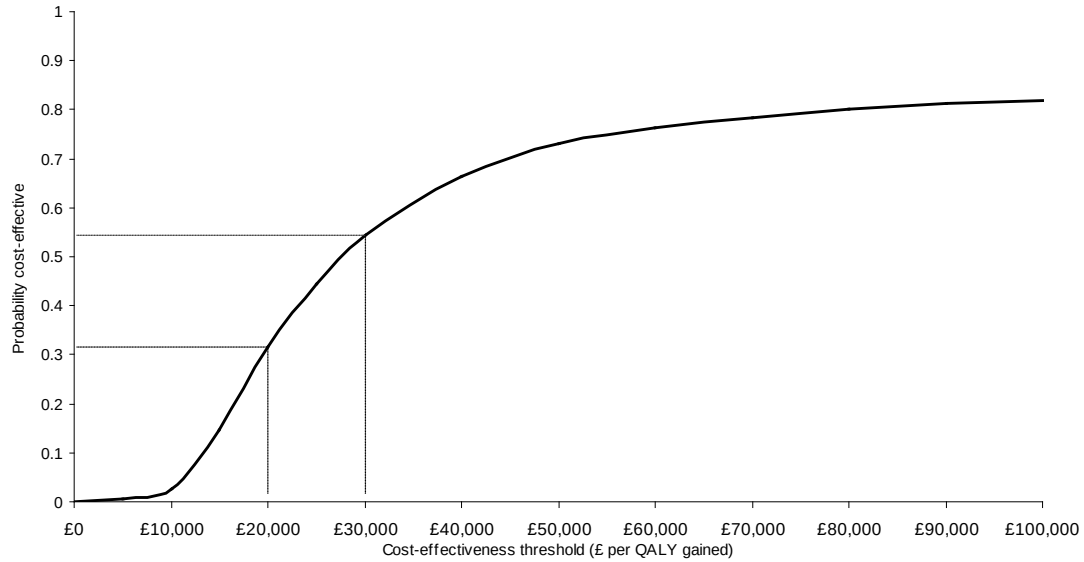


Figure 25. Cost-effectiveness acceptability curve: SCFI patients



[1b)Stage IVB Patients]

We are unable to perform an analysis on the stage IVB patients as there are too few patients in the trial to be able to apply the Lin methodology. We are therefore unable to estimate the effect of censored patients. The effect of the IVB patients on the analysis is reflected in the subgroups without IVB patients, which all have a slightly increased ICER when the IVB patients are removed. This suggests that the IVB patients are more cost effective that the general population from which they are removed.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

Results of the sensitivity analysis are shown in Tables 41 to 45 for the base-case licensed population and subgroups.

The assumptions regarding wastage of topotecan were varied (consistent with the SmPC) because of the variability of pharmacy practice, yet this only modestly affected the results. Sensitivity analysis around cisplatin vial utilisation was not performed, as this is common across both comparator regimens. As maximum wastage is assumed for cisplatin, this is likely to be conservative for topotecan as the number of cycles of topotecan plus cisplatin is likely to be greater than the number of cycles of cisplatin alone.

As anti-emetics are not routinely given for treatment with topotecan, a one-way sensitivity analysis was carried out examining the impact of giving pre-treatment on day one only for patients receiving topotecan plus cisplatin (versus the base case of anti-emetics on days 1-3). This decreased the ICERs by approximately 5%.

There is some uncertainty regarding the most widely used dosage and regimen of cisplatin in the UK. Oncologists stated that both weekly and three weekly dosing are standard options with dosing ranging from 40-50 mg/m^2 weekly and 50-100 mg/m^2 every 21 days. The dose of cisplatin used in GOG-0179 (50 mg/m^2 every 21 days) was selected on the basis of results from a previous GOG study in which there were no appreciable differences in PFS or OS between the doses studied (50 mg/m^2 every 21 days, 100 mg/m^2 every 21 days and 20 mg/m^2 daily x 5, every 21 days). We are not aware of clear evidence of increased survival for alternative cisplatin regimens (such as weekly dosing). The resource utilisation and chemotherapy costs of providing weekly regimens are likely to be higher than the costs for 3-weekly regimen used in the GOG-0179 study. Given these issues, and the robust data available from GOG-0179, no sensitivity analyses were undertaken on this issue.

