Evidence Review Group's Report

Title: Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix

Produced by Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE)

Authors [redacted]

Correspondence to

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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List of abbreviations

AE	Adverse event
AST	Aspartate aminotransferase
CI	Confidence interval
CR	Complete response
CUA	Cost-utility analysis
ERG	Evidence Review Group
FACT-G	Functional Assessment of Cancer Therapy-General
GOG	The Gynaecological Oncology Group
HRT	Health resource grouping
ICER	Incremental cost-effectiveness ratio
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Asssessment
ITT	Intention-to-treat
LYG	Life years gained
MR	Manufacturer's response
MS	Manufacturer's submission
NICE	National Institute of Clinical Excellence
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PWB	Physical well-being
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SCFI	Sustained cisplatin-free interval
SF-36	Short Form-36
SmPC	Summary of Product Characteristics

1 SUMMARY

1.1 Scope of the submission

This report presents the ERG's assessment of the manufacturer's (GlaxoSmithKline) submission to NICE on the use of topotecan (Hycamtin®) for the treatment of recurrent and stage IVB carcinoma of the cervix. The manufacturer's submission included a non-standard economic analysis consisting of two parts. The primary economic evaluation was an individual patient level data cost-utility analysis of topotecan in combination with cisplatin versus cisplatin monotherapy. In addition, a secondary modelled analysis using indirect evidence was undertaken to compare topotecan plus cisplatin versus paclitaxel plus cisplatin

The manufacturer's submission adhered to the scope for the appraisal issued by NICE in that it considered the use of topotecan plus cisplatin within the context of the licensed indication; women with recurrent or stage IVB carcinoma of the cervix who are not suitable for curative surgery and/or radiotherapy. The key study considered in the submission (GOG-0179) includes patients outside the licensed population and the manufacturer therefore undertook subgroup analyses to reflect the different subgroups within the licensed population, namely: licensed population including or excluding stage IVB patients, cisplatin naïve patients, and patients with sustained cisplatin-free interval (SCFI) >180 days.

1.2 Summary of submitted clinical effectiveness evidence

The manufacturer's submission focused on direct evidence from trial GOG-0179, comparing topotecan plus cisplatin with cisplatin monotherapy, and indirect clinical evidence from trial GOG-0169 comparing topotecan plus cisplatin with paclitaxel plus cisplatin. A second direct comparison trial (GOG-0204) was mentioned in the manufacturer's submission, which compared four cisplatin-based combination therapies: topotecan plus cisplatin, paclitaxel plus cisplatin, gemcitabine plus cisplatin, and vinorelbine plus cisplatin.

The GOG-0179 trial population included patients outside the license for topotecan plus cisplatin (ie. patients with persisent disease and patients with prior cisplatin <180 days). The median overall survival was greater for topotecan plus cisplatin compared with cisplatin monotherapy; 9.4 months versus 6.5 months. The

unadjusted hazard ratio (HR) 0.76 (95% CI: 0.59, 0.98, p=0.033). Translating into a 24% reduction in death rate with combination therapy.

Similar results were also reported for median progression-free survival in GOG-0179: 4.6 months (topotecan plus cisplatin) versus 2.9 months (cisplatin); HR 0.76 (95% CI: 0.60, 0.97, p=0.027). Translating into a 24% reduction in progression or death with combination therapy. Cox regression analysis adjusting for covariates (performance status, age, and disease status at entry) did not significantly alter the results for median overall or progression-free survival.

Response rates also showed an advantage with topotecan plus cisplatin (24%) compared to cisplatin monotherapy (12%) (p=0.0073). The response rates in patients receiving cisplatin monotherapy were very low, but the potential reasons for this were not discussed in the manufacturer's submission.

The safety profile of topotecan plus cisplatin was reported to be predictable and manageable, and there was reportedly no evidence to suggest that QoL was significantly reduced in patients receiving combination therapy. However, patients receiving topotecan plus cisplatin experience a greater number of adverse events and the ERG are concerned with some of the assumptions related to QoL.

Subgroup analyses were undertaken and showed favourable results towards topotecan plus cisplatin, but the results should be interpreted with caution as the number of patients in quite a few of the subgroups was small and some of the analyses were performed post-hoc.

The GOG-0169 trial (which compared paclitaxel plus cisplatin with cisplatin monotherapy) was used to provide an indirect comparison comparing topotecan plus cisplatin to paclitaxel plus cisplatin. However, the GOG-0169 trial excluded patients with prior chemotherapy (except as radiosensitisation), and therefore is not representative of the licensed population. Patients from GOG-0179 who had prior chemotherapy were excluded from the comparison, even so there were differences in the patient groups (fewer patients in GOG-0169 received radiosensitisation and they were unevenly divided between the two treatment groups). For overall survival, the indirect comparison showed non-significant results in favour of topotecan plus cisplatin compared to paclitaxel plus cisplatin; HR 0.72 (95% CI: 0.46, 1.15).

The manufacturer's original submission acknowledged a further direct comparison trial (GOG-0204). The trial was closed early as all experimental arms were unlikely to

demonstrate a significant advantage compared to paclitaxel plus cisplatin. The manufacturer did not formally include GOG-0204 in the submission based on different rationale, including early closure of the trial, and the evidence available in the public domain being very limited. The ERG argue that the population in trial GOG-0204 may be more representative of those in trial GOG-0179, and the two trials may be more comparable than GOG-0179 and GOG-0169. In response to the point for clarification raised by the ERG, the manufacturer reported direct and indirect comparisons, including data from GOG-0204. The direct comparison favoured paclitaxel plus cisplatin (HR: 1.27 (95% CI: 0.96, 1.69), while the pooled data using direct and indirect evidence favoured topotecan plus cisplatin; HR 0.98 (95% CI: 0.73, 1.23), but neither result was statistically significant (Manufacturer's Response (MR), pp.24) (see Appendix 1).

1.3 Summary of submitted cost effectiveness evidence

The manufacturer submitted two separate cost-effectiveness comparisons: a trial-based direct comparison between topotecan plus cisplatin and cisplatin monotherapy based on patient-level data from the GOG-0179 trial, considered by the manufacturer to be the primary analysis within their submission; and a model-based indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin, considered to be a secondary analysis. Justification for the analytic approaches employed (in particular the choice of a patient-level analysis as the main evaluation) was provided (Appendix 6 of the main submission (MS)). No further explanation was provided in response to a query by the ERG (MR, pp.43-47) (see Appendix 1).

In the base-case direct comparison, the ICER of topotecan plus cisplatin versus cisplatin monotherapy was £17,974 per QALY in the main licensed population, £10,928 per QALY in the cisplatin-naïve population (excluding stage IVB patients) and £32,463 per QALY in sustained cisplatin-free interval (SCFI) patients.

Results for the indirect comparison were only presented for a cisplatin-naïve population. In the base-case indirect comparison, paclitaxel plus cisplatin was dominated by topotecan plus cisplatin, which in turn had a cost-per-life-year-gained of £19,964 versus cisplatin monotherapy; where the hazard ratio used to calculate overall survival with paclitaxel plus cisplatin was taken from GOG-0204 (rather than derived from GOG-0169, as in the base-case), paclitaxel plus cisplatin was found to have a cost-per-life-year-gained of £982 versus topotecan plus cisplatin.

In response to the point for clarification raised by the ERG, the manufacturer submitted a revised indirect comparison incorporating HRQoL and a longer time horizon. Similar to the previous analysis, where the hazard ratio derived from GOG-0169 was employed, paclitaxel plus cisplatin was dominated by topotecan plus cisplatin, but where the hazard ratio from GOG-0204 was adopted paclitaxel plus cisplatin was found to have an ICER of £13,260 per QALY versus topotecan plus cisplatin.

The ERG made a number of revisions to this model, altering (among other things) the assumptions made over utility values, the costs of administering each treatment and the assumed number of vials of topotecan utilised per treatment cycle. Where the number of vials used was assumed to be minimised (maximised), the ERG found topotecan plus cisplatin to have an ICER versus cisplatin monotherapy of £26,778 (£34,327) in the cisplatin-naïve patient population and £58,872 (£73,833) in the full licensed population from GOG-0179. These ICERs were considered to be potentially conservative since no account was taken of the potential impact of dose reductions due to adverse events on the acquisition costs of the interventions. In order to consider the potential impact of dose reduction, the ERG employed a 'hybrid' approach combining estimates from the manufacturer's patient-level and the ERG's Excel analyses. Where wastage of vials was assumed to be minimised, the ICER of topotecan plus cisplatin versus cisplatin monotherapy fell to £19,815 in the cisplatin-naïve population and £53,868 in the licensed population; while assuming maximum wastage of topotecan, the ICER of topotecan plus cisplatin versus cisplatin monotherapy rose to £27,362 in the cisplatin-naïve population and £68,826 in the licensed population.

Where topotecan plus cisplatin, paclitaxel plus cisplatin and cisplatin monotherapy were compared in a fully incremental analysis, topotecan plus cisplatin was found to extendedly dominate paclitaxel plus cisplatin in most scenarios where the GOG-0169 hazard ratio was adopted, but was dominated by paclitaxel plus cisplatin in all scenarios where the GOG-0204 hazard ratio was adopted.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The main strength of the direct comparison is the *potential* for the results to have a very high internal validity due to the use of patient-level data from a recent, relevant and seemingly well-conducted trial (GOG-0179). This is only considered to be a

potential strength because the manufacturer did not provide in a timely manner the necessary code and datasets for the ERG to fully validate the programming of this comparison. A further strength of the direct comparison was the presentation of results for the main licensed population and a series of subgroups within that, highlighting the population gaining most benefit from treatment, and allowing variability in the cost-effectiveness estimates to be considered. However, these populations are subgroups of the trial population and the limitations of subgroup analyses should be borne in mind.

The main strength of the indirect comparison is a relatively high degree of transparency within the submitted Excel-model and a high degree of consistency between the electronic model and the submitted report.

1.4.2 Weaknesses

The lack of transparency regarding the literature search and rationale for exclusion of potentially relevant trials was a potential limitation in the main submission. This was not satisfactorily addressed in the manufacturers' response document.

It is acknowledged by the ERG that there is paucity in the evidence available for the clinical effects of topotecan plus cisplatin and the effects of palliative treatment in general (including various off-license drugs regularly used in UK clinical practice) for women with advanced and recurrent carcinoma of the cervix. One of the main weaknesses with the direct comparison was that results from GOG-0204 were not formally included in the submission. Further results will shortly be available from GOG-0204, but these were not available at the time of the manufacturer's submission.

For the indirect comparison, it is not clear that a comprehensive network of evidence was investigated. Potentially relevant studies were excluded by the manufacturer as they were not licensed for use in this population. However, the comparator selected for the indirect comparison (ie. paclitaxel plus cisplatin) is also not licensed. The rationale for this was not satisfactorily explained.

The analysis submitted for the cost-effectiveness evidence was incomplete and required extreme clarification. The lack of transparency regarding the programming of the direct comparison is a significant weakness – the SAS code is lengthy, poorly annotated, was submitted incomplete (in a non-executable form) with important sections of code missing (which were not provided in a timely fashion upon request

from the ERG). There is evidence that the manufacturer incorrectly applied an algorithm to convert FACT-G scores elicited during the GOG-0179 trial into utility weights (inexplicably this important algorithm was not reproduced in the submission) and concerns exist over the potential for double counting the impact of mortality. Both of these issues may potentially over-estimate the incremental QALY gains associated with topotecan plus cisplatin. The direct model also suffers from a lack of external validity as it makes no comparison between topotecan plus cisplatin and other relevant treatment comparators other than cisplatin monotherapy.

The most serious weakness in the indirect comparison initially submitted was that it neglected to consider HRQoL, reporting life-years-gained instead of QALYs – this was rectified following a request from the ERG (MR, pp.36). Other potential weaknesses were that results were only presented for a single population (cisplatin-naïve patients) and the model was not probabilistic, so that uncertainty surrounding the cost-effectiveness results could not be appropriately quantified.

Both comparisons also failed to properly justify a number of assumptions over costs, including the cost of administering treatments, the number of vials of topotecan needed per cycle and the costs of adverse events – all of these were considered for revision by the ERG (Section 6).

1.4.3 Areas of uncertainty

Response rates for cisplatin have been reported to range from 20% to 30% (Devita et al, 1997)[2]. The response rates in the cisplatin monotherapy arms in trials GOG-0169 and GOG-0179 were reported to be 19% and 13% respectively. Patients' prior cisplatin use and duration of response to prior platinum therapy could influence the clinical and cost-effectiveness of topotecan plus cisplatin (NICE draft remit, pp.11).

The ERG's clinical advisor also confirmed that if relapse occurs within the area previously targeted for radiation (ie. the pelvic area) then generally speaking, any drug treatments used are likely to produce a poor response rate, but if the disease relapses outside the area radiated, response rates are generally more positive. Patients relapsing within six to 12 months will not respond to cisplatin monotherapy or combination therapy (and taxanes or topotecan alone are then considered). Such details were not reported in the manufacturer's submission, thus the reason(s) for low response rates remain(s) unclear.

There is also uncertainty surrounding the population(s) that will benefit most from treatment with topotecan plus cisplatin. The number of patients who have received chemoradiation is likely to increase in the future, thus the number of cisplatin-naïve patients will diminish. This raises the question of the applicability of the results to current and future clinical practice. It is unclear whether patients receiving cisplatin as a radiosensitiser should still be considered as cisplatin naïve unlike those treated with cisplatin chemotherapy (MS, pp.26). Limitations in the submitted evidence impacts strongly on the generalisability of the manufacturer's conclusions to clinical practice (ie. "one size doesn't fit all") [Royal College of Physicians – NICE draft remit], particularly in patients with greater exposure to prior chemoradiotherapy with cisplatin (Hirte et al, 2007)[3].

The duration of the cisplatin free interval was not made explicit in the main submission, and the ERG requested further clarification for the assumption that this should be at least 180 days. The manufacturer responded by presenting an unplanned sub-group analysis, giving median survival in patients with prior cisplatin chemoradiotherapy and patients with recurrence less than 180 days after chemo-radiotherapy with cisplatin, which showed no significant difference between treatment arms. Patients with recurrence after 180 days showed greater benefit with topotecan plus cisplatin.

Both economic submissions are subject to significant uncertainty over the utility values and cost assumptions adopted by the manufacturer, and this uncertainty feeds into the results of the subsequent analyses.

In the direct model, it is not clear that the process used to convert FACT-G scores to utility weights is appropriate, nor is it clear that the alternative utility scores adopted by the manufacturer in a sensitivity analysis (and the revised indirect comparison) are appropriate since they were derived from a study into metabolic breast cancer (Brown 1998)[15] and not cervical cancer. As noted in Section 1.4.2, a number of assumptions over costs are not properly justified.

The manufacturer states that "it is noted in the SmPC that accurate assessment of PS at the time of therapy is important to ensure that patients have not deteriorated to PS3". Although the manufacturer reports patient PS status at baseline, it is not clear whether this was also recorded at subsequent treatment cycles to assess whether patients may have deteriorated over the course of treatment.

1.5 Key issues

Further trials or the implementation of registries are required to establish the efficacy and safety of topotecan plus cisplatin, and future trials should establish the efficacy of topotecan plus cisplatin relative to other treatments that are regularly used in this indication within UK clinical practice, including drugs that are not licensed.

In terms of the direct comparison, the key issues relate to the paucity of evidence, the limited use of results from GOG-0204, and the handling and reporting of quality of life data and whether the results are representative of the whole patient experience.

Key issues in relation to the direct comparison, relevant to the economic evaluation, are the appropriateness of the mapped utility values adopted, the reasonableness of the costing assumptions, the external validity of an analysis with only a single comparator, and (perhaps most importantly) the validity and transparency of the SAS analysis – the ERG was unable to replicate the manufacturer's analysis in the time available due to missing code and missing datasets, severely hampering the ERG's ability to thoroughly validate the comparison made.

In terms of the indirect comparison, the ERG believes that a potentially relevant network of indirect evidence has not been fully explored (see Section 4.1); although the ERG does acknowledge that the quality of such evidence would be limited.

Additional key issues in relation to the indirect comparison, relevant to the economic evaluation, were the lack of HRQoL considerations (now rectified by the manufacturer), the appropriateness of the metastatic breast cancer utility values adopted as a proxy in the absence of more suitable cervical cancer values, the reasonableness of the costing assumptions (particularly surrounding the cost of administering topotecan, the number of vials of topotecan required and the cost of adverse events), and the appropriate source of the hazard ratio used to estimate survival for paclitaxel plus cisplatin – deriving this hazard ratio from GOG-0169 favours topotecan plus cisplatin, while deriving it from GOG-0204 favours paclitaxel plus cisplatin.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer provides a clear summary of the different stages of carcinoma of the cervix and the difference in baseline characteristics between those newly diagnosed with stage IVB disease and those with recurrent disease.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer provides a reasonable overview, although certain specific points could be questioned. The decision problem addressed in the manufacturer's submission specified the relevant direct comparator to be cisplatin monotherapy and the relevant indirect comparator to be paclitaxel plus cisplatin, in accordance with the IMS Oncology Analyzer dataset (quarter 3 in 2004 to quarter 3 in 2008) and discussions with clinical experts from Scotland and Wales, (MS, pp.11). It was unclear whether the numbers reported by the IMS database were based on UK data only or included data from the five key European markets. The manufacturer provided revised estimates from Q3 2006 until Q3 2008 (as requested by NICE, MR, Appendix 1 pp.29), and confirmed that the total number of UK cervical patients collected was 229 patients, 30 of whom were eligible to receive topotecan.

The clinicians consulted by the manufacturer confirmed the pattern of treatment identified by the IMS database, but stated that the use of paclitaxel plus cisplatin may be higher than suggested, which questions whether the data presented is truly representative of UK clinical practice. Carboplatin plus paclitaxel appears to be the second most frequently used treatment in the population of interest, and, according to the ERG's clinical advisor, may be better tolerated than cisplatin and may produce better response rates. However, the manufacturer reasonably justifies the exclusion of this combination as a comparator due to the limited evidence available.

Topotecan plus cisplatin is licensed and indicated for a small population amounting to an estimated 470 women per year (MS, pp. 29). The main submission (Appendix 4 of the MS, pp.175) states that the populations identified by the IMS Oncology Analyzer were mostly women with stage IV disease (not limited to stage IVB) who had received chemotherapy after presenting with disease, and a small number of

women with recurrent disease who had received chemotherapy after radiotherapy, or after non-cisplatin containing chemoradiotherapy. None of the patients with recurrent disease had received prior chemotherapy more than 180 days after receiving cisplatin-based chemoradiotherapy. Thus questioning whether the population referred to in the IMS database reflects those included in the clinical trials.

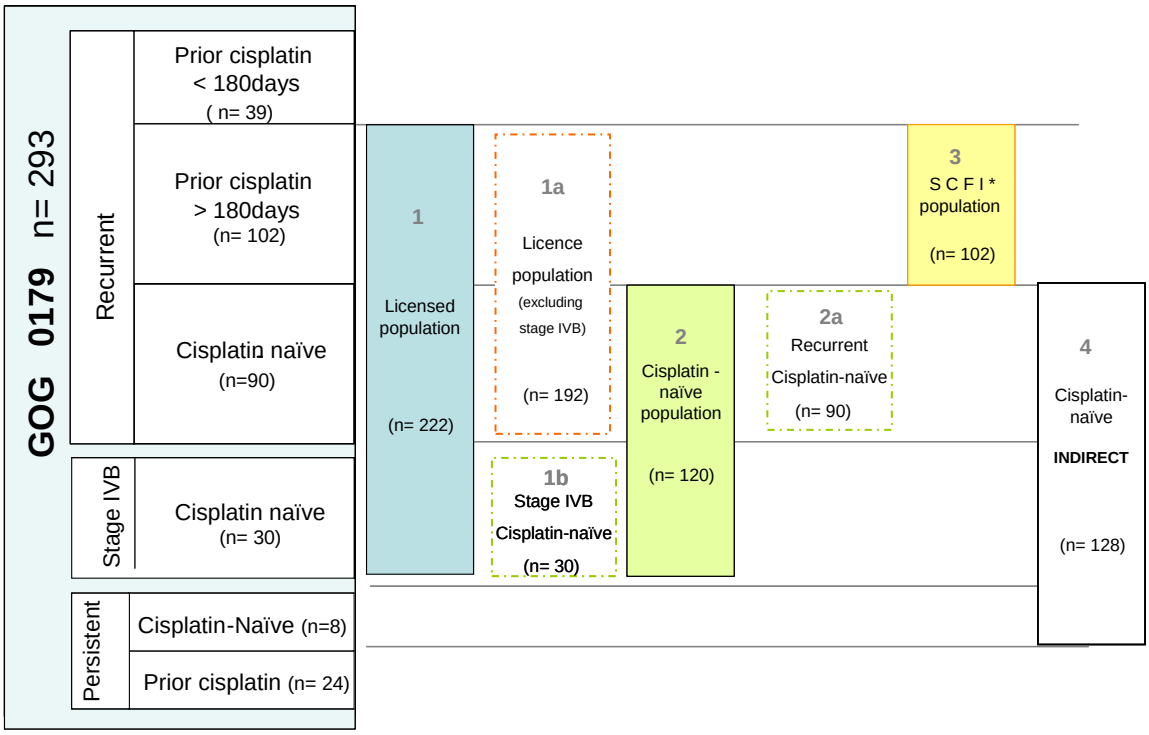
The manufacturer's rationale for not including other treatments identified by the IMS database was not clearly justified. The manufacturer states that "due to the limited and inconsistent use of other treatments they are not considered as key comparators in this appraisal of topotecan". However, according to the data presented in the IMS database, the use of topotecan plus cisplatin is equal to the use of most other treatments, which were not considered in the submission (MR pp.11 and 25). Although the numbers on which this is based are very small.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The manufacturer states that the population of interest is "women with carcinoma of the cervix recurrent after radiotherapy and patients newly presenting with stage IVB disease" (MS, pp.10). This reflects the licensed population specified in the final scope issued by NICE and the marketing license (ie. excluding women with persistent disease and women with no prior exposure to cisplatin).

Figure 3.1.1: Schematic of study population and subgroups analysed in the manufacturer's submission (taken from the MS, pp.13, 18, 46, 77 and 85).



* Sustained cisplatin-free interval

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
   2b. Stage IVB patients

3. Patients with a sustained cisplatin-free interval (SCFI; prior cisplatin >180 days)

4. A further subgroup was analysed specifically for an indirect comparison of topotecan plus cisplatin versus paclitaxel plus 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).

In response to the ERG's Points for Clarification requesting further details on patient characteristics, the manufacturer provided data on prior radiotherapy and cisplatin use for GOG-0179, but data for GOG-0169 were not available (MR, pp. 24). For ease of comparison, patient characteristics for GOG-0179, GOG-0169 and GOG-0204 are presented together in Table 1 (see Section 4.1.3 for more details of the trials).

The indirect comparison trials (GOG-0179 and GOG-0169) included women outside the licensed indication (ie. women with persistent cervical cancer). It was not possible to separate these women from the ITT population in GOG-0169 as individual patient level data were not available, although in GOG-0179 there were only eight women with persistent disease. Further differences in the trial populations were identified in the inclusion criteria; patients with prior chemotherapy were eligible for inclusion in GOG-0179 but not in GOG-0169 (except when chemotherapy was used for radiosensitisation). Fewer patients had received chemotherapy as a radiosensitiser in GOG-0169 (27%) compared to GOG-0179 (approximately 60%) and distribution among treatment arms was not equal. Furthermore, it was unclear how many patients received cisplatin as a radiosensitiser in GOG-0169.