It can be seen from the analyses that use of the breast cancer literature-based values increases the ICER, however in all the scenarios except for the SCFI patients (deterministic result, not bootstrap average) the ICERs are still below a £30,000/QALY threshold. Although FACT-G-based utilities were used in the base case (for reasons described in Section 7.2.8.3), there is uncertainty as to which method is the most accurate and this sensitivity analysis illustrates that the breast cancer literature-based utilities may provide a conservative estimate of cost-effectiveness. Applying assumptions of minimum wastage and a single day of pre-treatment to the FACT-G-based ICERs would further increase the cost-effectiveness of topotecan plus cisplatin. In addition, disutilities of febrile neutropenia and thrombocytopenia were specifically taken into account in the sensitivity analysis.

The sensitivity analysis demonstrates that under a reasonable range of alternative assumptions where parameter values are uncertain, the ICER remains below £30,000.

Table 41. Sensitivity analysis results for the licensed population

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Basecase					
Topotecan + Cisplatin	£6,074	0.83 (1.12)	£4,122	0.23 (0.27)	£17,974 (£15,091)
Cisplatin	£1,952	0.60 (0.84)			
Literature based breast cancer utilities					
Topotecan + Cisplatin	£6,074	0.56 (1.12)	£4,122	0.17 (0.27)	£24,440 (£15,091)
Cisplatin	£1,952	0.40 (0.84)			
Minimal wastage					
Topotecan + Cisplatin	£5,753	0.83 (1.12)	£3,782	0.23 (0.27)	£16,489 (£13,854)
Cisplatin	£1,952	0.60 (0.84)			
Maximum wastage (no vial re-use)					
Topotecan + Cisplatin	£6,413	0.83 (1.12)	£4,461	0.23 (0.27)	£19,453 (£16,333)
Cisplatin	£1,952	0.60 (0.84)			
Pre-treatment medication on day 1 only					
Topotecan + Cisplatin	£5,872	0.83 (1.12)	£3,921	0.23 (0.27)	£17,095 (£14,353)
Cisplatin	£1,952	0.60 (0.84)			

*All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years

Table 42. Sensitivity analysis results for the licensed population excluding stage IVB patients.

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Basecase					
Topotecan + Cisplatin	£6,889	0.81 (1.14)	£4,938	0.26 (0.31)	£18,991 (£15,691)
Cisplatin	£1,951	0.55 (0.83)			
Literature based breast cancer utilities					
Topotecan + Cisplatin	£6,889	0.51 (1.14)	£4,938	0.13 (0.31)	£37,526 (£15,691)
Cisplatin	£1,951	0.38 (0.83)			
Minimal wastage					
Topotecan + Cisplatin	£6,501	0.81 (1.14)	£4,559	0.26 (0.31)	£17,532 (£14,485)
Cisplatin	£1,951	0.55 (0.83)			
Maximum wastage (no vial re-use)					
Topotecan + Cisplatin	£7,267	0.81 (1.14)	£5,317	0.26 (0.31)	£20,446 (£16,893)
Cisplatin	£1,951	0.55 (0.83)			
Pre-treatment medication on day 1 only					
Topotecan + Cisplatin	£6,663	0.81 (1.14)	£4,712	0.26 (0.31)	£18,122 (£14,973)
Cisplatin	£1,951	0.55 (0.83)			

*All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years

Table 43. Sensitivity analysis results for the cisplatin naïve population excluding stage IVB patients.

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Basecase					
Topotecan + Cisplatin	£5,923	1.05 (1.39)	£3,954	0.46 (0.47)	£8,662 (£8,450)
Cisplatin	£1,968	0.59 (0.93)			
Literature based breast cancer utilities					
Topotecan + Cisplatin	£5,923	0.63 (1.39)	£3,954	0.20 (0.47)	£19,395 (£8,450)
Cisplatin	£1,968	0.42 (0.93)			
Minimal wastage					
Topotecan + Cisplatin	£5,554	1.05 (1.39)	£3,585	0.46 (0.47)	£7,854 (£7,661)
Cisplatin	£1,968	0.59 (0.93)			
Maximum wastage (no vial re-use)					
Topotecan + Cisplatin	£6,289	1.05 (1.39)	£4,321	0.46 (0.47)	£9,465 (£9,234)
Cisplatin	£1,968	0.59 (0.93)			
Pre-treatment medication on day 1 only					
Topotecan + Cisplatin	£5,712	1.05 (1.39)	£3,743	0.46 (0.47)	£8,199 (£7,999)
Cisplatin	£1,968	0.59 (0.93)			

*All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years

Table 44. Sensitivity analysis results for the cisplatin naïve population including stage IVB patients.

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Basecase					
Topotecan + Cisplatin	£5,522	0.98 (1.30)	£3,521	0.32 (0.37)	£10,928 (£9,564)
Cisplatin	£2,001	0.66 (0.93)			
Literature based breast cancer utilities					
Topotecan + Cisplatin	£5,522	0.66 (1.30)	£3,521	0.22 (0.37)	£15,761 (£9,564)
Cisplatin	£2,001	0.44 (0.93)			
Minimal wastage					
Topotecan + Cisplatin	£5,185	0.98 (1.30)	£3,184	0.32 (0.37)	£9,883 (£8,649)
Cisplatin	£2,001	0.66 (0.93)			
Maximum wastage (no vial re-use)					
Topotecan + Cisplatin	£5,857	0.98 (1.30)	£3,855	0.32 (0.37)	£11,966 (£10,472)
Cisplatin	£2,001	0.66 (0.93)			
Pre-treatment medication on day 1 only					
Topotecan + Cisplatin	£5,327	0.98 (1.30)	£3,326	0.32 (0.37)	£10,324 (£9,035)
Cisplatin	£2,001	0.66 (0.93)			

*All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years

Table 45. Sensitivity analysis results for the SCFI patients.

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Basecase					
Topotecan + Cisplatin	£5,855	0.67 (0.98)	£4,145	0.13 (0.20)	£32,463 (£20,757)
Cisplatin	£1,710	0.55 (0.87)			
Literature based breast cancer utilities					
Topotecan + Cisplatin	£5,855	0.47 (0.98)	£4,145	0.12 (0.20)	£34,609 (£20,757)
Cisplatin	£1,710	0.35 (0.87)			
Minimal wastage					
Topotecan + Cisplatin	£5,579	0.67 (0.98)	£3,869	0.13 (0.20)	£30,304 (£19,376)
Cisplatin	£1,710	0.55 (0.87)			
Maximum wastage (no vial re-use)					
Topotecan + Cisplatin	£6,131	0.67 (0.98)	£4,420	0.13 (0.20)	£34,623 (£22,138)
Cisplatin	£1,710	0.55 (0.87)			
Pre-treatment medication on day 1 only					
Topotecan + Cisplatin	£5,675	0.67 (0.98)	£3,965	0.13 (0.20)	£31,058 (19,859)
Cisplatin	£1,710	0.55 (0.87)			

*All costs and outcomes discounted at 3.5% per annum. LY=Life years, LYG=Life years gained, QALY=Quality adjusted life years

Indirect comparison sensitivity analysis

A sensitivity analysis has been performed in which the price of paclitaxel was assumed to be 50% lower than the branded Taxol price (as opposed to approximately 10% lower in the base case), the comparators in ascending order of costs were: 1: cisplatin, 2: paclitaxel plus cisplatin and 3: topotecan plus cisplatin. The ICER for paclitaxel plus cisplatin vs. cisplatin was £50,939 per life year gained. The ICER for topotecan plus cisplatin vs. paclitaxel plus cisplatin was £8,137; paclitaxel plus cisplatin and was therefore eliminated by extended dominance. The ICER for topotecan plus cisplatin vs. cisplatin was therefore the value calculated in the base case £19,964 per life year gained (Table 46).