GOG-0204 also includes a proportion of women with persistent disease and it is not possible to separate these patients from the licensed population, as individual patient data were not available. Similar to GOG-0169, women who had previously received chemotherapy were not eligible for inclusion, unless given concurrently with radiation. However, the proportion of patients who previously received cisplatin as a radiosensitiser (approximately 70%) appeared more comparable with the population included in GOG-0179, and more representative of the UK population, given the increasing number of patients receiving this treatment. Data on cisplatin free interval were not available and it was therefore unclear whether patients had been cisplatin-free for more than or less than 180 days.

3.2 Intervention

The NICE final scope indicates the relevant intervention to be topotecan plus cisplatin.

The manufacturer recommends that topotecan is administered in combination with cisplatin; 0.75 mg/m^2 per day of topotecan, administered as 30 minute intravenous infusion on days 1, 2 and 3, with one dose of 50 mg/m^2/day of cisplatin administered on day one following topotecan. Treatment is repeated every 21 days for six cycles

or until disease progression (MS, pp.8). The Summary of Product Characteristics (SmPC) states that, topotecan should not be re-administered unless the neutrophil count is more than or equal to 1.5 x 10^9/1, the platelet count is more than or equal to 100 x 10^9/1, and the haemoglobin level is more than or equal to 9g/dl (after transfusion if necessary). Standard oncology practice for the management of neutropenia is either to administer topotecan with other medications (eg. G-CSF) or to dose reduce to maintain neutrophil counts.

The ERG's clinical advisor confirmed that topotecan plus cisplatin is regularly used in clinical practice, but treatment is determined on a case-by-case basis.

Table 3.2.1: Patient characteristics for direct and indirect comparison

	GOG-0179 Long et al (2005)[4]		GOG-0169 Moore et al (2004)[5]		GOG-0204 Monk et al (2008)[6]			
Treatment arms	Cisplatin (n=146)	Topotecan + cisplatin (n=147)	Cisplatin (n=134)	Cisplatin + paclitaxel (n=130)	Cisplatin + paclitaxel (n=103)	Cisplatin + vinorelbine (n=108)	Cisplatin + gemcitabine (n=112)	Cisplatin + topotecan (n=111)
Inclusion criteria								
Neutrophil count (uL)	>1,500		>1,500		1,500			
Platelet count (uL)	>100,000		≥100,000		100,000			
Serum creatinine level (mg/dL)	<1.5		≤2.0		1.5			
Liver function								
Bilirubin	<1.5 x normal		≤1.5 x institutional norm		NR			
Asparate aminotransferase (AST)	<3 x normal		≤3 x institutional norm		NR			
Age (years)								
Median (range)	48 (27-76)	46 (22-84)	46 (22-84)	49 (21-77)	50	49	45	48
Number of cycles of therapy								
Median (range)	3 (0-7)	4 (0-7)	4 (0-11)[a]	5 (0-11)[a]	NR	NR	NR	NR
Not treated	2	7	4	1				
Performance status								
0: fully active (%)	68 (47)	69 (47)	64 (48)	59 (45)	(55)	(53)	(49)	(53)
1: restricted physically (%)	66 (45)	66 (45)	59 (44)	54 (42)	[(45)]	[(47)]	[(51)]	[(47)]
2: unable to work (%)	12 (8)	12 (8)	11 (8)	17 (13)	NE	NE	NE	NE
Race/ethnicity								
White (%)	108 (74)	105 (71)	92 (69)	75 (58)	(73)	(73)	(71)	(74)
Black (%)	23 (16)	29 (20)	29 (22)	47 (36)	NR	NR	NR	NR
Other (%)	15 (10)	13 (9)	13 (<10)	8 (6.5)	NR	NR	NR	NR
Disease stage								
Stage IVB (%)	16 (11)	14 (10)	NR	NR	(18)	(17)	(20)	(18)
Persistent (%)	12 (8)	20 (14)	NR	NR	(82)[b]	(83)[b]	(80)[b]	(82)[b]
Recurrent (%)	118 (81)	113 (77)	NR	NR				
Time to 1st recurrence (months)	NR	NR	NR	NR	16.9	17.1	14.0	18.6

Table 3.2.1: Patient characteristics for direct and indirect comparison (continued)

	GOG-0179 Long et al (2005)[4]		GOG-0169 Moore et al (2004)[5]		GOG-0204 Monk et al (2008)[6]			
Treatment arms	Cisplatin (n=146)	Topotecan + cisplatin (n=147)	Cisplatin (n=134)	Cisplatin + paclitaxel (n=130)	Cisplatin + paclitaxel (n=103)	Cisplatin + vinorelbine (n=108)	Cisplatin + gemcitabine (n=112)	Cisplatin + topotecan (n=111)
Site of disease								
Pelvic (%)	NR	NR	66 (49)	52 (40)	NR	NR	NR	NR
Distant (%)	NR	NR	49 (37)	61 (47)	NR	NR	NR	NR
Both (%)	NR	NR	19 (14)	17 (13)	NR	NR	NR	NR
Cell type								
Squamous (%)	121 (83)	128 (87)	NR	NR	81 (79)	80 [74]	[88] (79)	[85] (77)
Adenosquamous (%)	11 (8)	5 (3)	NR	NR	NR	NR	NR	NR
Adenocarcinoma (%)	9 (6)	9 (6)	NR	NR	NR	NR	NR	NR
Other (%)	5 (3)	5 (4)	NR	NR	NR	NR	NR	NR
Prior treatment								
Prior cisplatin (%)	82 (56)	83 (56)	NE	NE	NE	NE	NE	NE
No prior cisplatin (%)	64 (44)	64 (44)	NE	NE	NE	NE	NE	NE
Prior radiotherapy (%)	NR	NR	123 (92)	118 (91)	NR	NR	NR	NR
Prior chemoradiation/CCRT (%)	NR	NR	40 (30)	31 (24)	[72] (70)[c]	[79] (73)[c]	[72] (64)[c]	[81] (73)[c]

[a] number of cycles of protocol therapy
[b] Total number of patients with persistent or recurrent disease
[c] CCRT (combination chemotherapy and radiation therapy)

NB: cisplatin represents only one of four chemotherapeutic agents used alone or in combination as a radiation sensitiser, the other three agents are; fluorouracil, hydroxyurea, and navelbine.
[ ] = calculated
NR = not reported
NE = not eligible

3.3 Comparators

The final scope issued by NICE specifies platinum-based single and combination chemotherapy regimens to be the relevant comparators. The manufacturer identifies cisplatin monotherapy as the relevant direct comparator and paclitaxel plus cisplatin as the relevant indirect comparator.

The manufacturer states that cisplatin is administered as an intravenous infusion on day 1 at a dose of 50mg/m^2/day and repeated every 21 days for six cycles or until progressive disease (MS, pp.8). The SmPC states that the usual dose regimen for cisplatin monotherapy is 50-120 mg/m^2 by infusion once every 3-4 weeks or 15 - 20 mg/m^2 by infusion daily for 5 consecutive days, every 3-4 weeks. There is no SmPC for the administration of paclitaxel as this is not licensed in the population of interest.

As discussed in Section 2.2, the manufacturer identifies the regimens currently used in the UK, but did not appropriately justify the exclusion of other potentially relevant comparators used as [in]frequently as cisplatin plus topotecan, such as cisplatin plus 5-fluorouracil (5-FU) and cisplatin plus mitoxantrone. Inclusion of GOG-0204 would also have increased the number of potential comparators and broadened the indirect network of evidence, which, it could be argued, would more accurately represent current clinical practice (see Figure 4.1.3.1, Section 4.1.2). A peer reviewed journal article reporting results from GOG-0204 is due to be published in May 2009 (personal communication with Dr B Monk, 24th April 2009).

3.4 Outcomes

The outcomes considered in the manufacturer's submission reflected those specified in the NICE final scope: overall survival (OS) (all-cause mortality), progression free survival (PFS), response rates (complete response, and partial response), adverse effects of treatment, and health-related quality of life (using FACT-G).

OS was the primary endpoint, and was defined as the time from randomisation until death in the intention-to-treat (ITT) population, or until date of last contact, for patients who were still alive at this point. PFS was defined as the minimum amount of time from randomisation until clinical progression, death, or date of last contact. The ERG's clinical advisor highlighted the importance of PFS as this indicates that symptoms are palliated - overall survival does not necessarily mean good quality of life.

The manufacturer states that topotecan plus cisplatin should be administered intravenously for six cycles or until disease progression. Outcome assessments were recorded at four different time points: prior to randomisation, prior to cycle two, prior to cycle five, and nine months post-randomisation.

3.5 Time frame

Follow-up data were available for a 36-month time period in GOG-0179 and over a 24-month period in GOG-0169. For the patient-level economic analysis, the manufacturer adopted a time horizon of 36-months consistent with the follow-up period in GOG-0179. This was considered by the manufacturer to be an appropriate time frame for the economic analysis since the majority of patients in both treatment arms had died and hence most of the costs and outcomes had been incurred. For the main indirect comparison, only data for the first 24 months were considered for GOG-0179 for consistency with GOG-0169. In response to the ERG's Points for Clarification, the manufacturer states that the indirect comparison with GOG-0169 using a 24- month time horizon would potentially underestimate the cost-effectiveness of topotecan plus cisplatin, while comparison with GOG-0204 using this time horizon would potentially overestimate the cost-effectiveness of topotecan (MR, pp. 25). In the MR the time horizon of the indirect analysis was extended to 36-months to minimise these potential biases.

3.6 Other relevant factors

The ERG's clinical advisor highlighted other important factors that need to be taken into consideration, including patient's renal function and performance status, and where the patient lives (in terms of convenience and costs incurred when travelling back and forwards for treatment).

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

It is unclear from the manufacturer's submission whether a complete network of evidence has been identified and investigated. GOG-0179 was a generally well conducted RCT and it was reasonable for the manufacturer to use this as the direct comparison. However, head-to-head comparisons are also available from GOG-0204, and the manufacturer's rationale for not formally including this trial does not seem justified. A direct comparison of topotecan plus cisplatin versus pactlitaxel plus cisplatin would have been preferable to the indirect comparison used, particularly given the differences in patient populations between GOG-0169 and GOG-0179. The inclusion of trial GOG-0204 would also have increased the number of potential comparators and might enable the network of indirect evidence to be expanded. Figure 4.1.3.1 shows the network of evidence and potentially relevant comparators. The connector lines indicate which treatment arms were compared in the three trials GOG-0179, GOG-0169 and GOG-0204. Additional trials with at least one treatment arm in common with any of the treatments in the figure could be used to expand the network of evidence. From this it is clear that including GOG-0204 will increase the number of direct comparators and will also potentially expand the network of indirect evidence.

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The manufacturer's submission described the search strategy used to identify published studies of topotecan and comparator products in the treatment for recurrent or stage IVB carcinoma of the cervix. The submission stated that a general search strategy was presented in Appendix 2. Unfortunately, the manufacturer's original strategies did not provide sufficient detail and the ERG could not replicate the clinical and cost-effectiveness searches. The submission continues to explain that searches were undertaken to update an existing systematic review by The Cancer Care Ontario group (Hirte et al, 2006)[7]. The submission also made it clear that this strategy was used to identify comparator studies (RCTs of platinum-based chemotherapies for the treatment of women with recurrent or stage IVB cervical cancer).

In response to the ERG's Points for Clarification, the manufacturer supplied detailed search strategies for most of the relevant databases (MR, pp.1-9). The ERG's attempts to reproduce the searches raised a number of issues, which are detailed in Appendix 2 of this document.

The ERG gained access to the full search strategy provided by the Cancer Care Ontario group, and critically appraised the published systematic review (Hirte et al, 2007)[3]. In general, the Cancer Care Ontario systematic review was of poor quality and it is unclear whether the search would have identified all potentially relevant comparator studies (see Appendix 3 of this document).

The manufacturer's search strategy was poorly reported in the original submission and despite requests for clarification it has not been possible to reproduce the searches accurately. However, the search strategies provided in response to our requests appear appropriate. The ERG replicated the search and did not identify any additional relevant RCTs evaluating topotecan plus cisplatin to inform the direct comparison. However, given the limitations of the searches, the existence of additional RCTs which might inform an indirect comparison cannot be ruled out.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The original submission states that studies were eligible for inclusion if they were RCTs, systematic reviews or meta-analyses comparing topotecan plus cisplatin with a platinum-based single or combination chemotherapy regimen in female patients of any race with cancer of the cervix recurrent after radiotherapy or stage IVB disease.

A flow diagram of the number of studies included and excluded at each stage of the systematic review was presented in the main submission (pp. 34), but it was unclear which studies had been excluded or the reasons for their exclusion. The manufacturer was asked to provide transparent rationale for study selection, including a comprehensive list of trials considered at the data extraction stage, and where relevant, the reasons for exclusion, particularly the reasons for exclusion of some potentially relevant studies identified in the Cancer Care Ontario systematic review[7], but not mentioned in the manufacturer's submission.

The manufacturer confirmed the original inclusion/exclusion criteria, but also added that only Phase III RCTs were eligible, and that exclusion criteria for the indirect comparisons included the evaluation of unlicensed comparators and the use of only one treatment arm. Such criteria would disregard trial GOG-0169 as the indirect comparison as paclitaxel plus cisplatin is not licensed in this setting.

The manufacturer did not state how studies were selected for inclusion in the submission (eg. how many reviewers were involved), or how validity assessment and data extraction were performed.

4.1.3 What studies were included in the submission and what were excluded.

Included Studies

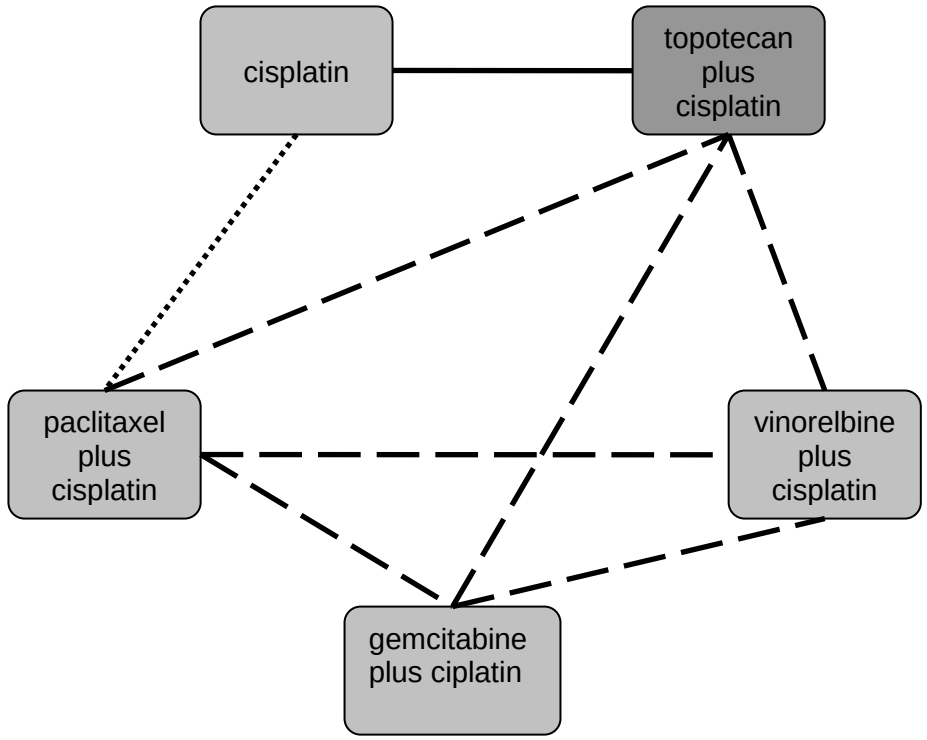
The main RCT used for the direct comparison (GOG-0179) compared topotecan plus cisplatin with cisplatin monotherapy. This trial originally included a third treatment arm; methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), but this arm was closed by the Data Safety Monitoring Board after four treatment-related deaths.

The main RCT used for the indirect comparison (GOG-0169) compared paclitaxel plus cisplatin with cisplatin monotherapy in patients with stage IVB, recurrent or persistent carcinoma of the cervix.

The manufacturer refers to GOG-0204 as additional evidence. This trial compared paclitaxel plus cisplatin, gemcitabine plus cisplatin, topotecan plus cisplatin, and vinorelbine plus cisplatin. The data presented by the manufacturer were limited (MS, pp.33), and the ERG requested clarification on why the available data presented by Monk et al (2008)[6] were not reported (MR, pp.24).

The manufacturer was also asked to clarify the inclusion of trial GSK-CRT-234 (MS, pp. 35) and reasons why no other phase II safety and efficacy studies of topotecan were mentioned, particularly trials that were of patients with stage IVB carcinoma of the cervix, who were not included as part of GSK-CRT-234 (MR, pp. 10). The manufacturer included this single arm Phase II study as supporting evidence, but did not provide justification for its inclusion as it did not meet the inclusion criteria, neither did they provide rationale for not including other similar, potentially relevant Phase II studies.

Figure 4.1.3.1: Network of evidence



Key to trials:

GOG-0179

GOG-0204

GOG-0169

Connector lines indicate which treatment arms were compared in the three trials GOG-0179, GOG-0169 and GOG-0204. Additional trials with at least one treatment arm in common with any of the treatments in the figure could be used to expand the network of evidence.

Excluded Studies

The manufacturer was asked to provide justification for not including/referring to several potentially relevant studies mentioned in the Cancer Care Ontario systematic review[7] (MR, pp. 10-14). Table 4.1.3.1 reports the manufacturer's reasons for exclusion for these studies, along with the GOG-0204 trial.

Although the ERG acknowledges that some of these studies are of poor quality[8-10], excluding these studies based on the rationale that the treatments are not licensed in cervical cancer is not justified given that GOG-0169 uses paclitaxel which is not licensed in this population.

Table 4.1.3.1: Reasons why studies were excluded from the indirect comparison analyses

Author	Reason for exclusion from indirect comparison analysis
Studies originally identified in the CCO systematic review	
Vermorken	BEMP not licensed in cervical cancer
Omura	Combination cisplatin + mitolactol and cisplatin + ifosfamide not licensed in cervical cancer
Garin	Irinotecan alone or in combination with cisplatin not licensed in cervical cancer
Alberts	Cisplatin +mitomycin-C and MVBC not licensed in cervical cancer
Cadron	PIF not licensed in cervical cancer, early closure, only 21 patients
Bloss	CIB and Cisplatin + ifosfamide not licensed, no common cisplatin alone arm
Bezwoda	Cisplatin + MTX not licensed, no common cisplatin alone arm
McGuire	Comparators not licensed in cervical cancer
Lira-Puerto	Comparators not licensed in cervical cancer
Thomsen	Comparators not licensed in cervical cancer
Studies identified by handsearching	
Monk	Early closure and data not yet mature

Although it is acknowledged by the ERG that study details for GOG-0204 are somewhat limited, data on overall survival and PFS were reported in Monk (2008)[6] and the omission of this data from the manufacturer's submission was not justified. Results from GOG-0204 are due to be published in full in a peer reviewed journal in May 2009, and may be useful to aid decision-making.

On-going Studies

The manufacturer reports that there are currently no ongoing clinical trials for topotecan in the UK for the proposed cervical indication (MS, pp. 7). A list of ongoing trials is presented (MS, pp 36, Table 1), and the ERG consulted the clinical trials website (www.clinicaltrials.gov), which indicated the following ongoing trials (all non-UK) involving topotecan that may be useful in contributing to the wider network of evidence:

- NCT00803062 (Phase III paclitaxel and cisplatin or topotecan with or without bevacizumab for the treatment of patients with stage IVB, persistent or recurrent cervical cancer). Gynaecological Oncology Group (National Cancer Institute) (4th December 2008).

- NCT00003065 (Phase II topotecan plus paclitaxel in treating patients with recurrent or metastatic cancer of the cervix. Herbert Irving Comprehensive Cancer Centre (1st November 1999).

- NCT00807079 (Phase I/II carboplatin plus topotecan in treating patients with relapsed or metastatic cervical cancer). Association de Recherche sur les Cancers dont Gynecologiques at Hopital de l'Hotel Dieu (10th December 2008).

The ERG also identified a Cochrane Collaboration Protocol (2009)[11], first published on the 18th April 2007, the objectives of which are to establish the effectiveness of single agent and combination chemotherapy in the treatment of patients with metastatic or recurrent cervical cancer. The ERG contacted the authors of the protocol and the review is due to be completed in June/July 2009.

4.1.4 Details of any relevant studies that were not included in the submission?

In response to the ERG's request for clarification and justification on study selection the the systematic review, the manufacturer presented key result data for studies evaluating unlicensed comparators (MR, pp. 13-14).

4.1.5 Description and critique of manufacturers approach to validity assessment

Assessment validity for GOG-0179 and GOG-0169 was generally adequate and was described in terms of allocation concealment, randomisation technique, justification of sample size, length of follow-up, blinding of outcome assessors, parallel/cross-over design, whether conducted in the UK/comparability with the UK, consistency of dosing regimens with the Summary of Product Characteristics (SPC), comparability of study groups, and appropriateness of statistical analyses, including the use of intention-to-treat (ITT) analysis.

GOG-0169 and GOG-0179 were conducted in the United States. It is unclear how comparable clinical practices are in the two countries, and therefore how generalisable the results are to a UK population.

The manufacturer acknowledges that the prevalence of prior cisplatin use and the length of the cisplatin-free interval in England and Wales are the main factors to potentially influence the efficacy of paclitaxel or topotecan plus cisplatin versus cisplatin monotherapy, compared with the results of the ITT populations from the respective studies. It is unclear what the implications are, again making it unclear how generalisable the results are to the UK population.

The ERG acknowledges the difficulties associated with blinding of such studies due to the scheduling of the treatment, but the potential for bias from open-label designs remains.

4.1.6 Description and critique of manufacturers outcome selection

To a certain extent, the manufacturer's main submission addresses each of the outcomes specified in the NICE final scope.

The primary outcome measure was overall survival (all-cause mortality), which measured survival (in months) from randomisation until death, or until the last date of contact in the ITT population.

Progression-free survival (PFS) was assessed as a secondary endpoint. After discussion with the ERG's clinical advisor, PFS was identified as a particularly important outcome in this population, as this suggests stable disease and palliated symptoms and therefore better QoL (overall survival may not mean good QoL). The ERG subsequently requested that the manufacturer provide comparisons for PFS (see Section 4.2.1, Tables 3 and 4). Response rates, health-related quality of life, and adverse events were also assessed as secondary outcomes. Although appropriate health-related quality of life measures were used, it is unclear whether the results truly reflect the impact on patient quality of life. There are concerns over the assumptions made for QoL. Quality of life data were obtained, where possible, from patients who were no longer receiving treatment in the trial and patients who were receiving palliative care.

Further limitations with the QoL reported for patients in GOG-0179 include the potential for bias in the results presented. Patients who completed the fourth QoL assessment at nine months post-randomisation may represent patients achieving a better clinical response, and by contrast, patients who failed to complete the final assessment may have been non-responders to chemotherapy with worse QoL. Data on QoL nine months post randomisation were requested, but the manufacturer did not have access to this information, and the ERG cannot therefore comment on the effects of treatment on longer term quality of life.

4.1.7 Describe and critique the statistical approach used

The manufacturer includes subgroups of the licensed population, as described in Section 3.1 and illustrated in Figure 3.1.1. There may be certain issues when this type of analysis is performed; the two main issues being the loss of statistical power and multiple testing, and this is discussed in more detail in Section 5.2.1.3 of this report.

The manufacturer states that "for time-to-event endpoints, the last data 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" (MR, pp.43). There are concerns with missing data due to

withdrawals, as this can introduce potential bias to the statistical analysis for complete or available data. The ERG requested data on censored patients. Reasons for censoring in study GOG-0179 were not clear as data were not available to the manufacturer. However, more patients in the topotecan plus cisplatin arm were censored (29; 19.7%) compared to cisplatin monotherapy (17; 11.6%) (MR, pp.18-19).

These issues are discussed in greater detail in Section 5.2.1.4.

4.1.8 Summary statement

The manufacturer does not appear to present a complete picture of the evidence available. The ERG were unable to replicate the search strategies presented in the original submission and response document, and the systematic review undertaken by the Cancer Care Ontario group was not of high quality, which means that potentially relevant studies may have been missed. Furthermore, the rationale presented for inclusion and exclusion criteria were not justified.

Direct Comparison

For the direct comparison, the main RCT included (GOG-0179) appeared to be a generally well conducted study. However, only restricted data were presented for GOG-0204, which was also a head-to-head comparison of relevant treatments, and the trial was not formally included in the analysis.

Indirect Comparison

For the indirect comparison, there are limitations in terms of patient differences between GOG-0179 and GOG-0169 and how representative these patients are to current and future populations. In addition, the omission of GOG-0204 limits the number of available comparators and precludes the potential expansion of the network of indirect evidence.

4.2 Summary of submitted evidence

4.2.1 Summary of results

GOG-0179

The manufacturer reported a longer median overall survival for treatment with topotecan plus cisplatin compared to cisplatin monotherapy (GOG-0179): 9.4 versus

6.5 months, HR 0.76 (95% CI: 0.59, 0.98, p=0.033), and longer progression-free survival with topotecan plus cisplatin versus cisplatin monotherapy: 4.6 versus 2.9 months, HR 0.76 (95% CI: 0.60, 0.97, 0.03) (MR, pp.21-22). The safety profile of topotecan plus cisplatin was reported to be predictable and manageable, and there was reportedly no evidence to suggest that QoL and adverse events changed over time across treatment groups, after adjusting for baseline scores and age at entry. However, there were four treatment related deaths with this combination therapy.

Median survival was greater for both treatment groups in patients who had not received prior cisplatin radiotherapy (cisplatin-naïve) compared to patients who had previously received cisplatin radiotherapy. However, this subgroup of patients may be diminishing:

The manufacturer states that due to the 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 (MS, pp.78). This was confirmed by the ERG's clinical advisor. Although the manufacturer reports median overall survival and progress-free survival in the ITT population for GOG-0179 (including licensed and unlicensed populations), the patients of greatest interest, in view of the above, would be the SCFI population. The subgroup analysis for this group of patients shows no significant statistical differences between the two treatment groups (see Table 4.2.1.1).

Response rates, toxicities, and health-related quality of life (HRQoL) were assessed as secondary outcome measures. Response rates were greater with topotecan plus cisplatin (29%) compared to cisplatin monotherapy (13%) (p=0.004). The ERG requested additional QoL data, including descriptive statistics and data for each of the FACT-G subscales and data on the UNISCALE. Descriptive data in terms of compliance rates for QoL scores were reported (see Table 4.2.1.2), which shows the large decrease in compliance rates prior to cycle five.

The manufacturer's response document stated that they did not have access to data for FACT-G subscales (physical well-being, functional well-being, social well-being and emotional well-being), thus this data is not presented. There were concerns over the BPI scores presented in the response document (MR, pp.16), which did not appear to reflect those figures reported in the original submission (MS, pp.52, Figure 11).

The manufacturer lists the most common toxicities associated with topotecan in trial GOG-0179 and reports that most complications were manageable with antibiotics, protocol specific dose modifications, and the addition of G-CSF (filgrastim) on subsequent treatment cycles (MS, pp.19). The ERG's clinical advisor highlighted that toxicities are usually cumulative and patients with PS2 are difficult to manage with cisplatin plus topotecan as they experience sickness and lethargy which has negative effects on QoL. Similarly, QoL is very important and if a patient is not tolerating a drug and their QoL is suffering, then they are reassessed after three cycles and judgements for treatment are made on a case-by-case basis.

The manufacturer concludes that topotecan plus cisplatin is an effective treatment in women with recurrent or stage IVB carcinoma of the cervix, who have very limited treatment options in the last stages of their disease.

The ERG requested data on vital status, medical history and physical examination, disease status, evidence of long term AEs and cancer therapy for 2-5 years following study completion (MS, pp.44). The manufacturer did not have access to this data, but did provide a break-down of post-study treatments (MR, pp.17-18).

GOG-0169

There was a significant difference in median PFS for patients receiving paclitaxel plus cisplatin (4.8 months) versus cisplatin monotherapy (2.8 months) ($p<0.001$), but no significant difference in median overall survival (9.7 versus 8.8, respectively). The most significant toxicity in both treatment arms was myelosuppression, with grade three to four anaemia and neutropenia more common among patients in the combination arm. Nausea and vomiting occurred frequently in patients in both treatment arms.

QoL declined progressively during the treatment period and there was a disproportionate number of drop-outs among patients randomly allocated to receive cisplatin monotherapy (50 of 133 patients) versus paclitaxel plus cisplatin (33 of 128 patients; $p<0.05$). However, there was no evidence that patients receiving the combination therapy experienced worse QoL.

Indirect comparison of topotecan plus cisplatin versus paclitaxel plus cisplatin generated a hazard ratio of 0.87 (95% CI: 0.62, 1.23), showing a non-statistically significant trend in favour of topotecan plus cisplatin.

Table 4.2.1.1: 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 %)

Table 4.2.1.2: Compliance rates of patients in the study by treatment over the 4 time points

	Cisplatin			Topotecan/Cisplatin		
Assessment Point	Died[a]/Refused[b]	Valid/Expected[c]	%	Died[a]/Refused[b]	Valid/Expected[c]	%
Prior to randomisation	0/1	**143**/145	99	0/2	**141**/145	97
Prior to cycle 2	10/2	**115**/134	86	14/4	**109**/1029	84
Prior to cycle 5	39/2	**67**/105	64	34/3	**79**/110	72
9 months post-randomisation	87/4	**31**/55	56	78[d]/2	**42**/67	63

a. Cumulative number of deaths
b. Refused for reason other than illness
c. Includes all patients except those who died or refused
d. One patient erroneously entered as death

GOG-0204

This trial was stopped early as all treatment arms were unlikely to demonstrate a significant advantage compared to paclitaxel plus cisplatin. Non-significant trends were reported for OS, PFS, QoL and response rates in favour of paclitaxel plus cisplatin (see Table 4.2.2.1). Toxicities were reported to be similar in the four treatment combinations.

The ERG requested further justification for not formally including GOG-0204. The direct comparison was favourable to the paclitaxel plus cisplatin arm (HR: 1.27 (95% CI: 0.96, 1.69). Pooled data from the indirect and direct evidence resulted in a non-significant trend towards the topotecan plus cisplatin arm; HR 0.98 (95% CI: 0.73, 1.23). Results for GOG-0204 available at the time of submission were from a conference presentation; a peer reviewed journal article reporting full results is due to be published in May 2009.

Number of treatment cycles

The number of treatment cycles for each treatment arm were reported, which will have important clinical implications in terms of patient quality of life, but will also have cost implications (see Section 5).

- GOG-0179 reports the median number of cycles completed for cisplatin monotherapy as three (ranging between one and 12), and four cycles for topotecan plus cisplatin (ranging between one and 20).

- GOG-0169 reports a median number of cycles for cisplatin monotherapy as four, and a median of five for paclitaxel plus cisplatin (ranging between zero and 11 for both treatment groups).

- Data on the number of cycles completed by patients in GOG-0204 was not available in the public domain at the time of the submission.

4.2.2 Critique of submitted evidence syntheses

The following points were raised:

Direct Comparison

- The issues raised in Section 4.1.7 with the use of subgroup analysis, including the loss of statistical power and multiple testing (see Section 5.2.1.3 for more details).

- Long et al (2005)[4] state that "the time from diagnosis to study entry for patients with recurrent disease is a strong prognostic factor even when physical status, age, and disease status at time of study entry have been taken into account". The manufacturer considers the time from diagnosis to study entry in terms of recurrent disease less than or more than 16 months from diagnosis to study entry, and the manufacturer states that the majority of patients (59%) with recurrent disease were within the <16 month subgroup. After consultation with the clinical advisor, the ERG were unsure why GOG-0179 had used 16 months as the cut-off point, as patients who had received previous chemoradiation and relapsed within 6 months were likely to be platinum resistant and therefore unlikely to respond well to topotecan plus cisplatin.

- The manufacturer was asked to provide hazard ratios and 95% confidence intervals for figure 12 (MS, pp.53). Confidence intervals were wide for most subgroup analyses, and the upper limit for the majority of subgroup analyses were greater than 1.00 (see MR, pp.22), which questions the reliability of the results.

- Formally including the direct comparison trial GOG-0204 would have increased the network of direct evidence.

Table 4.2.2.1: Treatment hazard ratios for progression-free and overall survival comparing cisplatin + paclitaxel versus other cisplatin combination treatment (GOG-0204)

	Cisplatin + vinorelbine	vs Cisplatin + paclitaxel	Cisplatin + gemcitabine	vs Cisplatin + paclitaxel	Cisplatin + topotecan	vs Cisplatin + paclitaxel
Progression free (n)	5	7	8	7	9	7
Failure (n)	103	96	104	96	102	96
Total (n)	108	103	112	103	111	103
Relative Hazard Ratio (Var(ln(HR))	1.357 (0.020)		1.394 (0.021)		1.268 (0.021)	
Overall (n)	23	29	20	29	22	29
Failure (n)	85	74	92	74	89	74
Total (n)	108	103	112	103	111	103
Relative Hazard Ratio (Var(ln(HR))	1.147 (0.026)		1.322 (0.025)		1.255 (0.025)	

Indirect Comparison

- Indirect/mixed treatment comparison involved the comparison of data from GOG-0179 versus GOG-0169. There were some important differences between the two patient groups; patients with prior chemotherapy were eligible for GOG-0179 but ineligible for GOG-0169 (except when used as a radiosensitiser. Fewer patients in GOG-0169 had received chemotherapy as a radiosensitiser (27%), and these patients were unevenly distributed to the different treatment arms, compared to patients in GOG-1079 (approximately 60%). Furthermore, the number of patients in GOG-0169 who had received cisplatin as a radiosensitiser was unknown, and the meta-analysis included patients in GOG-0169 with persistent disease. Thus highlighting limitations with the indirect meta-analysis.

- GOG-0204 also included patients with persistent disease, and although it was not possible to distinguish between patients who had and had not previously received cisplatin as a radiosensitiser, the proportion who had received radiosensitiser was more representative of the UK population and more comparable with GOG-0179.

- The manufacturer considered trial GOG-0204 to be limited as patients with PS2 were not represented, as they were, to some extent, in trials GOG-0169 and -0179 (MS, pp.33). The ERG's clinical advisor considered PS2 patients to be difficult to manage in this context as they experience side effects, which have a negative effect on QoL. Thus there may be implications for those patients who benefit most and those who do not benefit from the treatment in question.

- In response to the ERG's request for the inclusion of data from GOG-0204, the manufacturer conducted a meta-analysis to directly compare data from the topotecan plus cisplatin arm with the paclitaxel plus cisplatin arm from GOG-0204, and indirectly compare the same data with that reported by GOG-0179. The direct comparison favoured the paclitaxel plus cisplatin arm (HR 1.255) and the indirect comparison slightly, but not significantly, favoured the topotecan plus cisplatin arm (HR 0.98, 95% CI: 0.73, 1.23) (MR, pp. 24). However, there are concerns with the inclusion of pooled data from GOG-0169 and GOG-0204, given the direct evidence available in GOG-0204.

4.2.3 Summary

The evidence submitted suggests that combination chemotherapy results in a longer median survival than cisplatin monotherapy. However, the submitted evidence is limited; one main RCT directly comparing topotecan plus cisplatin versus cisplatin monotherapy, and one RCT (comparing paclitaxel plus cisplatin with cisplatin monotherapy) providing an indirect comparison of topotecan plus cisplatin with paclitaxel plus cisplatin. An RCT comparing four combination treatments including topotecan plus cisplatin and paclitaxel plus cisplatin was discussed but not formally included in the original submission.

None of the trial populations were the same as each other or the licensed population; therefore subgroup analyses were undertaken. Although this makes the populations more comparable, the limitations of the analysis should be borne in mind. The results from the sub-group analysis of the main RCT suggest that topotecan plus cisplatin has a longer median survival than cisplatin monotherapy in the licensed population. Issues surround the extent to which prior cisplatin-based chemotherapy and chemoradiotherapy may moderate the benefits of treatment.

The safety profile of topotecan plus cisplatin was reported to be predictable and manageable, and there was reportedly no evidence to suggest that QoL was significantly reduced in patients receiving combination therapy compared to monotherapy. However, patients receiving topotecan plus cisplatin experience a greater number of adverse events and the ERG are concerned with some of the assumptions related to QoL.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

The manufacturer's submission (MS) to NICE included:

1. A report on the economic evaluation conducted by the manufacturer (MS pp.82-144, Tables 18-46, Figures 13-25).

2. A SAS-based economic analysis, based on patient-level trial data from GOG-0179, providing a direct comparison of topotecan plus cisplatin versus cisplatin monotherapy.

3. A separate Excel-based economic model, based on aggregate-level data from GOG-0179 and GOG-0169 (and GOG-0204 as part of an additional sensitivity analysis), providing an indirect comparison of topotecan plus cisplatin versus paclitaxel plus cisplatin.

4. Base case cost-effectiveness results from the patient-level SAS analysis (MS pp.125-127, Tables 34-36, Figures 16-17) and subgroup analysis results (MS pp.127-135, Tables 37-40, Figures 18-25).

5. One-way sensitivity analysis results from the patient-level SAS analysis for the base case licensed population and subgroups (MS pp.135-141, Tables 41-45).

6. Cost-effectiveness results for the Excel-based indirect comparison with paclitaxel plus cisplatin (MS pp.127, Table 36) and one-way sensitivity analysis results (MS pp140-141, Table 46)

Following the points of clarification from the ERG, the manufacturer provided the following:

1. A description of the systematic search of the economic literature conducted by the manufacturer (MR pp.31, Section 6 and Appendix 5).

2. Clarification on aspects of the clinical effectiveness data relevant to both the direct and indirect comparisons (including further details and/or data on the systematic review, GOG-0179 and GOG-0169 trials, quality of life data, cross-over, censoring, and other miscellaneous clarifications).

3. Clarification on aspects of the cost-effectiveness data (including justification for the patient level approach to the cost-effectiveness analysis, utility mapping methodology, time horizons in subgroup analysis, adverse effects, missing data, and other miscellaneous clarifications).

4. Extra SAS code and datasets for the mapping of utility values derived from the FACT-G instrument.

5. A revised Excel-based economic model for the indirect comparison with paclitaxel plus cisplatin incorporating QALYs as the main outcome.

As detailed in Section 4.1.1, a systematic search of the literature was conducted by the manufacturer to identify published cost-effectiveness evaluations; however, no relevant cost-effectiveness studies were identified (MS pp.82). In the absence of any relevant published cost-effectiveness evidence, the manufacturer's *de novo* economic evaluation comprised the main submission.

The manufacturer's evaluation consisted of two separate elements:

- A trial-based direct comparison of topotecan plus cisplatin and cisplatin alone. This was based on individual patient-level data from the GOG-0179 trial in which data on clinical efficacy, safety and quality of life were obtained directly from the trial. Additional data on resource use were derived retrospectively from expert opinion and unit cost data were obtained from published sources including National Reference Costs. The trial-based direct comparison was considered by the manufacturer to be the primary analysis within their submission (MS pp.12). Separate analyses were undertaken for the main licensed population as well as subgroups therein, including both cisplatin-naïve and sustained cisplatin-free interval (SCFI) populations.

- A separate Excel-based indirect comparison of topotecan plus cisplatin and paclitaxel plus cisplatin. The main analysis was based on aggregate data derived from the GOG-0179 and GOG-0169 trials. However, an additional sensitivity analysis also included direct data on this comparison from the GOG-0204 trial. Patient-level data were not available for GOG-0169 and so there were considered to be limitations as to the populations which could be examined as part of this comparison; as such, "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... as few patients in the former group had prior exposure to cisplatin" (MS pp.85). The model-based indirect comparison was considered by the manufacturer to be a secondary analysis (MS pp.13).

Justification for the analytic approaches employed (in particular, the choice of a patient-level analysis as the main evaluation) was provided in response to a query by the ERG (MR,

pp.43-47). Given that the manufacturer had access to the patient-level trial data from GOG-0179, the manufacturer "felt that a modelled analysis would inevitably be less faithful to the data available and that it would be poor science not to make full use of these data" (MR pp.47), although it conceded that "the CUA of the patient-level data, while achieving high internal validity, cannot necessarily be generalised to other settings" (MR, pp.46). The separate Excel-based indirect comparison was provided in order to link to alternative comparators used in England and Wales, although the potential shortcomings considered by the manufacturer relating to this approach meant that this was presented as a secondary analysis.

5.1.1 Natural history

The indication for topotecan considered 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", excluding those patients with prior exposure to cisplatin who do not have a sustained treatment free interval of at least 180 days (MS, pp.84). These patients are referred to as the "licensed population" (MS, Figure 13, pP.85), and this population "broadly reflects the patients selected for study GOG-0179" (MS, pp.87).

The primary trial analysis describes the natural history by utilising the individual patient-level survival and quality of life data directly from the GOG-0179 trial for topotecan plus cisplatin and cisplatin monotherapy. Variability in the survival outcomes within the licensed population was assessed using separate patient-level data from the different subgroups in this trial. Quality of life benefits were incorporated by an algorithm linking a disease specific measure of quality of life (FACT-G) to utility. Sensitivity analysis was also employed to consider alternative sources of utility data.

The secondary model analysis describes the natural history using aggregate survival data from the GOG-0179 and GOG-0169 studies. The relative effectiveness of paclitaxel plus cisplatin compared to topotecan plus cisplatin was derived from an indirect comparison based on the results from these two studies. The GOG-0204 study was also considered as part of the sensitivity analysis since this provided a direct comparison between paclitaxel plus cisplatin and topotecan plus cisplatin. The indirect comparison presented within the MS did not attempt to evaluate any quality of life benefits and the results were expressed in terms of life-years only. As part of the MR, an additional indirect analysis was presented expressing outcomes in terms of both life-years and QALYs.

The time horizon for the patient-level evaluation was 36 months (MS, pp.91) for all populations except the subgroup of the SCFI patients (18 months), consistent with the follow-up period for GOG-0179. The time horizon for the indirect comparison was 24 months, consistent with the follow-up period for GOG-0169. As part of the MR, the time horizon for the indirect comparison was extended to 36 months.

5.1.2 Treatment effectiveness within the submission

Direct comparison between topotecan plus cisplatin and cisplatin

As discussed in Section 4.1.3, the pivotal topotecan trial for this comparison is GOG-0179, which compared treatment with topotecan plus cisplatin with cisplatin monotherapy. This study was the main source for the economic evaluation as it was the only study directly comparing these two regimens.

The manufacturer indicated that the licensed population consisted of several relevant subgroups (Figure 3.1.1). A cut-off point of 16 months for subgroup partitioning was chosen post-hoc. The subgroups analysed were:

(1) main licensed population, consisting of (1a) licensed population excluding stage IVB patients (69% of the ITT population) and (1b) stage IVB patients;

(2) cisplatin-naïve population, consisting of (2a) cisplatin-naïve recurrent population (21% of the ITT population) and (1b) Stage IVB patients; and

(3) patients with a sustained cisplatin-free interval (SCFI; >180 days between the last cisplatin dose and the recurrence of disease that resulted in eligibility for entry to GOG-0179).

These subgroups were analysed by re-running the cost-effectiveness analysis, selecting only the patients with the baseline characteristics of each subgroup.

The overall survival 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.

For the direct comparison, the time horizon (36 months of follow up period) was considered appropriate by the manufacturer given that the majority of patients in all treatment arms of the GOG-0179 trial had died and thus most of the costs and outcomes for the cohort had been incurred.

Trial data from the GOG-0179 trial on clinical efficacy, adverse events and quality of life were used directly in the primary cost-effectiveness analysis. As previously noted, additional inputs relating to resource utilisation and costs were derived retrospectively by combining data on clinical events from individual patients with expert opinion of their associated management and cost. The rationale for basing the main economic submission on patient-level data from the trial relied on several aspects, mainly on the available clinical data, and was discussed in detail as part of the MS (pp.179) and the MR (pp.43-47).

Indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin

An indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin was modelled using clinical effectiveness data from GOG-0179 and GOG-169. These two trials provide an indirect estimate with cisplatin monotherapy acting as a common comparator (Section 4.1.3).

The hazard ratio for overall survival derived from GOG-0169 for paclitaxel plus cisplatin versus cisplatin monotherapy was applied to the first 24 months of overall survival data for cisplatin from GOG-0179 to estimate the overall survival for paclitaxel plus cisplatin. This provided the basis for an indirect comparison of topotecan plus cisplatin versus paclitaxel plus cisplatin. However, since the main publication of GOG-0169 did not actually report the hazard ratio, the manufacturer estimated the ratio (HR= 0.87 favouring paclitaxel plus cisplatin) from the survival curves using published methods[12].

Although the manufacturer acknowledged that the GOG-0204 trial provided a direct comparison between topotecan plus cisplatin and paclitaxel plus cisplatin, a number of potential methodological limitations were identified, namely the early closure of the trial and the high proportion of patients with a good performance status. As a result, the comparison between topotecan and paclitaxel was presented as a separate sensitivity analysis. For this analysis the overall survival data for paclitaxel plus cisplatin was estimated from the hazard ratio for paclitaxel plus cisplatin versus topotecan plus cisplatin taken from GOG-0204 (1.255, favouring paclitaxel plus cisplatin). This hazard ratio was then applied to the first 24 months of overall survival data for topotecan plus cisplatin from GOG-0179.

5.1.3 Health related quality of life

Health related quality of life (HRQoL) was only evaluated in the patient-level direct comparison between topotecan plus cisplatin and cisplatin monotherapy. The indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin did not consider

HRQoL and the results were expressed in terms of life years gained (LYG) rather than quality-adjusted life years (QALYs).

Base case utility values

In the base case analysis, trial based utility estimates were used – these were mapped from the Functional Assessment of Cancer Therapy - General (FACT-G) scores collected in study GOG-0179. The FACT-G scores were recorded "at fixed time points in the trial and thus reflect patients' perceptions at these discrete points only" (MS, pp.102). Data were mapped to utility values using a published algorithm recently developed by researchers at the School of Public Health, University of Illinois at Chicago (Dobrez 2007)[13]. 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 individuals with cancers of various types, HIV/AIDS and over a range of severity of illness.

The algorithm comprises the following formulation:

$$Utility = 1 + \begin{pmatrix} -0.2222 & if\ q_1 = [0,1] \\ -0.1137 & if\ q_1 = [2,3] \end{pmatrix} + \left(-0.1537 \quad if \quad q_2 = 0\right) +$$

$$+ \left(-0.0431 \quad if \quad q_3 = [0,1]\right) + \begin{pmatrix} -0.1254 & if & q_4 = [0,1] \\ -0.0641 & if & q_4 = 2 \\ -0.0345 & if & q_4 = 3 \end{pmatrix}$$

Where q1 = Physical Well Being: lack of energy, q2 = Physical Well Being: feel sick, q3 = Functional Well Being: able to work, and q4 = Functional Well Being: able to enjoy life. The algorithm was reported as performing well in predicting mean utilities measured as EQ-5D (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 manufacturer noted that the algorithm over-predicted utility for poor health. The manufacturer also explored alternative sets of utility values that were described in the sensitivity analysis.