A further sensitivity analysis is performed examining the effect of using the hazard ratio reported in the GOG-204 trial in which paclitaxel/cisplatin combination is shown to have a non-statistically significant improved overall survival compared to topotecan/cisplatin. The hazard ratio of 1.255 in favour of paclitaxel is used to construct the paclitaxel/cisplatin curve based on the topotecan/cisplatin curve in the indirect comparison model. This analysis produces a cost per life year gained of £982 in favour of paclitaxel/cisplatin.

Table 46. Indirect comparison sensitivity analysis.

	Mean cost per patient	Incremental cost	Mean life years	Incremental life years	ICER: cost per life years gained
Sensitivity analysis: paclitaxel price 50% of branded Taxol®					
Cisplatin			0.87		
Paclitaxel + cisplatin	£5,860	£3,465	0.94	0.07	£50,939 (vs. C)
Topotecan + cisplatin	£7,310	£1,450	1.12	0.17	£8,137 (vs. P+C)
Elimination of dominated alternatives					
Cisplatin	£2,395		0.87		
Topotecan + cisplatin	£7,310	£4,915	1.12	0.25	£19,964 (vs. C)
Using OS hazard ratio of 1.255 for paclitaxel/cisplatin vs topotecan/cisplatin					
Topotecan + cisplatin	£7,587	£277	1.40	0.282	£982 (vs. T+C)

Abbreviations: C: Cisplatin, T: Topotecan, P: Paclitaxel

7.3.3.2 What are the key drivers of the cost effectiveness results?

The sensitivity analysis demonstrates that the utility values are the key drivers of cost effectiveness, and the subgroup analysis show that overall survival drives cost effectiveness as the cisplatin-naïve population has the best survival hazard ratio and has a lower ICER than the SCFI group which has the worst hazard ratio of the subgroups.

7.3.4 Interpretation of economic evidence

The results of the base case direct comparison analysis demonstrate that treatment with topotecan and cisplatin is cost effective compared to treatment with cisplatin monotherapy. This is supported by an estimated ICER of £17,974/QALY which is below a £20,000/QALY cost effectiveness threshold. Sensitivity analysis examining wastage assumptions, different utility values and pre-treatment options all results in ICERs that fall below a £30,000/QALY threshold. Of these sensitivity analyses, the utility values used are the key drivers of cost effectiveness.

Subgroup analysis shows that topotecan in combination with cisplatin is cost effective in all bar one sub population of patients (those who have previously received cisplatin, with a sustained treatment free interval), assuming a threshold of £30,000/QALY. In this group the deterministic ICER is £32,643/QALY, with a mean bootstrap ICER of £27,864/QALY. Sensitivity analysis of these subgroups demonstrates that in the majority of cases, the ICER remains below a £30,000/QALY threshold. An exploratory analysis to evaluate the potential impact of weighting the end of life QALYs gained by patients on treatment with topotecan plus cisplatin was performed in response to the new NICE guidance to Appraisal Committees on appraising end of life medicines. In this analysis the ICER for the SCFI population fell below £30,000 (to £24,382/QALY).

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published economic literature against which to compare the results of this analysis.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes, this evaluation covers all licensed populations.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Direct comparison

Strengths

- The analysis is based on a randomised, controlled clinical trial conducted independently by the Gynecologic Oncology Group. Trial-based methodology has high internal validity based on maintenance of the randomisation principle, and requiring fewer assumptions than a decision model.

- In a model, it is not always possible to assign reliable probabilities to each of the multiple paths representing events and states, because these probabilities cannot be inferred from the summary statistics that are found in trial study reports and published articles. Nor can the timing of the occurrence of events and the duration of residence in health states be deduced from aggregate data. The timing may differ between treatment groups, affecting the accrual of quality-adjusted survival and of costs. A trial based analysis circumvents this issue by using the observed outcomes for each patient within the trial.

- The full licensed population and appropriate subgroups are modelled.

- The analysis is based on a direct comparison data with cisplatin and thus there is no uncertainty introduced from comparing non-homogenous populations

- The Lin methodology used gives a published robust methodology for estimating the total cost and QALYs gained for censored patients.