Four observations during the course of the trial were recorded: (i) prior to randomisation; (ii) prior to cycle 2; (iii) prior to cycle 5 and (iv) 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.

With respect to missing data in the base case analysis, missing values were imputed using the last observation carried forward (LOCF). Three alternative methods were used to deal

with missing data: (i) using the unimputed utility data unadjusted, (ii) the LOCF assuming the last value is carried forward even after death, and (iii) LOCF assuming death results in a carry forward of 0. The later approach was employed in the base-case analysis. The summary values for FACT-G-based utility weights for the licensed population can be found in MS p.104, Table 20 and the results of this analysis of the alternative methods used are shown in MR, Table 28 (pp.35),.

An adaptation of the Lin et al (1997)[14] method was used to estimate quality-adjusted survival while accounting for censored observations. The MS mentions that, given the unknown proportion of survived patients during the final interval (36th month) due to censoring, the estimation of the mean quality-adjusted survival for the censored observations in this interval was based on the observed quality-adjusted survival of the last patient(s) who died multiplied by the probability of survival at the end of the study.

Alternative utility values

The MS expressed "some doubt as to whether the algorithm used to map FACT-G scores to utility values was applicable to the GOG-0179 population" (MS pp.104). Hence, the MS considered alternative utility values in a series of sensitivity analyses. The alternative values were based on a systematic literature search detailed on pp.104-105 of the MS. The manufacturer identified six studies presenting utility values for patients with cervical cancer (MS Table 21, pp.105). However, the MS noted that "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", and as such "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" (MS pp.104-105).

Further non-systematic literature searching identified three papers reporting "utility values according to outcomes" for "other gynaecological (including breast) cancers in advanced stages" (MS, pp.105). Of these papers, the manufacturer's clinical expert suggested that the utility values reported in the Brown (1998)[15] study into metastatic breast cancer would be a reasonable proxy in the absence of suitable cervical cancer data (MS, pp.106) – these utility values were therefore selected for use in the sensitivity analyses, with clinical events occurring in GOG-0179 assigned to health states reported in Brown (1998)[15] (MS, Table 23, pp.107).

The utility values for adverse events were applied for week-long intervals, after which time the previous utility value was reapplied. If a patient experienced two adverse events at the same time, the lower utility value was applied to that time period. Adverse event utility scores were not applied once a patient's disease had progressed as these scores were higher than the utility for progressive disease.

5.1.4 Resources and costs

Direct comparison between topotecan plus cisplatin and cisplatin monotherapy

In the direct analysis, costing was performed at the patient level. However, the trial protocol of GOG-0179 made no specific arrangements to record comprehensive resource utilisation prospectively to facilitate the population of an economic evaluation. The unit costs were assigned to resource items that were derived 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 (e.g. adverse 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. Therefore, the costing was carried out retrospectively from the NHS perspective.

The costs considered included acquisition costs of study drug (based on actual cycles and dosage administered), pre- and post-treatment medications, costs of healthcare resource utilisation for pharmacy preparation, treatment administration, monitoring and management of adverse events (MS, pp.109-119, Tables 24-31).

Observations for many patients were censored, so that subsequent resource utilisation and costs were unknown. To avoid bias due to censoring the MS states that the estimation of mean costs used was the "without cost histories" variant of the standard method described by Lin et al (1997)[14]. This variant of Lin's method, considers the trial follow-up period divided into several intervals (the study used 36 intervals, each of one month – the GOG-0179 follow-up period). The mean total cost per patient was 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.

Indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin

For the indirect analysis, costing was based on aggregate level data. The mean number of cycles was based on data from GOG-0179. Comparable data were not reported in GOG-0169 for paclitaxel plus cisplatin and hence this was assumed to be equal to that for topotecan plus cisplatin. No modifications were made to dosages and these were modelled in line with the SmPC.

The standard regimens for topotecan and cisplatin in GOG-0179 (and the SmPC for topotecan) and paclitaxel in GOG-0169 are reproduced in the Table 5.1.4.1 below 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 5.1.4.1. Chemotherapy drug dosage (assuming no dose modification) (MS p.110)

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

The following aspects are common to both the direct and indirect analyses.

Drug costs

The cost of each chemotherapy regimen was calculated using the unit prices from the British National Formulary (January 2009) (MS, pp.109). For all chemotherapies, a mean body surface area of 1.7 m^2 was assumed as neither surface area nor height/weight data were reported to be available for individual patients.

The MS analysed three scenarios regarding utilisation of vial contents and wastage: in the base case some re-use was assumed (approximately midrange between the two scenarios considered in the sensitivity analysis) and sensitivity analyses considered either minimum wastage or maximum wastage (no re-use). These scenarios all assumed that vials of topotecan are not shared between patients, although the minimum wastage scenario assumes that the same vial can be used on multiple visits for an individual patient. The MS

argued that these approaches are “all consistent with the topotecan SmPC” and “[do] not appear to contravene the NHS Multiple Use of Injections policy because topotecan is licensed, within the limitations described above, for multiple uses” (MS, pp.110). The SmPC’s guidance is that topotecan should be used immediately after reconstitution as it contains no antibacterial preservative. If reconstitution and dilution is performed under strict aseptic conditions (e.g. an LAF bench) the product should be used (*infusion completed*) within 12 hours at room temperature or 24 hours if stored at 2-8^{o}C after the first puncture of the vial. No sensitivity analysis around cisplatin vial utilisation was performed and maximum wastage was assumed for cisplatin, the MS suggested that “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” (MS, pp.110).

In the indirect comparison, the price of *generic* paclitaxel was used in the base case whilst a sensitivity analysis was performed using 50% of the price of branded paclitaxel, “given possible future price volatility” (MS, pp.110).

The costs of the standard doses of chemotherapy are given in Table 25 (p.111) of the submission.

Administration costs

Costs related to hospitalisation and chemotherapy administration were taken from the NHS National Reference Costs (2006/7), PSSRU (2008) and the BNF (2009). National Reference Costs were inflated to 2007/8 prices using the Hospital & Community Health Services inflator from the PSSRU.

The MS assumed that the administration of cisplatin required “a pre- and post-treatment hydration of two hours with at least one litre of 0.45-0.9% saline” (MS p.114). Therefore, administration of cisplatin, with or without topotecan, involved a single day case attendance. The day case cost was incurred only on day one of each cycle, and 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 plus cisplatin was assumed to be administered over three consecutive days. In addition to the day case on day one, out-patient visits are required for infusions on days two and three. The MS costed each of these two out-patient visits at £51 – “£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) at

each of these visits" (MS, pp.114). It should be emphasised that the cost-effectiveness of topotecan is sensitive to the assumptions made over the administration costs for the infusions on days two and three and that the MS chose not to base these on National Reference Costs data. This issue is discussed in more detail in later sections.

In the GOG-0169 study, administration of 135mg/m^2 paclitaxel occurred over 24 hours, but, "based on a clinician's opinion that this dose of paclitaxel is normally administered over 3 hours", it was assumed in the MS that administration of paclitaxel plus cisplatin requires attendance as day case (£277).

Other costs

The costs for pre- and post-treatment medication, follow-up costs and adverse event costs are given in the MS, pp.114-120.

5.1.5 Discounting

All costs and health benefits are discounted at an annual rate of 3.5%, in line with the NICE reference case (MS, pp.121).

5.1.6 Sensitivity analyses

The MS considered a number of sensitivity analyses for the direct patient-level comparison of topotecan plus cisplatin versus cisplatin monotherapy, and two sensitivity analyses for the indirect comparison.

Direct comparison

The MS considered alternative assumptions concerning: (i) the wastage of opened vials of topotecan; (ii) the pre-treatment medications provided; and (iii) the utility values used.

The MS considered two additional scenarios with differing assumptions over the wastage of opened vials of topotecan: minimal wastage and maximal wastage. In the minimal wastage scenario it was assumed that vials of topotecan would not necessarily be disposed of after 24 hours but would, where possible, be re-used over the three day period of administration. In the maximal wastage scenario it was assumed that any unused topotecan remaining in a vial was disposed of immediately. By contrast, the base case scenario assumed "some re-use (approximately midrange)" (MS, pp.110).

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 eight hours or metoclopramide 40mg twice daily (bid) for three to four days post-treatment. Based on a clinician's opinion a regimen of domperidone 20mg four times daily (qds) was assumed as more representative of UK practice and this was applied for five days for both treatment regimens.

The MS considered an analysis where the trial-based utility values were replaced by the alternative utility values detailed in Section 5.1.3.

Indirect comparison

For the indirect comparison, the manufacturer considered two separate sensitivity analyses:

(i) the price of paclitaxel was assumed to be 50% of the branded Taxol price, as opposed to the generic price assumed in the base case (itself around 10% lower than the Taxol price) (MS, pp.140). While this has the effect of reducing the apparent cost-effectiveness of Topotecan; the relevance of such an assumption is open to question.

(ii) alternative sources of effectiveness using the results from GOG-0204 in place of GOG-0169 was considered.

5.1.7 Model validation

The manufacturer mentioned that extensive guidance was provided by an external expert 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 SAS algorithms for the trial-based analysis were reported to have been independently checked and run by two external parties.

5.2 Critique of approach used

5.2.1 Direct comparison

Prior to a detailed critique of the methods employed, there are two general points

which should be highlighted:

1. While the ERG note the arguments made by the manufacturer with respect to the high internal validity of the approach taken, issues of external validity are an equally important consideration for cost-effectiveness analyses. It should be noted that an important limitation of the within-trial approach is that it precludes the inclusion of any additional evidence which may be considered relevant to the decision. This relates both to evidence on the specific comparison considered within the trial (topotecan plus cisplatin versus cisplatin alone) as well to as to other comparators which may be considered relevant to current NHS practice. Although a comparison with paclitaxel plus cisplatin is considered within the Excel-based model, this model has important limitations given that the final outcome considered (life-years) does not conform to the NICE Reference Case.

2. A comprehensive validation by the ERG of the SAS patient-level submission has not proven possible due to the nature of the evidence submitted, delays with the receipt of additional information following the initial points for clarification and ongoing problems with the submission of incomplete coding files and datasets. In addition, it should be noted that the SAS coding received comprised over 100 pages of code, which made a detailed line by line validation impossible within the time constraints of an STA. However, sufficient working code and accompanying datasets were submitted to ensure that the general methods outlined were followed and more detailed checks of parts of the code were undertaken for several key elements, notably the derivation of utility values and the calculation of costs.

5.2.1.1 Quality of life

The resulting utility scores used in the direct comparison are given in Table 20 of the MS (pp.104) while the FACT-G scores are plotted in the MS, Figure 11 (pp.52); the descriptive statistics for the plots in Figure 11 are given in the MR, Table 11 (pp.16). These statistics are consistent with the plot of FACT-G scores, although the statistics given for the BPI scores (not used in deriving the utility values) do not appear to be consistent with those plotted in Figure 11.

As noted in the previous section, the MS employed an algorithm to map the FACT-G scores recorded in study GOG-0179 to the utility scores used in the model. A side-by-side comparison of the plot of FACT-G scores with the utility values immediately raises potential questions about the face validity of the mapping process. From randomisation through to nine months post-randomisation, the FACT-G scores for both cisplatin and topotecan plus cisplatin remain relatively stable (in the region of 68.0 to 75.3); for both treatments the

scores tend to increase slightly over time, from 71.5 to 74.5 and from 68.0 to 74.4 for cisplatin monotherapy and topotecan plus cisplatin respectively (MR Table 7, pp.16). While cisplatin monotherapy had slightly higher FACT-G scores prior to randomisation and at nine months post-randomisation, topotecan plus cisplatin had slightly higher scores prior to cycle two and prior to cycle five. However, it is plausible that these slightly higher scores are the result of a higher percentage of patients receiving topotecan plus cisplatin being too ill to respond to the FACT-G questionnaire, thus potentially biasing the FACT-G scores for topotecan plus cisplatin upwards. Nevertheless, the fact remains that the FACT-G scores reported in the MS are similar for both treatments and remain relatively stable over time.

By contrast, the base case utility values derived from these FACT-G scores not only fall substantially but also diverge over the course of treatment (from 0.79 for both treatments prior to randomisation to 0.45 for topotecan plus cisplatin and just 0.33 for cisplatin nine months after randomisation). At face value it is difficult to reconcile these utility values with the FACT-G scores they are apparently derived from.

Given these potential concerns additional work was undertaken to validate the approaches used to mapping and imputation.

Issues with mapping

As previously mentioned in Section 5.1.3, health effects were expressed in terms of QALYs which were derived using the FACT-G instrument. An algorithm developed and validated in individuals with cancer of various types and over a range of severity of illness was used to map from the FACT-G data to utility values. The algorithm uses four items from the FACT-G (energy, feeling ill, ability to work and ability to enjoy life). As reported in Dobrez et al (2007)[13], the use of the algorithm to estimate utilities requires that all four items must be ordered so that a value of 0 indicates the worst possible response. This requires two of the selected questions (physical well-being [PWB]: lack of energy and PWB: feel sick) to be reversed prior to estimating the subsequent utility values.

The initial MS did not contain the complete datasets and coding necessary to validate these algorithms. Following two separate ERG requests the complete SAS code for the estimation of the utility values at each questionnaire assessment and estimation of QALYs for the overall period of assessment were eventually submitted. After examining the code it was found that the re-ordering of the PWB questions had not been carried out in the manufacturer's analysis, leading to an incorrect prediction of utility values.

Table 5.2.1.1.1 shows the utility values with and without the correct re-ordering of the PWB items (MR Table 28, p.35) based on the non-imputed analysis. It can be seen that the original submission overestimates utilities for both treatment arms at each follow-up points.

Table 5.2.1.1.1: Utility scores for cisplatin and topotecan plus cisplatin patients

Utility scores for Cisplatin and Topotecan plus Cisplatin patients	Original submission: Non-imputed data mean (sd)	Reversing PWB responses: Non-imputed data mean (sd)
Cisplatin (n=115)		
Prior to randomisation	0.79 (0.11)	0.72 (0.10)
Prior to cycle 2	0.77 (0.11)	0.72 (0.11)
Prior to cycle 5	0.77 (0.12)	0.72 (0.10)
9 months after randomisation	0.79 (0.13)	0.73 (0.11)
Topotecan + Cisplatin (n=107)		
Prior to randomisation	0.79 (0.12)	0.71 (0.10)
Prior to cycle 2	0.78 (0.11)	0.72 (0.10)
Prior to cycle 5	0.80 (0.10)	0.70 (0.11)
9 months after randomisation	0.80 (0.10)	0.72 (0.12)

In addition, as shown in the MS, Figure 11 (pp.52), while there is no difference reported between treatment arms in the FACT-G scores over time, the predicted mean utilities showed a slight advantage in favour of the topotecan plus cisplatin compared to cisplatin only (MS pp.104, Table 20). This difference is reversed when the correct ordering PWB responses is applied prior to using the algorithm to convert to utilities.

The failure to correctly re-order the PWB items thus results in two sources of possible bias in favour of topotecan plus cisplatin. Firstly, the mean utilities in the original submission demonstrate a marginal improvement with topotecan plus cisplatin during the follow-up periods which is no longer evident when the algorithm is correctly applied. Secondly, the incorrect algorithm results in an over-estimate of the mean QoL for both treatments. This is potentially important given the differential survival estimates for the two treatments, such that an inflated utility value is subsequently assigned to any additional survival reported for topotecan and cisplatin. Both of the sources of bias will over-estimate the incremental QALYs in favour of topotecan plus cisplatin in the direct comparison and will result in an optimistic estimate of the ICER.

Issues with imputation of missing data

With respect to missing data, the MS reports that missing values were imputed using the LOCF for surviving patients. Also, it was reported that if the baseline assessment was missing, a replacement by the mean utility value of baseline assessment on the overall population was performed.

The ERG considers the LOCF approach difficult to justify, given the strong assumptions required that are unlikely to hold in cancer populations. That is, that censored observations remain constant over time with respect to the last observation. In the presence of a time trend this will lead to biased estimates, with the direction of the bias depending on the (unknown) true effect. Furthermore, this approach can provide biased results if there are different rates of drop out or different time to drop out in a study (Manca *et al.* 2005)[16] This assumption may result in an over-estimate of the QALY gain given the additional survival duration with topotecan plus cisplatin.

An equally important issue relates to the manner in which missing data were handled when information was missing due to the death of a patient. More specifically, utility values for patients who died during the study were imputed as zero. The impact of the different methods of handling censored patients is reported in the MR (pp. 35, Table 28). The chosen method of imputation results in a marked decline in HRQoL in both arms but also increases the differential QoL between the two arms in favour of the topotecan plus cisplatin. However, it should be noted that adjustments for mortality also appear to be incorporated in the approach to estimating QALYs. That is, the Lin method employed in the estimation of QALYs already accounts for the mortality differences in estimating the probability of surviving each time interval and hence the utility values themselves, which are then weighted by the probability of survival in the Lin method, do not need to be separately adjusted by imputing a value of zero for patients who died. As a result, the impact of mortality appears to be double counted in the final estimation of QALYs and is likely to lead to an important source of bias in favour of topotecan plus cisplatin.

Alternative utility values

Given these concerns, the validity of the alternative utility values presented in the MS potentially assumes greater significance. The ERG acknowledges the limitations of published utility values in a cervical cancer population in terms of informing differential QoL according to particular events. However, the assumption that the Brown (1998)[15] utility values provide a suitable proxy in the absence of more appropriate cervical cancer data is questionable. This approach assumes that the entire set of values from the metastatic breast

cancer population reported in Brown (1998)[15] are directly exchangeable with those of a cervical cancer population. One implication of adopting these values directly is that all patients are assumed to start with a utility value of 0.64, which appears markedly lower than the utility of patients reported with cervical cancer. The ERG considers that it may be more appropriate to interpret the utility values given by Brown (1998)[15] as informing the increments to, or decrements from, a patient's initial utility value that might be expected as the patient progresses through treatment, and then to obtain the initial utility value from one or more of the studies reporting utility values relevant to cervical cancer (MS Table 21, pp.105). This approach has the advantage of allowing the utility values to be conditional upon the stage of the patient's disease when commencing treatment – the implications of this approach are explored in Section 6.1.2.

5.2.1.2 Resource utilisation and costs

As mentioned in Section 5.1.4, in the direct analysis, costing was performed at the patient level. However, the GOG-0179 trial did not record resource utilisation. Instead, this information was derived from the clinical events that occurred during the trial, supplemented with data from external sources. The submission was clear by stating that resource utilisation contingent on clinical events was based on the expert opinion of oncologists with experience of working in the UK.

The assumptions underlying the estimation of resource use were not thoroughly discussed in the manufacturer's written submission (although it was acknowledged on pages 98 and 119) and may not be accurately reflecting the true resource use of both treatment arms, resulting in a possible bias in favour of one of the interventions. However, it is unclear which direction this bias may operate, although the approach itself will certainly underestimate variability in resource use and costs due to the fact that the same event will be associated with the same resource use.

In reviewing the resource use and costing assumptions employed, the ERG identified four key issues:

(i) The assumptions made concerning the number of vials of topotecan utilised over the 3 day infusion;

(ii) The unit costs assigned to the administration of topotecan plus cisplatin over the 3 day infusion;

(iii) The lack of disaggregated cost data reported and potential concerns regarding the approach employed with respect to costing adverse events; and

(iv) The exclusion of longer-term costs due to additional life-extension.

These issues are discussed in more detail below.

The MS considered three scenarios concerning the number of vials of topotecan utilised over the 3 day infusion (MS pp.110). With 'minimum wastage' (where the unused content of vials is used over multiple days) the manufacturer calculated that four 1 mg vials would be required (as the total dose over the three IV administrations is 3.825 mg), at a total cost of £390.60; alternatively, with 'maximum wastage' (where vials are discarded immediately after use) six 1 mg vials would be required (two per day, as the dose per IV administration is 1.275 mg), at a total cost of £585.90. The manufacturer's base case assumption was that five vials would be needed (£488.25) as this was "approximately midrange", representing "some re-use" (MS pp.110).

The ERG considered this base case assumption to be unjustified. As noted in Section 5.1.4, the SmPC's guidance states that "[topotecan] should be used immediately after reconstitution as it contains no antibacterial preservative. If reconstitution and dilution is performed under strict aseptic conditions (e.g. an LAF bench) the product should be used (*infusion completed*) within 12 hours at room temperature or 24 hours if stored at 2-8^{o}C after the first puncture of the vial" (ref, emphasis added). The manufacturer's 'minimum wastage' assumption therefore contradicts the SmPC guidance unless the heroic assumption is made that infusion will be scheduled at a progressively earlier time on each of the subsequent days (so as to complete infusion within 24 hours of commencing the previous day's infusion). As such, the ERG believes that the 'maximum wastage' assumption is more appropriate. Meanwhile, the base-case assumption would only be appropriate if it was best-practice to re-use vials across two days but not three – not only would this contradict the SmPC's guidance but no evidence is given to support this assumption.

As noted previously, the administration of topotecan plus cisplatin is undertaken on separate visits over three consecutive days. This contrasts with administration of cisplatin and paclitaxel plus cisplatin which are both administered during a single visit. The initial attendance is therefore common to all treatments and was costed using a medical oncology day case (£277) attendance derived from National Reference Costs data (based on HRG code M98: Chemotherapy with a Female Reproductive System Primary Diagnosis). However, the additional administration costs assumed for the infusions on days two and three relating just to topotecan plus cisplatin were *not* taken from the same source and were substantially lower (just £51 for each day). This cost was based on nursing time (1 hour) and pharmacy time estimates to prepare an IV infusion. Although the ERG acknowledges

that the subsequent infusions require a shorter time than the initial infusion, there remain concerns regarding the robustness of, and justification for, the estimate employed by the manufacturer. In particular, it is unclear why alternative National Reference Cost estimates were not considered for these additional infusions. Indeed, comparable National Reference Costs data for 2006/07 for outpatient attendances related to the delivery of additional elements of a chemotherapy cycle are available (£195 per day, based on HRG code SB15Z: Deliver subsequent elements of a chemotherapy cycle: Outpatient). This suggests that the costs of administering topotecan plus cisplatin may be considerably higher than assumed by the manufacturer.

The cost results based on the direct comparison were not disaggregated in the main direct comparison and only total costs were presented. The ERG requested additional clarification on the breakdown of total costs into the separate elements (e.g. chemotherapy costs, administration costs, adverse event costs etc) to assist with the overall validation process. Although a more detailed breakdown was provided as part of the MR (pp.38), it should be noted that these separate estimates are based on assuming that the proportion of costs would be the same as in the indirect comparison model. Indeed the manufacturer noted that "the direct analysis has not been constructed with the functionality of breaking down aggregated costs into the individual components that would be required".

In the absence of the actual disaggregated data from the direct comparison it is difficult to establish the validity of the overall total cost estimates or to compare the cost estimates reported with those report in the indirect analysis. This is a potentially important limitation given the magnitude of the difference between the direct and indirect analyses. In general, it appears that the overall cost estimates from the direct comparison are lower than those reported for the indirect comparison for both topotecan plus cisplatin and cisplatin alone. This results in smaller incremental costs between the two treatments in the direct comparison than reported in the indirect comparison. In the absence of more detailed data it is not possible to robustly identify the source(s) of the difference. However, it is likely that these differences will be due to different approaches employed in costing chemotherapy and also potentially to the costing of adverse events.

In terms of chemotherapy costs considered in the direct comparison, these were based on the actual number of cycles and dosage received by individual patients in GOG-0179. As such, the chemotherapy costs will include any dose reductions applied for each regimen due to toxicity. However, in the indirect comparison model, the use of aggregate data precluded

a detailed consideration of the impact of dose reduction and hence drug costs were based on the licensed dose as opposed to actual dose received.

The other aspect considered by the ERG to be a potential source of driver of the difference reported in the direct and indirect comparisons relates to the costing of adverse events. A more thorough investigation of the SAS coding used to estimate adverse event costs was therefore undertaken. In the absence of a detailed description of the SAS coding provided by the manufacturer, comprehensive validation of the code was not possible. However, it does appear that the coding of adverse events only considers the highest single adverse event cost incurred by each individual patient during the entire course of therapy, as opposed to during a single cycle. Consequently, it appears that the costs of multiple adverse events incurred during separate treatment cycles may not have been included in the direct comparison. Unfortunately the ERG is not able to confirm this due to problems in interpreting the supplied code.

Finally, the MS reports that the costs considered were the costs of chemotherapy, pre- and post-treatment medication costs, pharmacy and treatment administration costs and monitoring and management of adverse events costs. It could be argued that other potential costs have been ignored, for example, the costs related to the fact that patients may have higher overall survival as a consequence of being subject to treatment. The extension of patient's survival time due to treatment effect is inevitably linked to a higher resource usage and consequently to higher costs. An underestimation of the true costs related to the intervention that produces higher survival is therefore likely.

5.2.1.3 Subgroup analysis

The manufacturer indicated that the population consists of several subgroups, resulting from breaking down the licensed population (n=222). The five subgroups considered are the following: licensed population excluding stage IVB patients (1a); stage IVB patients (1b); cisplatin-naïve population (2); cisplatin-naïve recurrent population (2a); and patients with a sustained cisplatin-free interval (3).

It was not clear what were the clinical reasons behind the procedure of splitting the licensed population into different subgroups. Furthermore, there might be problems when this type of analysis is performed; the two main issues being the loss of statistical power and multiple testing.

Statistical tests on subgroups will have only power to detect substantially larger effects on the same endpoint. Loss of compliance, drop out due to treatment effects, together with

adjustments for multiple testing, will exacerbate this lack of power (Yusuf, 1991)[17]. In consequence, when tested separately, many of the subgroups will fail to show the statistically significant treatment effect that was shown in the main population; at the same time, genuine differences in response to treatment (so-called heterogeneity) between study subpopulations may also go undetected.

Also, statistical investigation of large numbers of subgroups inevitably shows significant interactions with the effectiveness of the trial intervention. Trials with multiple comparisons to assess the comparability of randomised groups at baseline confirm this fact. In subgroup analysis, where a group of factors may influence outcome, the risk of false-positive results is high. Excessively animated analysis of subgroups can reveal statistically significant differences in outcome between subgroups even where neither arm of the study receives any intervention (Brookes, 2001)[18]. One way to partly overcome the abovementioned problems of subgroup analyses is using an interaction term in a regression model. The ERG thus considers that it may have been more appropriate to consider the separate subgroups within the same statistical model as opposed to subdividing the population. However, it not clear that the approach employed would necessarily introduce any significant bias into the results.

5.2.1.4 Survival analysis

As mentioned by the MS (pp.98) a variant of the Lin method was applied in order to estimate the mean total cost per patient, which is 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.

The Kaplan-Meier method is a non-parametric technique for estimating time-related events. It is a univariate analysis and is especially applicable when length of follow-up varies from patient to patient, taking into account those patients lost to follow-up or patients where the endpoint of analysis was not verified yet at end of follow-up.

However, this method implies the strong assumption of non-informative or independent censoring, that is, a subject censored at time t can be considered completely interchangeable with any other subject (on the same treatment) who has also survived up to time t (the censoring could have happened to any comparable subject). This assumption is emphasized in the discussion section of Lin et al (1997)[14]: “The assumption of independent

censoring requires some care. This assumption is clearly not satisfied if patients are withdrawn from the study for health- or cost-related reasons"…"One must carefully examine the independent censoring assumption before applying the proposed methodology.".

With respect to the intervention under analysis, informative censoring may be arising due to patients that dropped out were more likely to die sooner than similar non-censored subjects, that is, given that there is a relationship between their propensity to drop out and their survival, the factor that causes censoring is evidently related to that survival time. Also, those who were removed from the study due to adverse side-effects are subject to informative censoring. They are clearly very different from other patients who were still alive at the point they were removed; a patient without adverse symptoms would not have been censored at this time.

In order to overcome the abovementioned methodological limitations, Willan et al (2005)[19] proposed a method for estimating the difference in mean costs and the difference in effectiveness, together with their respective variances and covariance in the presence of dependent censoring. This method uses inverse-probability weighting for estimating the parameters required for performing a cost-effectiveness comparison of two groups when the measure of effectiveness is some function of survival and censoring is present. This methodology might have been more adequate in the current circumstances, where the probability of being observed may be estimated conditionally on a series of covariates. Again, as with the previous issue, although this appears to provide a more suitable analytic approach, it not clear that the approach employed would necessarily introduce any significant bias into the results.

5.2.2 Indirect comparison

As reported in Section 4.1.4, the ERG has concerns regarding the manufacturer's exclusion of a number of studies which may have contributed to a wider network of evidence on relevant comparators to topotecan plus cisplatin. The indirect comparison conducted by the manufacturer compared topotecan plus cisplatin to paclitaxel plus cisplatin only.

As discussed in Section 4.1.3, the indirect comparison of topotecan plus cisplatin versus paclitaxel plus cisplatin was carried out by comparing the results of GOG-0169 with those of GOG-0179. The MS concedes that there are "limitations to the analysis" (MS pp.84), most notably that the comparison does not consider changes to the HRQoL of patients as disease progresses. Consequently, this limits the cost-effectiveness analysis to a comparison of LYG associated with the alternative interventions. The justification given for the exclusion of

HRQoL data is that “progression-free survival periods... [are not] reported for the GOG-0169 study” (MS pp.96). This is incorrect, and was acknowledged by the manufacturer as an error in it’s response to the ERG’s queries. As such, the use of LYG instead of QALYs is clearly not justified.

Furthermore, the decision to base the main analysis on the results of the indirect comparison of studies GOG-0169 and GOG-0179 and not on the direct comparison reported GOG-0204, does not appear to be sufficiently justified. Although the manufacturer considers the impact of using GOG-0204 as part of a sensitivity analysis, their significance appears downplayed within the submission by asserting that the trial was “stopped early when it became evident that no statistical difference in [overall survival] would be observed between treatments” (MS pp.92). In fact, the trial was stopped early when it became evident that no alternative treatment would offer a statistically significant improvement in overall survival over that associated with paclitaxel plus cisplatin – a subtle but important distinction. Indeed, later in the MS submission it is reported that: “[the] initial results [of GOG-0204] show that there is a trend towards superiority in the paclitaxel arm of trial [sic] with a non statistically significant hazard ratio of 1.255 in favour of paclitaxel” (MS pp.123). As the results of the sensitivity analysis show (see Section 6.1.2), the results of GOG-0204 have an important impact on the cost-effectiveness estimates of topotecan plus cisplatin compared to paclitaxel plus cisplatin.

A further potential issue with the indirect comparison is that it considered only a two year follow-up, while GOG-0179 reports patient-level data for three years – the third year of data from GOG-0179 was disregarded. The MS justifies this as follows:

“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.” (MS pp.91)

This approach is likely to be conservative towards topotecan plus cisplatin based on the results of GOG-0169, as any additional survival benefit incurred after 24-months will not be reflected in the ICER estimates. However, the cost-effectiveness results compared to paclitaxel plus cisplatin will be optimistic towards topotecan plus cisplatin. An alternative approach would be to derive the hazard ratio for paclitaxel plus cisplatin versus cisplatin monotherapy from GOG-0169, and then apply this hazard ratio to all three years of data from GOG-0179. Although this assumes that the hazard ratio observed over a shorter period can be extrapolated to a longer follow-up period, this does seem to provide a more reasonable assumption than assuming that any additional benefits are not accrued over a

longer time period. Following queries by the ERG, this approach was undertaken by the manufacturer in a revision to the model and the results are reported in Section 6.

Finally, it should be noted that the manufacturer did not take a probabilistic approach to modelling the indirect comparison, so uncertainties relating to the hazard ratios and other important parameters are not captured, and the results are only applicable to a cisplatin-naïve population and not to the full licensed population (the ERG attempted to rectify this – see Section 6).

A quality-assessment of the indirect analysis using a modelling checklist is reported in Appendix 4.

5.3 Results included in manufacturer's submission

5.3.1 Direct comparison

Deterministic cost-effectiveness results for the licensed population are shown in the manufacturer's submission (pp.125, table 34). Bootstrap results were displayed as a scatter plot and a cost-effectiveness acceptability curve (CEAC) was also available in page 126, figure 16 and 17, respectively. The results showed that topotecan plus cisplatin has an ICER of £17,974 per QALY versus cisplatin monotherapy in the licensed population.

The results for the different subgroups were as follows:

Subgroup 1a (licensed population excluding stage IVB patients): topotecan plus cisplatin has an ICER of £18,991 per QALY versus cisplatin monotherapy. Bootstrap results were displayed as a scatter plot and a CEAC was also available (MS pp.128-129).

Subgroup 2 (cisplatin-naïve including stage IVB patients): topotecan plus cisplatin has an ICER of £10,928 per QALY versus cisplatin monotherapy. Bootstrap results were displayed as a scatter plot and a CEAC was also available (MS pp.130-131).

Subgroup 2a (cisplatin-naïve population (excluding stage IVB patients)): topotecan plus cisplatin has an ICER of £8,662 per QALY versus cisplatin monotherapy. Bootstrap results were displayed as a scatter plot and a CEAC was also available (MS pp.132-133).

Subgroup 3 (SCFI patients): topotecan plus cisplatin has an ICER of £32,463 per QALY versus cisplatin monotherapy. Bootstrap results were displayed as a scatter plot and a CEAC was also available (MS p.134).

Subgroup 1b (Stage IVB Patients): the analysis was not performed on the stage IVB patients. The manufacturer points out that there were too few patients in the trial to be able to apply the Lin methodology which lead to the inability of estimating the effect of censored patients.

In the licensed population, the results for the different sensitivity analyses were as follows:

Adopting the alternative utility values increased the ICER of topotecan plus cisplatin versus cisplatin monotherapy by £6466 per QALY to £24,440 per QALY;

Assuming minimum (maximum) wastage of vials of topotecan lowered (raised) the ICER by £1485 (£1479) per QALY to £16,489 (£19,453) per QALY;

Assuming pre-treatment medication on day 1 only lowered the ICER by £879 per QALY to £17,095 per QALY.

For each of the subgroups, each sensitivity analysis moved the ICER in the same direction as in the licensed population. The full tables of results are given in the MS, Tables 41-45 (pp.136-140).

5.3.2 Indirect comparison

In the base case, paclitaxel plus cisplatin was found to be dominated by topotecan plus cisplatin, which in turn had a cost per life year gained of £19,964 versus cisplatin monotherapy.

Where the cost of paclitaxel was assumed to be 50% of the current branded price of Taxol, paclitaxel plus cisplatin was found to be extendedly dominated by topotecan plus cisplatin (which had the same cost per life year gained of £19,964 versus cisplatin monotherapy as in the base case analysis).

Where the hazard ratio from GOG-0204 was adopted instead of that derived from GOG-0169, paclitaxel plus cisplatin was found to have a cost per life year gained of £982 versus topotecan plus cisplatin, casting extreme doubt upon the cost-effectiveness of topotecan.

5.4 Comment on validity of results presented with reference to methodology used

As previously discussed, a complete validation by the ERG of the coding used to implement the SAS individual patient-level direct comparison was not possible. The complexity and opacity of this SAS code and the inexistence of an detailed 'road map', combined with the failure to submit the full datasets and algorithms within the original submission, were considered fundamental to the difficulties caused to the ERG in their attempt to replicate and validate thoroughly all the analysis performed by the manufacturer in an appropriate time line. The coding that was supplied was often repetitive and contained both redundant and unclear code information with substantial use of sparsely annotated algorithms. Indeed, the number of pages of SAS code that were made available in the initial MS was over 100 which highlights the inevitable difficulties that arise given the lack of detailed explanation of the coding.

Despite these important reservations, the ERG received and could decipher sufficient code to ensure that, in general, the approach outlined within the report was followed within the detailed patient level evaluation. However, in depth scrutiny of the code and subsequent responses to the points of clarification revealed a number of potential shortcomings. In particular, the quality of life estimates do not appear to have been derived accurately due to incorrect mapping of data utility values, the impact of mortality appears to have been double counted and concerns exist regarding the imputation methodology. Whilst the manufacturer provided more detail of this process in response to a query from the ERG (MR pp.14-15,,34-36) the ERG remains unconvinced that this estimation process generated reliable estimates of the QoL of each of the assessment points and for each treatment options, and the main issues identified appear likely to result in an overestimate of the incremental QALY difference in favour of topotecan plus cisplatin.

In terms of the associated resource use and cost assumptions employed, the ERG found it difficult to establish the validity of the overall total cost estimates or to compare the cost estimates reported with those report in the indirect analysis given that costs were not presented in the main analysis in a disaggregated form. The ERG considered that the administration costs assigned to topotecan plus cisplatin during the second and third day's administration were potentially significantly under-estimated. In addition, the ERG noted issues regarding the costing of adverse events and the potential exclusion of cost-generating events incurred if multiple adverse events were incurred across separate cycles of treatment.

As a result of these issues the ERG does not regard the ICERs generated by the individual patient-level economic analysis as providing a reliable estimate of the cost-effectiveness of topotecan plus cisplatin compared to cisplatin only. The key issues identified appear to result in a potential overestimation of the incremental QALYs, and the underestimation of the incremental costs (due to issues discussed in 5.2.2), such that the ICER results reported in Section 5.3 are likely to be an underestimate of the true ICER. That is, the ERG consider that the true underlying ICER related to the topotecan plus cisplatin treatment is likely to be higher, when compared to cisplatin alone treatment.

The ERG also has a number of concerns around the indirect comparison. The manufacturer neglected to consider HRQoL within this comparison and reported results in terms of cost-per-life-year-gained rather than cost per QALY. The manufacturer also favoured indirect evidence in calculating overall survival with paclitaxel plus cisplatin - deriving a hazard ratio by comparing the cisplatin arm from GOG-0179 (cisplatin-naïve patients only) to the paclitaxel plus cisplatin arm from GOG-0169 (full ITT population) – and relegated the direct evidence from GOG-0204 to a single sensitivity analysis. It is not clear that the hazard ratio derived from comparing GOG-0179 to GOG-0169 can be appropriately applied to all of the populations of interest. The manufacturer did not take into account dose reduction in the indirect comparison. Furthermore, the manufacturer did not take a probabilistic approach to the indirect modelling, so the uncertainties in each hazard ratio (and in other parameters) are not captured.

Perhaps most significantly, there appears to be inconsistency between the costing of the direct patient-level comparison and that of the indirect comparison: the MS reports that mean costs associated with cisplatin-naïve (including stage IVB) patients given topotecan plus cisplatin is £5,522 in the direct comparison (p.139) but £7,310 in the indirect comparison (the mean costs for patients given cisplatin monotherapy are £2,001 and £2,395 respectively). While a breakdown of the costs in the indirect comparison can be obtained from the Excel model provided, no such breakdown was possible for the direct comparison; the ERG requested such a breakdown from the manufacturer and this was provided in the MR for the licensed population only (Table 31, p.38). However, the manufacturer notes that this breakdown was calculated by "based on the indirect analysis results, assuming that the proportion of cost in each area would remain the same in the direct analysis" (MR p.38), so does not explain the differences observed between the two comparisons.

The ERG believes that these differences may be explained either by differences in the costing of adverse events, or in the failure to take into account dose reduction in the indirect

comparison, or both. The ERG attempted to address these potential shortcomings in Section 6.

Despite these significant criticisms, the indirect comparison does potentially have greater external validity than the direct comparison as it considers an additional comparator; it is also considerably more transparent. As such, this comparison formed the basis of further work by the ERG (Section 6).

5.5 Summary of uncertainties and issues

Both economic submissions are subject to significant uncertainty over the utility values and cost assumptions adopted by the manufacturer, and this uncertainty feeds into the results of the subsequent analyses.

In the direct model, it is not clear that the process used to convert FACT-G scores to utility weights is appropriate, nor is it clear that the alternative utility scores adopted by the manufacturer in a sensitivity analysis (and the revised indirect comparison) are appropriate since they were derived from a study into metabolic breast cancer (Brown, 1998)[15] and not cervical cancer. As noted in Section 1.4.2, a number of assumptions over costs are not properly justified.

The key issues in relation to the direct comparison are the appropriateness of the mapped utility values adopted, the reasonableness of the costing assumptions, the external validity of an analysis with only a single comparator, and (perhaps most importantly) the validity and transparency of the SAS analysis – the ERG was unable to replicate the manufacturer's analysis in the time available due to missing code and missing datasets, severely hampering the ERG's ability to thoroughly validate the comparison made.

The key issues in relation to the indirect comparison were the lack of HRQoL considerations (now rectified by the manufacturer), the appropriateness of the metastatic breast cancer utility values adopted as a proxy in the absence of more suitable cervical cancer values, the reasonableness of the costing assumptions (particularly surrounding the cost of administering topotecan, the number of vials of topotecan required and the cost of adverse events), and the appropriate source of the hazard ratio used to estimate survival for paclitaxel plus cisplatin – deriving this hazard ratio from GOG-0169 favours topotecan plus cisplatin, while deriving it from GOG-0204 favours paclitaxel plus cisplatin.

6 Additional work undertaken by the manufacturer and the ERG

As discussed in section 5, the ERG was unable to comprehensively validate the patient-level analysis due to the manufacturer's failure to provide a fully executable SAS-based model. However, the validation that was possible indicated that there were several sources of potential bias acting in favour of topotecan plus cisplatin. The lack of transparency in the SAS coding and the failure to submit a fully working analysis meant that the ERG could not investigate the potential impact of alternative assumptions directly within the patient-level SAS analysis. Instead, the ERG focused on the Excel-based analysis since this was fully executable, reasonably transparent and importantly allowed a more thorough investigation of the robustness of the ICER estimates submitted by the manufacturer. Hence, the Excel-based analysis formed the basis of the additional work undertaken by the ERG.

The indirect analysis originally submitted by the manufacturer had a number of limitations (see section 5). In particular:

- the analysis did not consider HRQoL, so did not report results in terms of cost-per-QALY;
- the cost of administering topotecan was potentially underestimated;
- only a two year time horizon was considered;
- only the cisplatin-naive patient population was considered (subgroup 4, as defined earlier); and
- the direct data informing the comparison of paclitaxel plus cisplatin and topotecan plus cisplatin from GOG-0204 was only considered in a sensitivity analysis.

6.1.1 Manufacturer revisions

In response to the points for clarification from the ERG, the manufacturer submitted a revised Excel model with the following amendments:

- The time-horizon of the indirect analysis was extended to 36 months. The overall survival hazard ratio for paclitaxel versus cisplatin derived from GOG-0169 (with a 24 month follow-up) was applied to the 36 month data on overall survival with cisplatin

from GOG-0179 to estimate the 36 month survival with paclitaxel. The 36 month survival data for topotecan plus cisplatin were taken directly from GOG-0179.

- The model was extended to evaluate outcomes in terms of both LYG and QALYs. The manufacturer acknowledged that it was an "error" (MR pp.26) to state in the MS that GOG-0169 did not report data on progression-free survival – the manufacturer therefore calculated the progression-free survival hazard ratio for paclitaxel plus cisplatin versus cisplatin monotherapy over the 24 month time-horizon of GOG-0169 and applied this to the 36 month data on progression-free survival for cisplatin monotherapy from GOG-0179 to estimate the 36 month progression-free survival for paclitaxel plus cisplatin. It was assumed that, before progression, patients had either a 'complete-response' to treatment or a 'non-complete response'. The utility weights from Brown 1998[15] (discussed in Section 5.1.3; weights given in MS Table 23, pp.107 and MR Table 19, pp.28) were applied to each health state. Adverse events were assumed to occur only in the first monthly cycle, with the respective utility decrement applied for the entirety of that initial month. Although a utility weight for 'terminal' was reported in the MS (p.107) and is reproduced in the updated Excel model, it was not actually used in any of the calculations of HRQoL.

The manufacturer repeated the analysis using the overall and progression-free survival hazard ratios from GOG-0204 (presented in Monk 2008)[6] in place of the hazard ratios derived from GOG-0169 (MR pp.27). The results of both analyses are presented side-by-side in Table 20 of the MR (p.28). Where the hazard ratios derived from GOG-0169 were used, topotecan plus cisplatin was found to dominate paclitaxel plus cisplatin; where the hazard ratios from GOG-0204 were adopted instead, paclitaxel plus cisplatin was found to have an ICER of £13,260 per QALY versus topotecan plus cisplatin. Note that the analyses reported in Table 20 labelled as 'Branded Taxol price' are in fact based on the generic price for paclitaxel.

6.1.2 ERG revisions

The ERG made a number of further revisions to the model in an attempt to address some of the issues which remained outstanding. These revisions are described in turn below.

Validation

The ERG considered the revisions made to the model by the manufacturer to be appropriate and generally well-implemented. Following a thorough validation of the model, the ERG

noted an inconsistency between the prices of each vial of generic paclitaxel reported in the latest BNF and the prices assumed in the model – these were amended (see Table 6.1.2.1). The ERG also amended the choice of vials used to make up 85ml of cisplatin from 2 x 50ml (£50.74) to 1 x 50ml + 4 x 10ml (£48.77), as this reflected the minimum cost of making up the licensed dose of cisplatin. All subsequent revisions to the model were carried out with these amended assumptions.

Table 6.1.2.1: Revised prices of vials of generic paclitaxel

Vial size	Manufacturer's assumed price	ERG's amended price (from BNF)
5ml	£106.69	£111.41
16.7ml	£319.77	£333.91
25ml	£532.95	£500.86
50ml	£959.31	£1,001.72

Populations

The manufacturer argued in the original submission that "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... as few patients in the former group had prior exposure to cisplatin" (MS pp.85). However, this approach precludes consideration of the wider licensed population within the Excel model. This is a potentially important limitation since the Excel model can be used to inform the direct comparison between topotecan plus cisplatin versus cisplatin alone as well as the indirect comparison against paclitaxel plus cisplatin. For the former of these approaches, a comparison within the different populations is important, particularly given the concerns outlined previously regarding the potential biases within the primary SAS evaluation.

Since the manufacturer's submission and response to the ERG's queries contained sufficient information to repeat each analysis using data from either the cisplatin-naïve population or the main licensed population of GOG-0179, for completeness the ERG has performed analyses utilising both populations and has reported the results for each population separately. Furthermore, the ERG has extended this approach to the indirect comparison

against paclitaxel plus cisplatin. This extension makes the assumption that the same relative effect of paclitaxel plus cisplatin versus topotecan plus cisplatin will hold across the separate populations.

Utility values

As discussed in section 5, the ERG does not consider the utility weights taken from the Brown (1998)[15] study for metastatic breast cancer as necessarily representing a reasonable proxy for the complete set of utility weights associated with cervical cancer. Indeed, the starting utility weight of 0.64 from this source is lower than the starting utility weight derived by the manufacturer from the FACT-G data (0.79, subsequently revised to 0.72 by the ERG) and the mean utility values associated with 'stage I/local' (0.76) or 'stage II/III/regional' (0.68) cervical cancer given in Table 21 of the MS (pp.105). The ERG considered the impact on the model's results of incorporating alternative assumptions regarding the utility weights applied in the model. Three separate scenarios were considered:

- The original 'Brown 1998' weights adopted by the manufacturer, with a starting utility weight of 0.64 ('Utility weights 1').