- HTA agencies, and NICE in particular, expect the use of probabilistic methods to characterise parameter uncertainty. In a modelled analysis, this is usually estimated by means of applying relevant distributions to key parameters and estimating the joint uncertainty by means of simulation. Rarely is it possible to estimate the correlation between uncertain parameters, but the default assumption of no correlation may lead to overestimation of credibility intervals. In trial-based analysis, part of the parameter uncertainty takes the form of the sampling uncertainty inherent in a trial dataset. This uncertainty is normally handled by means of bootstrap analysis of differences between

actually observed costs and outcomes in pairs of subjects. Hence, the method requires no assumptions about correlations between costs and outcomes as any such correlations are already embodied within the trial data. Insofar as the choice is between modelling from a single trial and analysing patient level data from the same trial, the precision of estimation is arguably greater when the latter method is used.

- Utility values are sourced directly from the trial and so there is no uncertainty as to the relevance or appropriateness for the analysed population. This is often a problem in evaluations where utility values have to be sourced from literature not relating to the study population.

Weaknesses

- A trial based analysis means that the analysis is not generalisable to other treatments or populations.

- The model is not extrapolated beyond the trial period.

- There are weaknesses in using the Lin methodology in subgroups of patients where the number of patients is very small. This has meant that it has not been possible to estimate ICERs for IVB patients. The cost effectiveness of these patients has had to be inferred by observing the change in the ICER in populations where these patients have been removed.

- Utility values, whilst being sourced from the trial are based on a mapping from FACT-G which has some weaknesses. The mapping tends to overestimate patients with poor quality of life and thus the utility gains of end stage cervical cancer patients may be high. Sensitivity analysis using breast cancer utility values may provide are more reflective view of the utility in these patients, however the ICERs estimated using these values are still within cost effective thresholds.

Indirect comparison

The indirect comparison is included as a secondary analysis in an attempt to provide some preliminary insight into the potential comparisons between topotecan/cisplatin and other cisplatin combinations. The main weakness of this analysis is that the two trials in the comparison contain patients from non-homogenous populations and assumptions have had to be made to ensure fair comparison. It has also been impossible to apply utility values to the model and thus results are only presented as cost per life year gained. Interpretation of the results from this analysis should be done with care.

Overall conclusion

In the UK, patients with recurrent or stage IVB cervical cancer are currently mostly treated with cisplatin (~39%) and carboplatin/paclitaxel combination (~18%). There are various other unlicensed combinations, including the paclitaxel/cisplatin combination, that individually have minimal usage in the UK (<4%). There are no randomised trials comparing carboplatin, or carboplatin plus paclitaxel, to any cisplatin-based regimen in this patient group. Therefore it was not possible to undertake any robust economic analyses for these regimens.

Given the limited evidence available for these alternative regimens, it may be reasonable to assume that the direct economic evaluation presented here is broadly representative of the comparison of topotecan plus cisplatin with carboplatin, whilst the indirect analysis may be relevant to consideration of the cost-effectiveness of topotecan plus cisplatin versus carboplatin plus paclitaxel.

The estimated base case ICER for topotecan plus cisplatin (compared to cisplatin) in the Licensed population is £17,974 per QALY. Extending the lives of these patients is clearly worthwhile as they are, on average, only 50 years old, and the majority are likely to have a PS of 0 or 1 (i.e. either fully active or ambulatory, but restricted in strenuous activity). Topotecan plus cisplatin is the only licensed combination therapy available to these patients and provides significant clinical benefits over cisplatin.

In an indirect analysis topotecan plus cisplatin dominates paclitaxel plus cisplatin at current prices, subject to the constraints imposed by lack of head-to-head clinical data. Even if the price of generic paclitaxel is decreased to 50% of the current branded price, topotecan plus cisplatin is more cost-effective than this regimen.

As it likely to be cost-effective at the £20,000 threshold we believe that topotecan plus cisplatin should be recommended for use in the UK within its licensed indication.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results

The availability of individual patient level data from the GOG-0169 trial would allow an indirect comparison with a paclitaxel/cisplatin regime to be performed on homogenous populations. This would allow us to apply qualitiy of life estimates to the patiens and would enhance the roubustness and completeness of the analysis allowing more certain conclusions to be drawn from the indirect analysis.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

It is estimated that the cost of replacing treatment with cisplatin will be an increased annual cost of £578,463 and the cost of replacing paclitaxel/cisplatin combination (as a proxy of other combinations) will be a cost offset of £137,760. This results in an estimated total annual budgetary impact of £440,703 (Table 47).