- A hybrid set of utility weights, with the starting weight (0.67) derived from the literature estimates of mean utility associated with cervical cancer given by the manufacturer (MS Table 21, pp.105) weighted according to the proportion of patients reporting with each grade/stage of disease in GOG-0179 (MS Table 3, pp.40), and the weights for subsequent health states calculated by applying the respective decrement from Brown (1998)[15] to this starting weight. It was further assumed that a patient's utility remained stable at its starting value until the patient progressed (save for a temporary decrement due to an adverse event), and did not (as in the manufacturer's model) increase significantly in the short-term following a 'response' to treatment. The ERG was not convinced that the manufacturer had demonstrated such an improvement in utility to be justified based on the data presented in the submission ('Utility weights 2);.

- An alternative hybrid set of utility weights, similar to the set previously described, except that the starting weight (0.72) is derived from the FACT-G data collected alongside GOG-0179 (recalculated by the ERG using the correct interpretation of the algorithm). Again, the decrements from Brown 1998 are applied to this starting utility weight, and the patient is assumed to remain in this starting utility weight until progression ('Utility weights 3').

The base case results of the revised model are reported in Table 6.1.2.2 for each of these sets of utility weights for the cisplatin-naïve population and the overall licensed population. It can be seen that the ICERs for topotecan plus cisplatin versus cisplatin are broadly similar in each case, suggesting that the ICERs appear reasonably robust to alternative assumptions concerning the choice of utility values. The ERG considered that the most appropriate set of utility weights was probably the third set in which the decrements from Brown (1998)[15] were applied to the revised FACT-G-derived starting weight of 0.72, as this best represents the starting utility of the patients of interest. Subsequent revisions to the model therefore adopted this set of utility weights.

Table 6.1.2.2: Results of ERG-revised model following revisions to utility weights

Cisplatin-naïve population

Treatment	*Costs*	*Utility weights 1*		*Utility weights 2*		*Utility weights 3*	
	Costs	**QALYs**	**ICER**	**QALYs**	**ICER**	**QALYs**	**ICER**
Cisplatin	£2,386	0.4749	N/A	0.5019	N/A	0.5428	N/A
Topotecan + cisplatin	£7,300	0.6690	**£25,309**	0.6897	**£26,156**	0.7433	**£24,513**

Licensed population

Treatment	*Costs*	*Utility weights 1*		*Utility weights 2*		*Utility weights 3*	
	Costs	**QALYs**	**ICER**	**QALYs**	**ICER**	**QALYs**	**ICER**
Cisplatin	£2,196	0.4276	N/A	0.4511	N/A	0.4872	N/A
Topotecan + cisplatin	£6,733	0.5087	**£55,926**	0.5274	**£59,406**	0.5707	**£54,352**

Costs of administration

The ERG was unable to validate the estimates adopted by the manufacturer relating to the administration costs of each treatment, and was concerned that the costs assigned to subsequent infusions of topotecan were potential underestimates of the true costs. The ERG considered that more appropriate estimates of the administration costs for each treatment could be taken from HRG codes SB14Z ("'Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance: Other") and SB15Z ("'Deliver subsequent elements of a chemotherapy cycle: Outpatient") given in the NHS Reference Costs 2006/07, with the former cost (£289, inflated to £299 at 2007/08 prices using the PSSRU price inflator of 1.033 given in the MS) assumed to be that of administering any one of cisplatin, paclitaxel plus cisplatin, or the first day of infusion with topotecan plus cisplatin, and the latter cost (£189, inflated to £195 at 2007/08 prices) assumed to be that of administering each subsequent day of infusion with topotecan plus cisplatin.

The total cost of administering topotecan plus cisplatin was therefore assumed by the ERG to be £689 per cycle, while the cost of administering cisplatin monotherapy or paclitaxel plus cisplatin was assumed to be £299 per cycle. The base case results are given below for both the manufacturer's assumptions over administration costs and the ERG's revised administration costs.

Table 6.1.2.3 demonstrates that these revised assumptions have a significant impact on the cost-effectiveness of topotecan. The ICER of topotecan plus cisplatin compared to cisplatin increases from £24,513 per QALY, using the manufacturer's original assumptions, to £31,831 per QALY in the cisplatin-naïve population (and from £54,352 to £68,885 per QALY in the main licensed population. The ERG considers that the revised administration costs are potentially a more reliable estimate of the true costs that would be incurred by the NHS since they are derived from National Reference Cost data as opposed to being informed by assumptions. These revised costs are therefore adopted in subsequent revisions of the model.

Table 6.1.2.3: Results of ERG-revised model following revisions to administration costs

Manufacturer's assumed administration costs

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,386	0.5428	N/A	£2,196	0.4872	N/A
Topotecan + cisplatin	£7,300	0.7433	**£24,513**	£6,733	0.5707	**£54,352**

ERG's preferred administration costs

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Topotecan + cisplatin	£8,724	0.7433	**£31,831**	£7,909	0.5707	**£68,885**

Number of vials of topotecan

As discussed in section 5.2.1.2, the ERG has concerns surrounding the assumption over the number of vials of topotecan that would be utilised in practice. While the ERG believes that the manufacturer's 'maximum wastage' assumption is most consistent with the SmPC's guidance, the manufacturer's submission also reported that "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" (MS pp.110).

Given the lack of a clear position regarding the correct interpretation of the SmPC guidance, the ERG has considered both these scenarios. However, unlike the manufacturer, the ERG does not consider an average scenario, since it appears more appropriate to assume that re-

use is (or equally is not) in accordance with the guidance, in order to assess the implications for the ICER estimates. In the first scenario, it was assumed that vials were reused over a patient's three day administration ('minimum wastage'), in which case a single 4 mg vial (£290.62) is more cost-effective than four 1 mg vials (£390.60); in the second scenario, it was assumed that vials were discarded immediately after use ('maximum wastage'), in which case six 1 mg vials would be most cost-effective (£585.90).

The revised results from the ERG revised model are reported in Table 6.1.2.4. The results demonstrate the ICER results are potentially sensitive to the wastage assumption applied to topotecan. The only ICER estimate below £30,000 per QALY is for the cisplatin-naïve population assuming part re-use of vials.

Table 6.1.2.4: Results of ERG-revised model following revisions to number of vials of topotecan utilised

Minimum wastage (vials of topotecan may be re-used over 3 day administration)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Topotecan + cisplatin	£7,711	0.7433	**£26,778**	£7,073	0.5707	**£58,872**

Maximum wastage (vials of topotecan disposed of immediately following use)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Topotecan + cisplatin	£9,224	0.7433	**£34,327**	£8,322	0.5707	**£73,833**

Costs associated with dose reduction

As noted in section 5.4, there appears to be some inconsistency in the mean cost estimates obtained based on the direct and indirect comparisons. A thorough investigation of these differences was not possible since the patient-level cost data was not presented in a disaggregated form to facilitate a comparison with the indirect cost estimates. However, this difference was considered, in part at least, to be due to the inclusion of dose reduction due to adverse events on the acquisition costs of topotecan in the patient-level SAS analysis. While the direct comparison modelled dose reduction on a patient-level basis and applied lower drug costs to patients subject to dose reductions, the indirect model did not take dose reductions into account in the costing. Since the intention of the manufacturer's indirect model was to compare topotecan plus cisplatin directly with paclitaxel plus cisplatin, this omission may be justified on the basis that the adverse event profiles of topotecan and paclitaxel, on which dose reductions are driven, are not significantly different (MS Table 19, pp.94), and so the effect of the dose reduction may 'net out' of the model's results. However, where the Excel model is used to compare topotecan plus cisplatin versus cisplatin monotherapy – treatments with quite different adverse event profiles – this omission potentially biases the results against topotecan by overstating the costs of topotecan treatment.

The ERG was unable to replicate the dose reduction methodology employed in the patient level analysis into the Excel model; as such, an alternative approach was taken by the ERG. The ERG calculated the differences between the mean costs associated with each treatment in the manufacturer's revised Excel model and those in the ERG's revised Excel model. These differences are reported in Table 6.1.2.5. For example, the manufacturer calculated a mean cost for topotecan plus cisplatin of £7310 in the cisplatin-naive population, whereas the ERG calculated a mean cost in the same population of £7711 with minimum wastage of topotecan (or £9224 with maximum wastage of topotecan). These differences were driven by the ERG's revised administration costs, more efficient choice of cisplatin vials and alternative number of vials of topotecan assumed to be required each cycle. The ERG then applied these differences in mean costs to the absolute estimates of mean costs reported in the results of the manufacturer's relevant *direct* comparison. These estimates were then compared with the mean QALY results from the ERG's revised Excel model, and the respective ICERs were then re-calculated. These results are reported in Table 6.1.2.6.

While this 'hybrid' analysis may be viewed as somewhat unsatisfactory since the ERG is unable to fully validate the patient-level analysis from which the baseline costs are derived,

this would appear to be the only method of integrating the ERG's revised cost and utility assumptions with a method of costing which takes into account the effects of dose reduction.

Table 6.1.2.5: Cost differences between the manufacturer's revised Excel model and the ERG's revised Excel model

Licensed population

Treatment	Manufacturer's average cost	ERG's cost (minimum wastage)		ERG's cost (maximum wastage)	
		Average	Difference	Average	Difference
Topotecan + cisplatin	£6742	£7073	£331	£8322	£1580
Cisplatin	£2203	£2158	-£45	£2158	-£45

Cisplatin-naive population

Treatment	Manufacturer's average cost	ERG's cost (minimum wastage)		ERG's cost (maximum wastage)	
		Average	Difference	Average	Difference
Topotecan + cisplatin	£7310	£7711	£401	£9224	£1914
Cisplatin	£2395	£2344	-£51	£2344	-£51

Table 6.1.2.6: Results of hybrid analysis incorporating dose reduction

Minimum wastage (vials of topotecan may be re-used over 3 day administration)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£1,950	0.5428	N/A	£1,907	0.4872	N/A
Topotecan + cisplatin	£5,923	0.7433	**£19,815**	£6,405	0.5707	**£53,868**

Maximum wastage (vials of topotecan disposed of immediately following use)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£1,950	0.5428	N/A	£1,907	0.4872	N/A
Topotecan + cisplatin	£7,436	0.7433	**£27,362**	£7,654	0.5707	**£68,826**

The results of the 'hybrid' analysis demonstrate the potential significance of the assumption related to dose reduction. The ICER estimates for the cisplatin-naïve population are less than £30,000 per QALY under either the minimum or maximum wastage assumptions. In contrast, the ICER estimates for the entire licensed population exceed £50,000 per QALY under both assumptions.

In the absence of comparable data for paclitaxel on the impact of dose reduction, the fully incremental analysis reported below reverts back to the previous scenario in which dose reduction is not modelled by the ERG.

Comparison with paclitaxel plus cisplatin – fully incremental analysis

The manufacturer's revised model was not equipped to report an ICER for any treatment versus cisplatin since the utility associated with cisplatin monotherapy had not been calculated. The ERG integrated these utility values in the revised Excel model so that

cisplatin could be considered as a comparator alongside topotecan plus cisplatin and paclitaxel plus cisplatin, allowing for a simultaneous incremental cost-per-QALY analysis to be carried out between the three comparators. As with the manufacturer's revised model, the results critically depend on whether the hazard ratios used to calculate overall and progression-free survival for paclitaxel are derived from GOG-0169 (favouring topotecan over paclitaxel) or taken from GOG-0204 (favouring paclitaxel over topotecan). The fully-incremental results are reported separately in Table 6.1.2.7 for both these hazard ratios. These are presented as separate scenarios, rather than attempting to combine the results, based on the concerns noted in section 4.2.2 regarding pooling data from GOG-0169 and GOG-0204, given the direct evidence presented in GOG-0204.

Table 6.1.2.7: Results of ERG-revised model considering paclitaxel plus cisplatin as comparator in fully-incremental analysis

GOG-0169 hazard ratio employed

Minimum wastage (vials of topotecan may be re-used over 3 day administration)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Paclitaxel + cisplatin	£7,694	0.6107	**ED**	£6,638	0.5562	**ED**
Topotecan + cisplatin	£7,711	0.7433	**£26,778**	£7,073	0.5707	**£58,872**

ED = Extendedly dominated

Maximum wastage (vials of topotecan disposed of immediately following use)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Paclitaxel + cisplatin	£7,694	0.6107	**ED**	£6,638	0.5562	**£64,865**
Topotecan + cisplatin	£9,224	0.7433	**£34,327**	£8,322	0.5707	**£116,788**

ED = Extendedly dominated

GOG-0204 hazard ratio employed

Minimum wastage (vials of topotecan may be re-used over 3 day administration)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Paclitaxel + cisplatin	£7,694	0.8572	**£17,021**	£6,638	0.6915	**£21,926**
Topotecan + cisplatin	£7,711	0.7433	**D**	£7,073	0.5707	**D**

D = Dominated

Maximum wastage (vials of topotecan disposed of immediately following use)

	Cisplatin-naïve population			*Licensed population*		
Treatment	**Costs**	**QALYs**	**ICER**	**Costs**	**QALYs**	**ICER**
Cisplatin	£2,344	0.5428	N/A	£2,158	0.4872	N/A
Paclitaxel + cisplatin	£7,694	0.8572	**£17,021**	£6,638	0.6915	**£21,926**
Topotecan + cisplatin	£9,224	0.7433	**D**	£8,322	0.5707	**D**

D = Dominated

Summary of additional work undertaken by the manufacturer and the ERG

Given the difficulties encountered in validating the patient-level SAS analysis and the potential sources of bias identified, the Excel-based analysis formed the basis of the additional work undertaken by the ERG. However, the Excel analysis originally submitted by the manufacturer had a number of limitations (see section 5). In response to the points for clarification from the ERG, the manufacturer submitted a revised Excel model which satisfactorily addressed some but not all of these issues. The ERG therefore carried out a number of additional analyses to explore the robustness of the ICER estimates to alternative assumptions. ICER estimates were presented for a pairwise comparison of topotecan plus cisplatin versus cisplatin monotherapy as well as for a fully incremental analysis incorporating paclitaxel plus cisplatin.

The ERG considered that an alternative set of utility weights may be more appropriate for patients receiving treatment for cervical cancer than those presented by the manufacturer. Where these preferred utility weights were adopted, the ICER of topotecan plus cisplatin versus cisplatin monotherapy was found to be £24,513 per QALY in the cisplatin-naive population and £54,352 in the licensed population.

The ERG highlighted that the manufacturer had also potentially underestimated the costs associated with administering topotecan. Where these revised administration costs were adopted, the ICER of topotecan plus cisplatin versus cisplatin monotherapy rose to £31,831 per QALY in the cisplatin-naive population and £68,885 in the licensed population.

The ERG questioned the manufacturer's assumptions over the number of vials of topotecan required in practice. The manufacturer's 'minimum wastage' assumption appears to contradict the SmPC's guidance, which in turn casts doubt on the appropriateness of the manufacturer's base-case assumption which took the mid-point of this 'minimum wastage' and the 'maximum wastage' assumptions. Nevertheless, in the absence of firm guidance on this issue, the ERG presented results separately for both a revised 'minimum wastage' scenario and a 'maximum wastage' scenario: under 'minimum wastage' of topotecan, the ICER of topotecan plus cisplatin versus cisplatin monotherapy fell to £26,778 in the cisplatin-naive population and £58,872 in the licensed population; while under 'maximum wastage' of topotecan, the ICER of topotecan plus cisplatin versus cisplatin monotherapy rose to £34,327 in the cisplatin-naive population and £73,833 in the licensed population.

There appeared be some inconsistency between the mean cost estimates obtained in the direct and indirect comparisons, potentially due in part to the inclusion of dose reduction due to adverse events in the patient-level analysis but not in the costing of the indirect Excel-based analysis. The ERG was unable to replicate the dose reduction methodology employed in the patient level analysis into the Excel model and so took an alternative 'hybrid approach combining estimates from the patient-level and Excel analyses. Assuming 'minimum wastage' of topotecan, the ICER of topotecan plus cisplatin versus cisplatin monotherapy fell to £19,815 in the cisplatin-naive population and £53,868 in the licensed population; while assuming 'maximum wastage' of topotecan, the ICER of topotecan plus cisplatin versus cisplatin monotherapy rose to £27,362 in the cisplatin-naive population and £68,826 in the licensed population.

Finally, the ERG considered a comparison with paclitaxel in a fully incremental analysis. Where the hazard ratio derived from GOG-0169 was adopted, paclitaxel plus cisplatin was found to be extendedly dominated by topotecan plus cisplatin, except in the licensed population under 'maximum wastage' of topotecan, where both topotecan plus cisplatin and paclitaxel plus cisplatin had ICERs exceeding £60,000 per QALY. Where the hazard ratio derived from GOG-0204 was adopted, paclitaxel plus cisplatin was found to dominate topotecan plus cisplatin under every scenario.

It should be noted that these results are subject to a number of remaining uncertainties, in particular:

- concerns noted in earlier sections regarding whether a comprehensive network of evidence (and the inclusion of other potentially relevant comparators) was investigated;

- the appropriate assumptions to make concerning the re-use of vials of topotecan;
- the most appropriate source of data with which to calculate overall and progression-free survival with paclitaxel (GOG-0169 or GOG-0204; see section 4.2);
- difficulties in establishing whether the differences in the cost estimates in the patient-level and indirect analyses were attributed solely to dose reduction or not;
- the lack of a probabilistic analysis for the Excel analysis such that uncertainty surrounding the ICER estimates are not considered;
- and the impact of considering dose reduction on the costing of all relevant comparators in the fully incremental analysis.

7 Discussion

7.1 Summary of clinical effectiveness issues

The manufacturer's submission presents the results of a systematic review of the literature. However, due to the lack of clarity in the review process, it is not clear whether all relevant evidence was identified. The ERG have not identified any new direct evidence, but note that results of GOG-0204 are due to be published in a peer reviewed journal article in May 2009 (personal communication with B Monk, 24th April 2009).

The network of evidence for the indirect comparison was restricted to one trial evaluating paclitaxel plus cisplatin compared with cisplatin monotherapy. Other potentially relevant trials (eg. Vermorken, 2001[8]) were excluded based on the rationale that the treatments being assessed were not licensed in the population of interest. This is not justified as paclitaxel is not licensed in this population either. The ERG acknowledge that the quality of such evidence is likely to be very limited, but it should be noted that there is a Cochrane Collaboration review due to be completed within the next couple of months.

If GOG-0204 had been formally included, this would have widened the indirect network of evidence to include other trials evaluating cisplatin plus gemcitabine, cisplatin plus vinorelbine, in addition to trials assessing cisplatin plus topotecan and cisplatin plus paclitaxel.

The direct comparison (GOG-0179) reported a trend in favour of the combination therapy, with a median overall survival of 9.4 months with topotecan plus cisplatin versus 6.5 months with cisplatin monotherapy; HR 0.76 (95% CI: 0.59, 0.98, p=0.033). A similar trend was

reported for median progression-free survival: 4.6 months (topotecan/cisplatin) versus 2.9 months (cisplatin); HR 0.76 (95% CI: 0.60, 0.97, p=0.027).

Patients in both treatment groups who had not received prior cisplatin radiotherapy (cisplatin-naïve) reported greater benefit in median overall survival compared to patients who had previously received cisplatin radiotherapy. The safety profile of topotecan plus cisplatin was reported to be predictable and manageable, and there was reportedly no evidence to suggest that QoL was significantly reduced in patients receiving combination therapy.

The manufacturer's original submission acknowledged a further trial (GOG-0204), which directly compares four cisplatin-containing combinations, including topotecan plus cisplatin and paclitaxel plus cisplatin. The trial was closed early as all experimental arms were unlikely to demonstrate a significant advantage compared to paclitaxel plus cisplatin. The manufacturer does not formally include GOG-0204 as part of the submission based on the rationale that the evidence available in the public domain was very limited.

In response to the point for clarification raised by the ERG, the manufacturer reported direct and indirect comparison including GOG-0204. The direct comparison was favourable to the cisplatin plus paclitaxel arm (HR: 1.27 (95% CI: 0.96, 1.69). Pooled data from the indirect and direct evidence resulted in a non-significant trend towards the cisplatin plus topotecan arm; HR 0.98 (95% CI: 0.73, 1.23).

The ERG highlights the importance in the difference between the licensed population and the trial populations included in the submission. Although GOG-0179 reports individual data to identify the licensed population, this was not possible for patients included in GOG-0169 and GOG-0204.

There is also uncertainty over the population that will benefit most from treatment with topotecan plus cisplatin. The number of patients who have received chemoradiation is likely to reduce in the future, thus the number of cisplatin-naïve patients will diminish, which raises the question as to how applicable the results are to a 2009 population.

7.2 Summary of cost effectiveness issues

The manufacturer submitted two separate cost-effectiveness comparisons: a trial-based direct comparison between topotecan plus cisplatin and cisplatin monotherapy based on patient-level data from the GOG-0179 trial, considered by the manufacturer to be the primary analysis within their submission; and a model-based indirect comparison between topotecan plus cisplatin and paclitaxel plus cisplatin, considered to be a secondary analysis.

Justification for the analytic approaches employed (in particular the choice of a patient-level analysis as the main evaluation) was provided in response to a query by the ERG (MR Appendix 1, pp.43-47).

In the base-case direct comparison, the ICER of topotecan plus cisplatin versus cisplatin monotherapy was £17,974 per QALY in the licensed population, £10,928 per QALY in the cisplatin-naive population (excluding IVB patients) and £32,463 per QALY in SCFI patients. In the base-case indirect comparison, paclitaxel plus cisplatin was dominated by topotecan plus cisplatin, which in turn had a cost-per-life-year-gained of £19,964 versus cisplatin monotherapy; where the hazard ratio used to calculate overall survival with paclitaxel plus cisplatin was taken from GOG-0204 (rather than derived from GOG-0169, as in the base-case), paclitaxel plus cisplatin was found to have a cost-per-life-year-gained of £982 versus topotecan plus cisplatin.

The ERG was unable to properly validate the direct patient-level comparison due to the manufacturer's failure to provide fully-executable SAS code in a timely fashion; as such, and in light of the issues with this comparison discussed previously, the ERG does not regard the ICERs generated by this comparison as a reliable indication of the cost-effectiveness of topotecan. While there were a number of issues evident with the indirect comparison, the supplied Excel model was relatively transparent and executable – as such, the ERG decided that the most reliable indication of the cost-effectiveness of topotecan would result from revising this model to amend these issues as best as possible.

In response to queries from the ERG, the manufacturer submitted a revised indirect comparison incorporating HRQoL and a longer time horizon; again, where the hazard ratio derived from GOG-0169 was employed paclitaxel plus cisplatin was dominated by topotecan plus cisplatin, but where the hazard ratio from GOG-0204 was adopted paclitaxel plus cisplatin was found to have an ICER of £13,260 per QALY versus topotecan plus cisplatin.

The ERG made a number of revisions to this model, revising (among other things) the assumptions made over utility values, the costs of administering each treatment and the assumed number of vials of topotecan utilised per treatment cycle. Where the number of vials used was minimised (maximised), the ERG found topotecan plus cisplatin to have an ICER versus cisplatin monotherapy of £26,778 (£34,327) in the cisplatin-naive patient population and £58,872 (£73,833) in the full ITT population of GOG-0179. Where topotecan plus cisplatin, paclitaxel plus cisplatin and cisplatin monotherapy were compared in a fully incremental analysis, topotecan plus cisplatin was found to extendedly dominate paclitaxel plus cisplatin in most scenarios where the GOG-0169 hazard ratio was adopted, but was

dominated by paclitaxel plus cisplatin in all scenarios were the GOG-0204 hazard ratio was adopted.

7.3 Implications for research

The existing research in this area is limited. Further trials are required to establish the efficacy of topotecan plus cisplatin relative to other treatments that are used in UK clinical practice, for example, carboplatin single or combination therapy. Such research should assess all aspects of quality of life, including the impact of treatment toxicities, scheduling and convenience to the patient. It is also important to further untangle which patients will benefit the most from treatments and what factors may moderate the benefits of treatment. For example, further randomised trials in patients with prior cisplatin-based chemoradiotherapy, as there is concern that as more patients receive cisplatin as part of primary chemoradiotherapy, the median survival benefit with first-line combination cisplatin-based chemoradiotherapy may reduce.

The cost-effectiveness results were subject to a number of potential sources of uncertainty. Further research could be undertaken in order to obtain more robust estimates of the potential cost-effectiveness of topotecan plus cisplatin. This research could seek to identify the full network of evidence in order to demonstrate cost-effectiveness against a more complete range of potential comparators. In addition, existing evidence on the quality of life for patients with cervical cancer is limited in terms of informing the development and population of economic models. Further research to provide appropriate utility values for this patient group, reflecting both the stage and course of disease (e.g. impact of disease progression) as well as the specific impact of individual therapies, would be beneficial.

The inclusion of direct evidence from GOG-0204 and evidence from the forthcoming Cochrane Review, both due to be published in Spring/Summer 2009, would increase the network of evidence and enable further assessment of the clinical and cost-effectiveness of treatments used in current UK practice.

Appendix 1: Topotecan NICE submission: response document

The NICE submission for topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix was finalised in February 2009. The submission dossier has now been reviewed by the Evidence Review Group (ERG), Centre for Review and Dissemination/Centre for Health Economics York, and the technical team at NICE. In general terms, both groups felt that the dossier is well presented and clear. However, the ERG and NICE technical team would like further clarification relating to the clinical and cost effectiveness data. This document presents the GSK response to the letter from NICE.

Section A. Clarification on clinical effectiveness

A1. Please provide the full search strategies for each of the individual databases search for both cost effectiveness and clinical effectiveness. The information currently supplied as a general search strategy (pages 171 – 172 has a considerable number of limitations and omissions including:

- The exact syntax, terms and keywords entered into each individual database;
- How the general search strategy was translated for each individual database;
- The number of records identified for each database and the final result set number used:
- The way in which the separate results were combined;
- Accurate numbering of search sets in reported search strategy results.
-

The full search strategies for each of the individual databases searched on DataStar for both cost-effectiveness and clinical effectiveness are presented in Table 1. The clinical effectiveness search identified 179 unique citations and 37 unique citations were identified from the cost effectiveness search.

Table 1. DataStar systematic search strategy

No.	Database	Search term	Results
CP		[Clipboard]	0
1	EMBA	RANDOMIZED ADJ CONTROLLED ADJ TRIALS OR RANDOMIZED ADJ CONTROLLED ADJ TRIAL OR RANDOMISED ADJ CONTROLLED ADJ TRIALS OR RANDOMISED ADJ CONTROLLED ADJ TRIAL OR RANDOMIZED ADJ CLINICAL ADJ TRIAL OR RANDOMIZED ADJ CLINICAL ADJ TRIALS OR RANDOMISED ADJ CLINICAL ADJ TRIAL OR RANDOMISED ADJ CLINICAL ADJ TRIALS OR RCT	1534
2	EMBA	RANDOM ADJ ALLOCATION OR RANDOMIZATION OR RANDOMISATION OR RANDOM ADJ SELECTION	248
3	EMBA	DOUBLE-BLIND OR DOUBLE ADJ BLIND OR SINGLE-BLIND OR SINGLE ADJ BLIND	838
4	EMBA	CLINICAL ADJ TRIAL OR CLINICAL ADJ TRIALS OR PHASE ADJ II OR PHASE ADJ '2' OR PHASE ADJ III OR PHASE ADJ '3' OR PHASE ADJ IV OR PHASE ADJ '4'	3297
5	EMBA	(CLINICAL OR CONTROLLED OR COMPARATIVE OR PLACEBO OR PROSPECTIVE OR RANDOMISED OR RANDOMIZED) NEAR (TRIAL OR STUDY)	6319
6	EMBA	(OPEN-LABEL OR OPEN ADJ LABEL OR NON-BLINDED OR NON ADJ BLINDED) NEAR (TRIAL OR STUDY)	259

No.	Database	Search term	Results
7	EMBA	(RANDOM OR RANDOMISE$ OR RANODMIZE$ OR RANDOMISA$ OR RANDOMIZA$) NEAR (ALLOCATE$ OR ALLOT$ OR ASSIGN$ OR BASIS$ OR DIVID$ OR ORDER$)	130
8	EMBA	(SINGLE OR SINGLE$ OR DOUBLE OR DOUBL$ OR TRIPLE OR TRIPL$) NEAR (BLIND OR BLINDED OR BLINDS OR BLIND$ OR MASK OR MASKS OR MASKED OR MASK$)	961
9	EMBA	META-ANALYSIS OR META-ANALASES OR META ADJ ANALYSIS OR META ADJ ANALYSES OR META ADJ (ANALYSIS OR ANALYSES) OR META-ANALYS$	744
10	EMBA	SYSTEMATIC ADJ REVIEW OR SYSTEMATIC NEAR (RESEARCH OR REVIEW OR SEARCH OR OVERVIEW)	706
11	EMBA	SYNTHES$ NEAR (LITERATURE$ OR STUDIES OR STUDY OR DATA OR RESEARCH$)	379
13	EMBA	(REVIEW OR REVIEWS OR REVIEWED OR REVIEWING OR REVIEWER OR REVIEWERS OR REVIEW$ OR RESEARCH OR researching) SAME (SYSTEMATIC$ OR METHODOLOGIC$ OR QUANTITATIVE$ OR EFFECTIVE$)	4317
14	EMBA	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 13	13240
15	EMBA	PT=EDITORIAL OR PT=LETTER	11628
16	EMBA	CASE ADJ (STUDY OR STUDIES OR REPORT OR REPORTS)	2757
17	EMBA	CROSS-OVER OR CROSS ADJ OVER OR CROSSOVER	474
18	EMBA	15 OR 16 OR 17	14778
19	EMBA	14 NOT 18	12651
20	EMBA	CANCER OR CANCERS OR CANCEROUS	15037
21	EMBA	CARCINOMA OR CARCINOMAS	3915
22	EMBA	MALIGNANT OR MALIGNANCY OR MALIGNANCIES	3291
23	EMBA	TUMOUR OR TUMOURS	1667
24	EMBA	TUMOR OR TUMORS OR TUMOROUS	9032
25	EMBA	NEOPLASM$	1326
26	EMBA	20 OR 21 OR 22 OR 23 OR 24 OR 25	21782
27	EMBA	CERVIX OR CERVICAL	1349
28	EMBA	26 AND 27	682
29	EMBA	28 AND (recurrent OR recurring OR recurr$ OR stage ADJ IVb OR stage ADJ 4b)	82
30	EMBA	HYCAMTIN OR TOPOTECAN OR EVOTOPIN OR HICAMTIN OR HYCAMTIM	35
31	EMBA	platinum ADJ chemotherapy OR platinum-based ADJ chemotherapy OR platinum ADJ based ADJ chemotherapy	41
32	EMBA	PLATINOL OR Cisplatin OR D00275 OR D-0025 OR D ADJ '00275'	393
33	EMBA	oxaliplatin OR Foloxatine OR Transplatin OR Eloxatin OR Eloxatine OR Elplat OR L-platin OR DACPLAT OR l-OHP OR ACT-078 OR act078 OR act ADJ '078'	111
34	EMBA	PARAPLATIN OR Carboplatin OR SPERA OR Satraplatin OR D05807 OR d-05807 OR D ADJ '05807' OR Triplatin ADJ Tertranitrate OR BBR3464 OR bbr-3464 OR bbr ADJ '3464'	133
35	EMBA	AQUPLA OR Nedaplatin OR C2H6N2O3Pt OR CCRIS4088 OR CCRIS ADJ '4088' OR CCRIS-4088 OR NSC ADJ 375101D OR NSC-375101D OR NSC375101D	5
36	EMBA	30 OR 31 OR 32 OR 33 OR 34 OR 35	643

No.	Database	Search term	Results
37	EMBA	19 AND 29 AND 36	2
40	EMBA	ECONOMIC OR ECONOMICS OR ECONOMICAL OR COSTS OR COSTING OR COST OR COSTED OR COST$ OR COST-BENEFIT OR COST ADJ BENEFIT OR COST-EFFECTIVENESS OR COST ADJ EFFECTIVENESS OR COST ADJ EFFECTIVE OR COST-EFFECTIVE OR COST-UTILITY OR COST ADJ UTILITY	4453
41	EMBA	PATIENT ADJ RELATED ADJ COSTS OR PATIENT ADJ RELATED ADJ COST OR BURDEN OR COST ADJ OF ADJ (TREATMENT OR TREATMENTS OR TREATING) OR COSTS ADJ OF ADJ (TREATMENT OR TREATMENTS OR TREATING) OR PHARMACOECONOMIC$ OR ILLNESS ADJ COST OR ILLNESS ADJ COSTS	1204
42	EMBA	(DIRECT OR INDIRECT OR HEALTHCARE) NEAR (COST OR COSTS)	190
43	EMBA	COST-CONSEQUENCE OR COST ADJ CONSEQUENCE	0
44	EMBA	40 OR 41 OR 42 OR 43	5370
45	EMBA	29 AND 36 AND 44	0
46	MEZZ	PT=RANDOMIZED-CONTROLLED-TRIAL OR RANDOMIZED-CONTROLLED-TRIALS.DE. OR RANDOMIZED ADJ CONTROLLED ADJ TRIALS OR RANDOMIZED ADJ CONTROLLED ADJ TRIAL OR RANDOMISED ADJ CONTROLLED ADJ TRIALS OR RANDOMISED ADJ CONTROLLED ADJ TRIAL OR RANDOMIZED ADJ CLINICAL ADJ TRIAL OR RANDOMIZED ADJ CLINICAL ADJ TRIALS OR RANDOMISED ADJ CLINICAL ADJ TRIAL OR RANDOMISED ADJ CLINICAL ADJ TRIALS OR RCT	328020
47	MEZZ	RANDOM-ALLOCATION.DE. OR RANDOMIZATION OR RANDOMISATION OR RANDOM ADJ SELECTION	73779
48	MEZZ	DOUBLE-BLIND-METHOD.DE. OR DOUBLE-BLIND OR DOUBLE ADJ BLIND	118387
49	MEZZ	SINGLE-BLIND-METHOD.DE. OR SINGLE-BLIND OR SINGLE ADJ BLIND	15644
50	MEZZ	PT=CONTROLLED-CLINICAL-TRIAL OR CONTROLLED-CLINICAL-TRIALS.DE. OR CONTROLLED ADJ CLINICAL ADJ (TRIAL OR TRIALS)	92892
51	MEZZ	PT=CLINICAL-TRIAL# OR PT=CLINICAL-TRIAL-PHASE-II OR PT=CLINICAL-TRIAL-PHASE-III OR PT=CLINICAL-TRIAL-PHASE-IV OR CLINICAL-TRIALS.DE. OR CLINICAL ADJ (TRIAL OR TRIALS) OR PHASE ADJ II OR PHASE ADJ '2' OR PHASE ADJ III OR PHASE ADJ '3' OR PHASE ADJ IV OR PHASE ADJ '4'	719883
52	MEZZ	(CLINICAL OR CONTROLLED OR COMPARATIVE OR PLACEBO OR PROSPECTIVE OR RANDOMISED OR RANDOMIZED) NEAR (TRIAL OR STUDY)	1980287
53	MEZZ	(OPEN-LABEL OR OPEN ADJ LABEL OR NON-BLINDED OR NON ADJ BLINDED) NEAR (TRIAL OR STUDY)	9828
54	MEZZ	RANDOM$ NEAR (ALLOCATE$ OR ALLOT$ OR ASSIGN$ OR BASIS$ OR DIVID$ OR ORDER$)	88064
55	MEZZ	(SINGLE OR SINGLE$ OR DOUBLE OR DOUBL$ OR TRIPLE OR TRIPL$) NEAR (BLIND OR BLINDED OR BLINDS OR BLIND$ OR MASK OR MASKS OR MASKED OR MASK$)	135486
56	MEZZ	META-ANALYSIS.DE. OR PT=META-ANALYSIS OR META-ANALYSIS OR META-ANALYSES OR META ADJ ANALYSIS OR META ADJ ANALYSES OR META-ANALYS$ OR META ADJ ANALYS$	35502
57	MEZZ	SYSTEMATIC ADJ REVIEW OR SYSTEMATIC NEAR (RESEARCH OR REVIEW OR SEARCH OR OVERVIEW)	20050
58	MEZZ	SYNTHES$ NEAR (LITERATURE$ OR STUDIES OR STUDY OR DATA OR RESEARCH$)	26981

No.	Database	Search term	Results
59	MEZZ	(REVIEW OR REVIEWS OR REVIEWED OR REVIEWING OR REVIEWER OR REVIEWERS OR REVIEW$ OR RESEARCH$) SAME (SYSTEMATIC$ OR METHODOLOGIC$ OR QUANTITATIVE$ OR EFFECTIVE$)	170338
60	MEZZ	46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59	2381636
61	MEZZ	PT=CASE-REPORTS OR PT=COMMENT OR PT=EDITORIAL OR PT=LETTER	2200034
62	MEZZ	CROSS-OVER-STUDIES.DE.	22637
63	MEZZ	CROSS-OVER OR CROSS ADJ OVER OR CROSSOVER	49709
64	MEZZ	61 OR 62 OR 63	2248834
65	MEZZ	60 NOT 64	2248856
66	MEZZ	ANIMALS.W..DE.	4281803
67	MEZZ	HUMANS.W..DE.	10402118
68	MEZZ	66 NOT (66 AND 67)	3220280
69	MEZZ	65 NOT 68	1833212
70	MEZZ	UTERINE-CERVICAL-NEOPLASMS.DE.	46621
71	MEZZ	CANCER OR CANCERS OR CANCEROUS	992706
72	MEZZ	CARCINOMA OR CARCINOMAS	480634
73	MEZZ	MALIGNAN$	304547
74	MEZZ	TUMOUR$	158063
75	MEZZ	TUMOR OR TUMORS OR TUMOROUS	931945
76	MEZZ	NEOPLASM OR NEOPLASMS OR NEOPLASMIC	1624461
77	MEZZ	71 OR 72 OR 73 OR 74 OR 75 OR 76	2271170
78	MEZZ	CERVIX OR CERVICAL	166677
79	MEZZ	77 AND 78	77302
80	MEZZ	(70 OR 79) AND (RECURR$ OR STAGE ADJ IVB OR STAGE ADJ 4B)	8225
81	MEZZ	HYCAMTIN OR TOPOTECAN OR EVOTOPIN OR HICAMTIN OR HYCAMTIM OR 123948-87-8.RN.	1932
82	MEZZ	PLATINUM ADJ CHEMOTHERAPY OR PLATINUM-BASED ADJ CHEMOTHERAPY OR PLATINUM ADJ BASED ADJ CHEMOTHERAPY	1419
83	MEZZ	PLATINOL OR Cisplatin OR D00275 OR D-0025 OR D ADJ '00275'	39912
84	MEZZ	oxaliplatin OR Foloxatine OR Transplatin OR Eloxatin OR Eloxatine OR Elplat OR L-platin OR DACPLAT OR l-OHP OR ACT-078 OR act078 OR act ADJ '078'	3003
85	MEZZ	PARAPLATIN OR Carboplatin OR SPERA OR Satraplatin OR D05807 OR d-05807 OR D ADJ '05807' OR Triplatin ADJ Tertranitrate OR BBR3464 OR bbr-3464 OR bbr ADJ '3464'	9120
86	MEZZ	AQUPLA OR Nedaplatin OR C2H6N2O3Pt OR CCRIS4088 OR CCRIS ADJ '4088' OR CCRIS-4088 OR NSC ADJ 375101D OR NSC-375101D OR NSC375101D	297
87	MEZZ	81 OR 82 OR 83 OR 84 OR 85 OR 86	49571
88	MEZZ	69 AND 80 AND 87	329
89	MEZZ	YEAR=2008 OR YEAR=2007 OR YEAR=2006	2123812
90	MEZZ	88 AND 89	56

No.	Database	Search term	Results
91	MEZZ	ECONOMIC$ OR COSTS OR COSTING OR COST OR COSTED OR COST$ OR COST-BENEFIT OR COST ADJ BENEFIT OR COST-EFFECTIVENESS OR COST ADJ EFFECTIVENESS OR COST ADJ EFFECTIVE OR COST-EFFECTIVE OR COST-UTILITY OR COST ADJ UTILITY	536228
92	MEZZ	PATIENT ADJ RELATED ADJ COSTS OR PATIENT ADJ RELATED ADJ COST OR BURDEN OR COST ADJ OF ADJ TREAT$ OR COSTS ADJ OF ADJ TREAT$ OR PHARMACOECONOMIC$ OR ILLNESS ADJ COST OR ILLNESS ADJ COSTS	54608
93	MEZZ	COSTS-AND-COST-ANALYSIS.DE. OR COST-OF-ILLNESS.DE. OR ECONOMICS.W..DE.	287008
94	MEZZ	COST-BENEFIT-ANALYSIS.DE.	43817
95	MEZZ	ECONOMICS-HOSPITAL.DE. OR ECONOMICS-MEDICAL.DE. OR ECONOMICS-NURSING.DE. OR ECONOMICS-PHARMACEUTICAL.DE.	20910
96	MEZZ	(DIRECT OR INDIRECT OR HEALTHCARE) NEAR (COST OR COSTS)	10412
97	MEZZ	COST-CONSEQUENCE OR COST ADJ CONSEQUENCE	77
98	MEZZ	91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97	575909
99	MEZZ	80 AND 87 AND 98	7
100	EMZZ	RANDOMIZED-CONTROLLED-TRIAL.DE. OR RANDOMIZED ADJ CONTROLLED ADJ TRIALS OR RANDOMIZED ADJ CONTROLLED ADJ TRIAL OR RANDOMISED ADJ CONTROLLED ADJ TRIALS OR RANDOMISED ADJ CONTROLLED ADJ TRIAL OR RANDOMIZED ADJ CLINICAL ADJ TRIAL OR RANDOMIZED ADJ CLINICAL ADJ TRIALS OR RANDOMISED ADJ CLINICAL ADJ TRIAL OR RANDOMISED ADJ CLINICAL ADJ TRIALS OR RCT	190499
101	EMZZ	RANDOMIZATION.W..DE. OR RANDOMIZATION OR RANDOMISATION OR RANDOM ADJ SELECTION	35844
102	EMZZ	DOUBLE-BLIND-PROCEDURE.DE. OR DOUBLE-BLIND OR DOUBLE ADJ BLIND	110949
103	EMZZ	SINGLE-BLIND-PROCEDURE.DE. OR SINGLE-BLIND OR SINGLE ADJ BLIND	11760
104	EMZZ	CONTROLLED-CLINICAL-TRIAL.DE. OR CLINICAL-TRIAL.DE. OR CONTROLLED ADJ CLINICAL ADJ (TRIAL OR TRIALS)	553384
105	EMZZ	CLINICAL ADJ TRIALS OR CLINICAL ADJ TRIAL OR PHASE ADJ II OR PHASE ADJ '2' OR PHASE ADJ III OR PHASE ADJ '3' OR PHASE ADJ IV OR PHASE ADJ '4'	630574
106	EMZZ	(CLINICAL OR CONTROLLED OR COMPARATIVE OR PLACEBO OR PROSPECTIVE OR RANDOMISED OR RANDOMIZED) NEAR (TRIAL OR STUDY)	4270797
107	EMZZ	(OPEN-LABEL OR OPEN ADJ LABEL OR NON-BLINDED OR NON ADJ BLINDED) NEAR (TRIAL OR STUDY)	9810
108	EMZZ	RANDOM$ NEAR (ALLOCATE$ OR ALLOT$ OR ASSIGN$ OR BASIS$ OR DIVID$ OR ORDER$)	79653
109	EMZZ	(SINGLE OR SINGLE$ OR DOUBLE OR DOUBL$ OR TRIPLE OR TRIPL$) NEAR (BLIND OR BLINDED OR BLINDS OR BLIND$ OR MASK OR MASKS OR MASKED OR MASK$)	124065
110	EMZZ	META-ANALYSIS.DE. OR META-ANALYSIS OR META-ANALASES OR META ADJ ANALYSIS OR META ADJ ANALYSES OR META ADJ (ANALYSIS OR ANALYSES) OR META-ANALYS$	43374
111	EMZZ	SYSTEMATIC-REVIEW.DE. OR SYSTEMATIC ADJ REVIEW OR SYSTEMATIC NEAR (RESEARCH OR REVIEW OR SEARCH OR OVERVIEW)	34946

No.	Database	Search term	Results
112	EMZZ	(SYNTHESI$ OR SYNTHESE$ OR SYNTHES) NEAR (LITERATURE$ OR STUDIES OR STUDY OR DATA OR RESEARCH$)	20475
113	EMZZ	(REVIEW OR REVIEWS OR REVIEWED OR REVIEWING OR REVIEWER OR REVIEWERS OR REVIEW$ OR RESEARCH$) SAME (SYSTEMATIC$ OR METHODOLOGIC$ OR QUANTITATIVE$ OR EFFECTIVE$)	184376
114	EMZZ	PHASE-2-CLINICAL-TRIAL.DE. OR PHASE-3-CLINICAL-TRIAL.DE. OR PHASE-4-CLINICAL-TRIAL.DE.	26893
115	EMZZ	100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114	4443698
116	EMZZ	PT=EDITORIAL OR PT=LETTER	666007
117	EMZZ	CASE ADJ (STUDY OR STUDIES OR REPORT OR REPORTS)	1104700
118	EMZZ	CROSSOVER-PROCEDURE.DE.	20812
119	EMZZ	CROSS-OVER OR CROSS ADJ OVER OR CROSSOVER	45506
120	EMZZ	116 OR 117 OR 118 OR 119	1723243
121	EMZZ	115 NOT 120	4256293
122	EMZZ	ANIMAL.W..DE.	26500
123	EMZZ	HUMAN.W..DE.	6366538
124	EMZZ	122 NOT (122 AND 123)	22488
125	EMZZ	121 NOT 124	4253636
126	EMZZ	UTERINE-CERVIX-CANCER#.DE.	37886
127	EMZZ	CANCER OR CANCERS OR CANCEROUS	1582266
128	EMZZ	CARCINOMA OR CARCINOMAS	442187
129	EMZZ	MALIGNANT OR MALIGNANCY OR MALIGNANCIES	281509
130	EMZZ	TUMOUR OR TUMOURS	141403
131	EMZZ	TUMOR OR TUMORS OR TUMOROUS	855266
132	EMZZ	NEOPLASM$	69484
133	EMZZ	127 OR 128 OR 129 OR 130 OR 131 OR 132	1930494
134	EMZZ	CERVIX OR CERVICAL	133587
135	EMZZ	133 AND 134	62198
136	EMZZ	(126 OR 135) AND (RECURRENT OR RECURRING OR RECURR$ OR STAGE ADJ IVB OR STAGE ADJ 4B)	7309
137	EMZZ	HYCAMTIN OR TOPOTECAN OR EVOTOPIN OR HICAMTIN OR HYCAMTIM OR 123948-87-8.RN.	5155
138	EMZZ	PLATINUM ADJ CHEMOTHERAPY OR PLATINUM-BASED ADJ CHEMOTHERAPY OR PLATINUM ADJ BASED ADJ CHEMOTHERAPY	1402
139	EMZZ	PLATINOL OR Cisplatin OR D00275 OR D-0025 OR D ADJ '00275'	76634
140	EMZZ	oxaliplatin OR Foloxatine OR Transplatin OR Eloxatin OR Eloxatine OR Elplat OR L-platin OR DACPLAT OR l-OHP OR ACT-078 OR act078 OR act ADJ '078'	7360
141	EMZZ	PARAPLATIN OR Carboplatin OR SPERA OR Satraplatin OR D05807 OR d-05807 OR D ADJ '05807' OR Triplatin ADJ Tertranitrate OR BBR3464 OR bbr-3464 OR bbr ADJ '3464'	24061
142	EMZZ	AQUPLA OR Nedaplatin OR C2H6N2O3Pt OR CCRIS4088 OR CCRIS ADJ '4088' OR CCRIS-4088 OR NSC ADJ 375101D OR NSC-375101D OR NSC375101D	452
143	EMZZ	137 OR 138 OR 139 OR 140 OR 141 OR 142	93751
144	EMZZ	125 AND 136 AND 143	645
145	EMZZ	YEAR=2008 OR YEAR=2007 OR YEAR=2006	1716594
146	EMZZ	144 AND 145	165
147	EMZZ	ECONOMIC OR ECONOMICS OR ECONOMICAL OR COSTS OR COSTING OR COST OR COSTED OR COST$ OR COST-BENEFIT OR COST ADJ BENEFIT OR COST-EFFECTIVENESS OR COST ADJ	580317