Table 47. Summary of budgetary impact

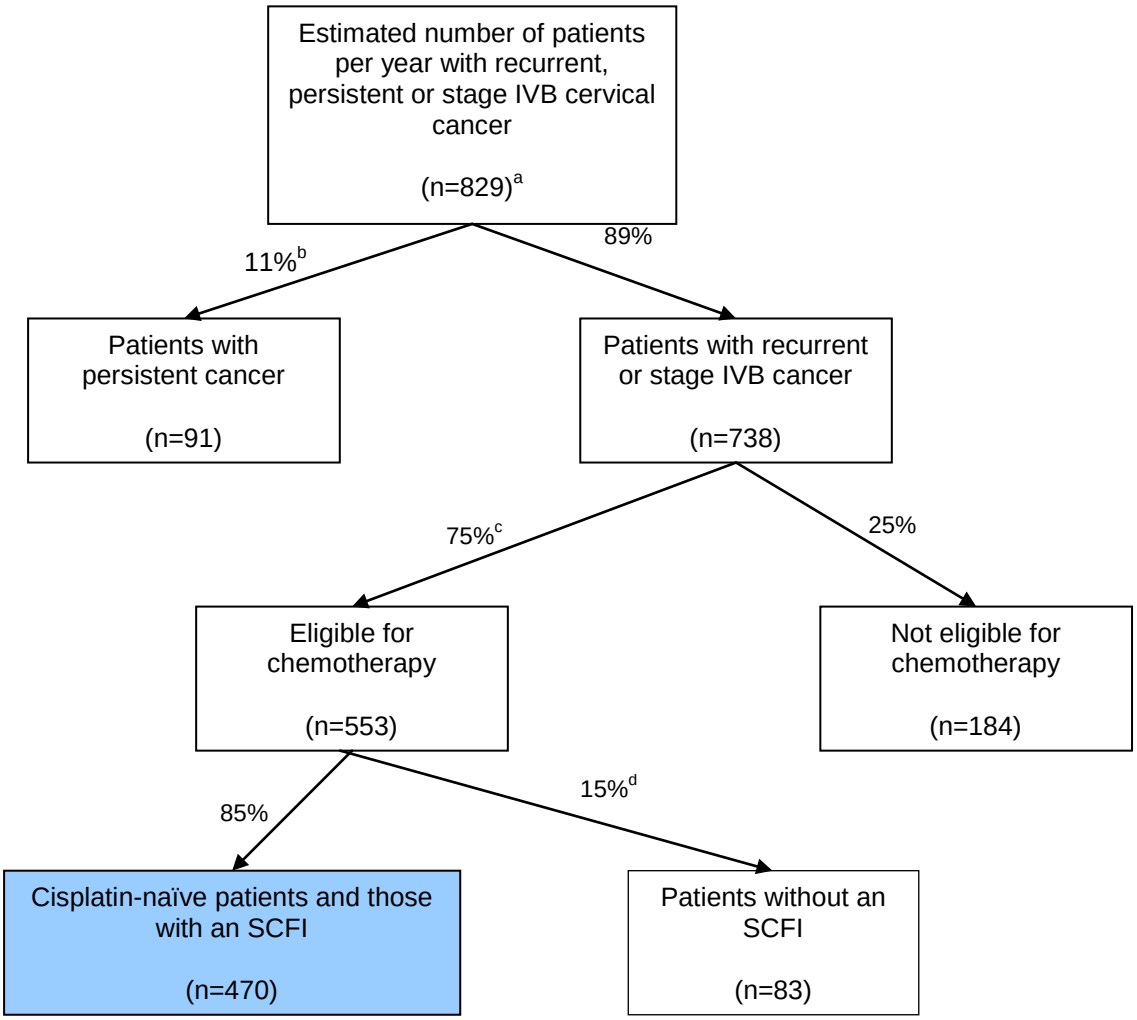
Treatment	Number of patients	Total cost of course of treatment	Cost of treatment with topotecan/cisplatin	Budget impact
Total patients	470			
Cisplatin patients (39%)	183	£272,853	£851,316	£578,463
Paclitaxel plus cisplatin (61%)	287	£1,472,884	£1,335,124	-£137,760
			Total	**£440,703**

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The specific condition relating to the indication under consideration is recurrent (after radiotherapy) or stage IVB carcinoma of the cervix. Patients with this condition form a small subset of all patients with cervical cancer.

According to UK Cancer Research figures, there were 829 deaths from cervical cancer in 2006 in England and Wales. We assume that this mortality rate will remain constant over time. It is likely that these patients will either have had recurrent, persistent or stage IVB disease and we use the distribution of patients in the GOG-0179 trial to approximate the distribution of these patient subgroups. Persistent patients are removed from the patient pool, as were those patients with recurrent or stage IVB disease that were not eligible for chemotherapy. The total population eligible for topotecan plus cisplatin was therefore estimated at 470 patients per year (the shaded box in Figure 26).

Figure 26. Number of patients eligible for topotecan plus cisplatin in England and Wales



Notes:

a) Assumed from number of deaths per year in England and Wales
b) Assumed as the percentage of patients in the ITT population of GOG-0179 with persistent disease
c) Personal communication, Dr Paul Symonds
d) Assumed as the percentage of patients in the stage IVB and recurrent population of GOG-0179 without a SCFI

It should be noted that the eligible population is likely to be smaller than 470 patients per year as other sources[58] indicate that between approximately 20% and 87% of recurrent and stage IVB patients are eligible for chemotherapy.

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

It is assumed that 39% of these patients are currently receiving cisplatin alone and the remainder receive paclitaxel/cisplatin combination. The cisplatin usage reflects that observed in the IMS analysis shown in Table 18 and paclitaxel/cisplatin is used as a proxy for the costs of treating with all other combinations.

8.4 What assumption(s) were made about market share (where relevant)?

To assess the maximum budgetary impact and for simplicity, we assume that all the eligible patients receive topotecan/cisplatin combination.

8.5 What unit costs were assumed? How were these calculated?

The annual costs associated with treatment are assumed to include the costs of:

- Chemotherapy
- Administration of chemotherapy including:
    - hospital attendances
    - pharmacy costs
    - pre- and post-treatment medication

Per cycle costs are presented in Table 48 below and assumptions are described in detail in Section 7. Patient-level data were not available for GOG-0169. To allow for consistency with the method used to estimate the direct cost of paclitaxel plus cisplatin, the mean total direct costs of topotecan plus cisplatin and cisplatin alone were calculated using the mean number of completed cycles and not calculated on a patient-level as was done for the main direct economic analyses. Mid-range vial wastage was assumed for topotecan (Table 25). The mean number of cycles was calculated from all patients in the licensed population of GOG-0179 for cisplatin and topotecan plus cisplatin. The mean number of cycles for paclitaxel plus cisplatin was assumed to equal that for topotecan plus cisplatin.

Table 48. Direct costs per cycle and per course

Treatment	Costs per cycle					Mean no. of cycles	Total scheduled direct costs per course
	Drug acquisition cost	Administration cost	Pre-treatment medication	Post-treatment medication	Total Scheduled direct costs per cycle		
Cisplatin	£50.74	£300.00	£27.06	£2.48	£380.28	3.92	£1,491
Topotecan plus cisplatin	£538.99	£402.00	£81.18	£2.48	£1,024.65	4.54	£4,652
Paclitaxel* plus cisplatin	£796.97	£300.00	£29.94	£3.56	£1,130.47	4.54	£5,132

*generic paclitaxel

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Section 8.5 includes the cost of administration of treatment, which includes hospital attendances. There are adverse events associated with treatment, the cost of which are described in section 7, however these have not been included in the budgetary impact.

8.7 Were there any estimates of resource savings? If so, what were they?

Resource savings occur in the comparison with paclitaxel and cisplatin, in which the cost of drug aquisition is £357.98 cheaper per treatment cycle.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

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