No.	Database	Search term	Results
		EFFECTIVENESS OR COST ADJ EFFECTIVE OR COST-EFFECTIVE OR COST-UTILITY OR COST ADJ UTILITY	
148	EMZZ	PATIENT ADJ RELATED ADJ COSTS OR PATIENT ADJ RELATED ADJ COST OR BURDEN OR COST ADJ OF ADJ (TREATMENT OR TREATMENTS OR TREATING) OR COSTS ADJ OF ADJ (TREATMENT OR TREATMENTS OR TREATING) OR PHARMACOECONOMIC$ OR ILLNESS ADJ COST OR ILLNESS ADJ COSTS	86095
149	EMZZ	COST.W..DE. OR COST-BENEFIT-ANALYSIS.DE. OR COST-EFFECTIVENESS-ANALYSIS.DE. OR HEALTH-CARE-COST.DE. OR COST-OF-ILLNESS.DE.	153721
150	EMZZ	ECONOMICS.W..DE. OR HEALTH-ECONOMICS.DE. OR PHARMACOECONOMICS.W..DE.	57236
151	EMZZ	(DIRECT OR INDIRECT OR HEALTHCARE) NEAR (COST OR COSTS)	8778
152	EMZZ	COST-CONSEQUENCE OR COST ADJ CONSEQUENCE	70
153	EMZZ	147 OR 148 OR 149 OR 150 OR 151 OR 152	614926
154	EMZZ	136 AND 143 AND 153	30
155	EMBA EMZZ MEZZ [all]	combined sets 37, 90, 146	223
156	EMBA EMZZ MEZZ [all]	dropped duplicates from 155	44
157	EMBA EMZZ MEZZ [all]	unique records from 155	179
158	MEZZ	split set 157	56
159	EMBA	split set 157	1
160	EMZZ	split set 157	122
161	EMBA EMZZ MEZZ [all]	combined sets 45, 99, 154	37
162	EMBA EMZZ MEZZ [all]	dropped duplicates from 161	3
163	EMBA EMZZ MEZZ [all]	unique records from 161	34
164	MEZZ	split set 163	7
165	EMBA	split set 163	0
166	EMZZ	split set 163	27

EMBA: Embase Alert; EMZZ: Embase; MEZZ: Medline.

The systematic search strategy for the Cochrane Library is presented overleaf (Table 2). Pooling the DataStar and Cochrane clinical effectiveness search results resulted in 203 unique citations.

Table 2. Cochrane Library systematic search strategy

ID	Search	Hits
#1	MeSH descriptor **Uterine Cervical Neoplasms**, this term only	1173
#2	(cancer*) or (carcinoma*) or (malignan*) or (tumour* or tumor*) or (neoplasm*)	64379
#3	(cervix or cervical)	7096
#4	(#2 AND #3)	2279
#5	(#1 OR #4)	2279
#6	(hycamtin or topotecan or evotopin or hicamtin or hycamtim) or (123948-87-8)	207
#7	(platinum chemotherapy) or (platinum-based chemotherapy) or (platinum based chemotherapy)	731
#8	(PLATINOL OR Cisplatin OR D00275 OR D-0025 OR "D 00275")	4817
#9	(oxaliplatin OR Foloxatine OR Transplatin OR Eloxatin OR Eloxatine OR Elplat OR L-platin) or (DACPLAT OR l-OHP OR ACT-078 OR act078 OR "act 078")	287
#10	(PARAPLATIN OR Carboplatin OR SPERA OR Satraplatin OR D05807 OR d-05807 OR "D 05807") or (Triplatin Tertranitrate OR BBR3464 OR bbr-3464 OR "bbr 3464")	1564
#11	(AQUPLA OR Nedaplatin OR C2H6N2O3Pt OR CCRIS4088 OR "CCRIS 4088") or (CCRIS-4088 OR "NSC 375101D" OR NSC-375101D OR NSC375101D)	8
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	6320
#13	(recurr* OR stage IVb stage 4b)	23317
#14	(#5 AND #12 AND #13)	94
#15	(#14), from 2006 to 2008	26

A2. Please clarify whether Medline In-Process Citations was searched, if it was not searched, please provide a reason for not doing so.
The Medline In-Process database was included in the Medline search.

A3 Please provide the full HEED search strategy for the cost-utility search described in Appendix 5.
The full HEED search strategy is presented below (Table 3).

Table 3. HEED systematic search strategy

ID	Search	Hits
#1	AX= 'CANCER*' OR 'CARCINOMA*' OR 'MALIGNAN*'	4629
#2	AX='tumor*' or 'tumour*' or 'neoplasm*'	1000
#3	CS=1 OR 2	4859
#4	AX='CERVIX' OR 'CERVICAL'	542
#5	CS=3 AND 4	375
#6	AX='HYCAMTIN' OR 'TOPOTECAN' OR 'EVOTOPIN' OR 'HICAMTIN' OR 'HYCAMTIM'	27
#7	AX='platinum*' AND 'chemotherapy'	18
#8	AX='PLATINOL' OR 'Cisplatin' OR 'D00275' OR 'D-0025' OR 'D 00275'	159
#9	Ax='oxaliplatin' OR 'Foloxatine' OR 'Transplatin' OR 'Eloxatin' OR 'eloxatine' OR 'Elplat' OR 'L-platin'	25
#10	AX='DACPLAT' OR 'l-OHP' OR 'ACT-078' OR 'act078' OR 'act 078'	0
#11	AX='PARAPLATIN' OR 'Carboplatin' OR 'SPERA' OR 'Satraplatin' OR 'D05807' OR 'd-05807' OR 'D 05807' OR 'Triplatin Tertranitrate' OR 'BBR3464' OR 'bbr-3464' OR 'bbr 3464'	57
#12	AX='AQUPLA' OR 'Nedaplatin' OR 'C2H6N2O3Pt' OR 'CCRIS4088' OR 'CCRIS 4088' OR 'CCRIS-4088' OR 'NSC 375101D' OR 'NSC-375101D' OR 'NSC375101D'	1
#13	CS=6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	226
#14	AX='recurr*' OR 'stage IVb' OR 'Stage 4b'	1094
#15	CS=5 AND 13 AND 14	0

A4. Please provide the URL for the page from which you searched and the search terms used for the following resources:

- **American Society of Clinical Oncology (ASCO) website (http://www.asco.org) annual meeting abstracts**
- **European Society of Medical Oncology (ESMO) website (http://wwwesmo.org) annual meeting abstracts**
- **Canadian Medical Association Infobase website**

ASCO annual meeting abstracts for the years 2005 to 2008 were searched using the term "cervical cancer" in the title field at the following URL: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts

ESMO annual meeting abstracts for gynaecological cancers for the years 2005 to 2008 were identified at the following URL:http://www.esmo.org/research/abstracts.html

The Canadian Medical Association Infobase website was searched for "cervical cancer" at the following URL:http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm

Study selection

A5. Please provide a clear and transparent rationale for the study selection in the systematic review. This should include a comprehensive list of trials considered at the data extraction stage (with study details e.g. design (Phase II/III), population, comparators, data reported on OS and/or PFS) and, where relevant, the reason for exclusion. The following three points provide specific examples of where further information is required:

- **Please list the specific inclusion and exclusion criteria used to select comparator studies and clarify why data from studies stopped early were not**

included (e.g. Cadron et al, 2005: Report of an Early Stopped Randomized Trial Comparing Cisplatin vs Cisplatin/Ifosamide/5-Flurouracil in Recurrent Cervical Cancer).

- **Please explain the reasons for not including some of the single-agent cisplatin studies included in The Cancer Care Ontario systematic review (e.g. Omura, 1997 and Cadron, 2005) (page 34).**
- **Please explain the inclusion of trial GSK-CRT-234 (page 35) and reasons for not including other Phase II safety and efficacy studies of topotecan, particularly trials that may have included stage IVB patients, which were not included in GSK-CRT-234.**

As described in the original submission, an analysis of the IMS Oncology Analyzer database was conducted, capturing data from Q3 2004 until Q3 2008. This analysis demonstrated that cisplatin monotherapy constitutes the key alternative intervention in the population in which combination therapy with topotecan and cisplatin is licensed. Feedback from UK clinicians 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 was addressed in the submission. Due to the limited and inconsistent use of other treatments they were not considered as key comparators in this appraisal of topotecan.

Eligible studies for the systematic review were Phase III 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 the submission).
-

For the indirect comparisons, all of the above inclusion criteria needed to be achieved. Exclusion criteria for the indirect comparisons included the evaluation of unlicensed comparators and the presence of only one treatment arm.
It should be noted that GSK-CRT-234, a single arm Phase II study, was included in the submission dossier as supporting data only.
Table 4 provides a summary of studies that were eligible for data extraction and the reasons why studies were not incorporated in the indirect comparison analyses, using the common comparator, cisplatin – a prerequisite for an indirect comparison.

Table 4. Reasons why studies were excluded from the indirect comparison analyses

Author	Reason for exclusion from indirect comparison analysis
Studies identified directly from the systematic literature search	
Franckena[1]	Trial uses data from Ph I and Ph II and follow up study and combined with thermometry
Long[2]	Endometrial cancer
Pectasides[3]	Non-systematic review
Watanabe[4]	Only one treatment arm
Hsiao[5]	Only one treatment arm
Hirte[6]	**CCO Systematic review – identified studies from this discussed below**
du Bois[7]	All pts received PLD and carboplatin (non-randomised)
Benjapibal[8]	Only one treatment arm
van Lujik[9]	Only one treatment arm
Matulonis[10]	Only one treatment arm
Maluf[11]	Only one treatment arm
Choi[12]	Only one treatment arm
Smith[13]	Only one treatment arm
Studies originally identified in the CCO systematic review	
Vermorken[14]	BEMP not licensed in cervical cancer
Omura[15]	Combination cisplatin + mitolactol and cisplatin + ifosfamide not licensed in cervical cancer
Garin[16]	Irinotecan alone or in combination with cisplatin not licensed in cervical cancer
Alberts[17]	Cisplatin +mitomycin-C and MVBC not licensed in cervical cancer
Cadron[18]	PIF not licensed in cervical cancer, early closure, only 21 patients
Bloss[19]	CIB and Cisplatin + ifosfamide not licensed, no common cisplatin alone arm
Bezwoda[20]	Cisplatin + MTX not licensed, no common cisplatin alone arm
McGuire[21]	Comparators not licensed in cervical cancer
Lira-Puerto[22]	Comparators not licensed in cervical cancer
Thomsen[23]	Comparators not licensed in cervical cancer

Author	Reason for exclusion from indirect comparison analysis
Studies identified by handsearching	
Stamatovic[24]	Cisplatin pre-treated, capecitabine in trial
Padilla[25]	Only one treatment arm
Lee[26]	Only one treatment arm
Kuo[27]	Only one treatment arm
Wenzel[28]	Only QoL recorded & limited info on trial
Monk[29]	Early closure and data not yet mature
Rubio[30]	Topotecan arm only – unlicensed in cervical cancer

For completeness, key result data are presented below in Table 5 for the single arm studies and studies evaluating unlicensed comparators described in Table 4, above.

Table 5. Key results data for single arm studies and studies evaluating unlicensed comparators

Author	Number of pts	Treatment Arms	Response rate	Median Survival (months)	Median PFS (months)
Studies identified directly from the systematic literature search					
Watanabe	20	Docetaxel + nedaplatin	9-13 %	NR	NR
Hsiao	21	Cisplatin + fluorouracil + leucovorin	25%	10.5	2.3
du Bois	31/140	Pegylated liposomal doxorubicin + carboplatin	12%	NR	NR
Benjapibal	16	Capecitabine +cisplatin	50%	23	9
van Lujik	161	BEMP	27%	12.9	6.2
Matulonis	28	Cisplatin + gemcitabine	NR	11.9	NR
Maluf	30	Tirapazamine + cisplatin	27.80%	NR	NR
Choi	53	Paclitaxel + ifosfamide + cisplatin	46.70%	19	8
Smith	56	Cisplatin + tirapazamine	32.10%	6.9	4.7
Studies originally identified in the CCO systematic review					
Vermorken 2001	144	Cisplatin	20 (14%)	9.3	4.5
	143	BEMP	35 (24%) p=0.005	10.1	5.3
Omura 1997	140	Cisplatin	25 (18%)	8	3.2

Author	Number of pts	Treatment Arms	Response rate	Median Survival (months)	Median PFS (months)
	147	Cisplatin + mitolactol	31 (21%)	7.3	3.3
	151	Cisplatin + ifosfamide	47 (34%) p=0.004	8.3	4.6 p=0.003
Garin 2001	31	Cisplatin	6 (19%)	NR	NR
	27	Cisplatin + irinotecan	10 (37%)	NR	NR
	39	Irinotecan	5 (13%)	NR	NR
Alberts 1987	9	Cisplatin	3 (33%)	17	NR
	51	Cisplatin + mitomycin-C	13 (25%)	7	NR
	54	MVBC	12 (22%)	6.9	NR
Cadron 2005	11	Cisplatin	1 (9%)	13	NR
	10	PIF	4 (40%)	12.3	NR
Bloss 2002	146	Cisplatin + ifosfamide	47 (32%)	8.5	4.6
	141	CIB	44 (32%)	8.4	5.1

Author	Number of pts	Treatment Arms	Response rate	Median Survival (months)	Median PFS (months)
Bezwoda 1986	37	Cisplatin + MTX	21 (57%)	11	NR
	13	Hydroxyurea	0%	9	NR
McGuire 1989	175	Carboplatin	27 (15%)	6.2	2.7
	177	Iproplatin	19 (11%)	5.5	3
Lira-Puerto 1991	46	Carboplatin	12 (26%)	7.5	NR
	40	Iproplatin	12 (30%)	7.6	NR
Thomsen 1998	12	Carboplatin	4 (33%)	9.2	4.6
	14	Teniposide	4 (29%)	9.5	3.9
Studies identified by hand searching (ASCO abstracts)					
Padilla	NR	Topotecan + cisplatin + radiation therapy	NR	NR	NR
Lee	39	Fluorouracil + cisplatin	45.70%	45	NR
Kuo	17	Oxaliplatin + paclitaxel	29%	NR	21 weeks
Monk 2008	138	Paclitaxel + cisplatin	29.1	NR	NR
	138	Vinorelbine + cisplatin	25.9	NR	NR
	119	Gemcitabine + cisplatin	22.3	NR	NR
	118	Topotecan + cisplatin	23.4	NR	NR
Rubio	33	Topotecan	NR	14	4.17

Direct comparison

A6. Please provide additional QoL data. Specifically:
The descriptive statistics for the data presented in Figure 11, e.g. mean (SD), number of patients at each time point
Data for each of the FACT-G subscales – e.g. mean (SD), number of patients at each time point
Data for the UNISCALE results.

Please also clarify whether there is any QoL data available after the 9-month post randomisation period.
145 patients in each treatment group were included in the QoL component of the study. (Three patients in the ITT population chose not to participate in the QoL part of the study.) Table 6, below, shows (in **bold**) the number of patients with valid QoL scores at each of the 4 time points. The proportion of patients with valid data decreased by a similar amount in both arms of the study over the 4 time points.

Table 6. Compliance rates of patients in the study by treatment over the 4 time points

	Cisplatin			Topotecan/Cisplatin		
Assessment Point	Died[a]/Refused[b]	Valid/Expected[c]	%	Died[a]/Refused[b]	Valid/Expected[c]	%
Prior to randomisation	0/1	**143**/145	99	0/2	**141**/145	97
Prior to cycle 2	10/2	**115**/134	86	14/4	**109**/1029	84
Prior to cycle 5	39/2	**67**/105	64	34/3	**79**/110	72
9 months post-randomisation	87/4	**31**/55	56	78[d]/2	**42**/67	63

a. Cumulative number of deaths
b. Refused for reason other than illness
c. Includes all patients except those who died or refused
d. One patient erroneously entered as death

Descriptive statistics for the data presented in Figure 11 of the submission are presented in Table 7, including data for the cervical cancer and neurotoxicity subscales and data for the UNISCALE results at each of the 4 time points. Data for the FACT-G subscales, physical well-being, functional well-being, social well-being and emotional wellbeing, were not presented by the GOG study group in the study publications or the clinical study report. GSK do not have access to this data.
There are no QoL data available after the 9-month post randomisation period. Even if these had been collected, it is doubtful how representative they would be as it is likely that the number and proportion of valid questionnaires would be small.

Table 7. Mean QoL scores over time by treatment group in the GOG-0179 trial

Instrument	Cisplatin		Topotecan/cisplatin	
	Mean	**SD**	**Mean**	**SD**
Prior to randomisation	*n=143*		*n=141*	
FACT-G	71.5	16.7	68.0	17.1
Cx	40.5	8.6	39.3	8.1
NTX	6.7	6.2	6.7	6.4
BPI	47.6	35.9	52.2	35.9
UNISCALE	6.3	2.2	6.1	2.2
Prior to cycle 2	*n=115*		*n=109*	
FACT-G	70.7	18.0	70.8	18.5
Cx	39.3	8.2	40.4	8.8
NTX	7.1	6.6	6.5	5.5
BPI	44.4	36.9	40.2	33.2
UNISCALE	6.0	2.2	6.3	2.0
Prior to cycle 5	*n=67*		*n=79*	
FACT-G	71.5	18.7	75.3	17.3
Cx	40.1	8.2	41.7	8.6
NTX	6.4	5.4	6.7	5.5
BPI	37.1	32.0	37.9	33.6
UNISCALE	6.2	2.1	7.0	4.7
9 months post-randomisation	*n=31*		*n=42*	
FACT-G	74.5	18.8	74.4	17.8
Cx	38.9	9.9	41.3	7.8
NTX	10.1	8.9	8.9	7.0
BPI	35.9	34.3	39.7	32.8
UNISCALE	6.7	2.2	6.4	2.3

BPI: Brief Pain Inventory; Cx: Cervix Subscale; FACT-G: Functional Assessment of Cancer Therapy-General; NTX: Neurotoxicity Subscale

FACT-G subscale data and QoL data after the 9-month post randomisation period were not provided by the Gynecologic Oncology Group.

A7. Please clarify whether any patients were crossed over to other treatments (e.g. after treatment for haematological toxicities, were patients continued with the same treatment or were they started on a different treatment). Please provide details of any subsequent therapies received by patients in each treatment arm. This relates both to cross-over but also non-study drugs as well.

If toxicities necessitated stopping treatment therapy, then the patient was recorded as having discontinued therapy and was withdrawn from the study. There were no cross-over treatments for patients discontinuing therapy for any reason. Whether a patient was withdrawn from treatment due to toxicity was a decision made by the prescribing physician. Dose modifications were allowed.

Irrespective of whether a patient discontinued treatment early or completed all cycles of study treatment, all patients were followed up. All study participants were monitored every 3 months for up to 2 years following study completion or withdrawal, and every 6 months during years 2-5 following study completion or withdrawal. All follow-up therapies and toxicities were reported until progression was documented.

Approximately half of patients in both treatments groups received no post-study therapy. The two treatment groups were similar with respect to the number of patients receiving different categories of post-study therapy. Among patients treated with cisplatin, 17 had post-study therapies including cisplatin and 9 had post-study therapies including topotecan. Among patients treated with topotecan/cisplatin, 21 had post-study therapies including cisplatin and 7 had post-study therapies including topotecan.

Table 8. Post-study therapies by treatment group, ITT population

Post-study therapy	**Cisplatin (n=146)**		**Topotecan/cisplatin (n=147)**	
	N	**(%)**	**N**	**(%)**
No follow-up data	11	7.53	8	5.44
No subsequent therapy	73	50.00	74	50.34
One salvage chemotherapy	36	24.66	33	22.45
One salvage chemotherapy + radiotherapy	0	0	3	2.04
Two salvage chemotherapies	25	17.12	28	19.05
Two salvage chemotherapies + radiotherapy	0	0	1	0.68
Unknown therapy	1	0.68	0	0

ITT: Intent-to-treat

Listing 8 of the clinical study report of GOG-0179 presents data on post-study therapies for all participants (Table 9).

Table 9. Breakdown of post-study therapies

	Cisplatin (n=146)	Topotecan/cisplatin (n=147)
Post study Therapy	**N**	**N**
5-FU	2	1
CIS	**17**	**21**
CRB	9	7
CPT	0	0
DOC	0	1
GEM	11	9
IFN	0	1
IFS	3	7
LED	5	3
NAV	5	7
OXP	2	1
TAX	33	30
TPT	**9**	**7**
VP-16	1	0
XEL	1	2
RT	0	4
OTH	7	13

5-FU: 5-Flurouracil; CIS: Cisplatin; CRB: Carboplatin; CPT-11: Irinotecan; DOC: Docetaxol, Taxotere; GEM: Gemcitabine, Gemzar; IFN: Interferon; IFS: Ifosfamide, Mitoxana; LED: Liposomal encapsulated doxorubicin, Doxil; NAV: Navelbine; OXP: Oxaliplatin; TAX: Paclitaxel, Taxol; TPT: Topotecan; V16: VP-16, Etoposide; XEL: Xeloda, Capecitabine; RT: Radiotherapy; OTH=Other.

A8. Please provide tabulated data on censored patients and reasons for censoring (page 43 of MS). Please also provide details on reasons for withdrawal and data on patients followed up 2-5 years following study completion (page 44 of MS). Please present this data in the CONSORT flow chart (page 41 of MS).

Table 10 provides a summary of the distribution of censored events for the survival analysis. Censoring for survival means that the subject is still alive at the time of analysis or was known to be alive when the subject was last followed-up. The Gynecologic Oncology Group did not provide a breakdown of reasons for censoring as it is understood that these patients were alive at the time of analysis or at last follow-up.

Table 10. Censored events, overall survival

	Cisplatin (n=146)	**Topotecan/cisplatin (n=147)**
Overall survival time		
Censored events (%)	17 (11.6)	29 (19.7)

Table 11 provides a summary of the withdrawal data for GOG-0179.

Table 11. Number (%) of patients who completed GOG-0179 or were withdrawn, by reason for study withdrawal, ITT population

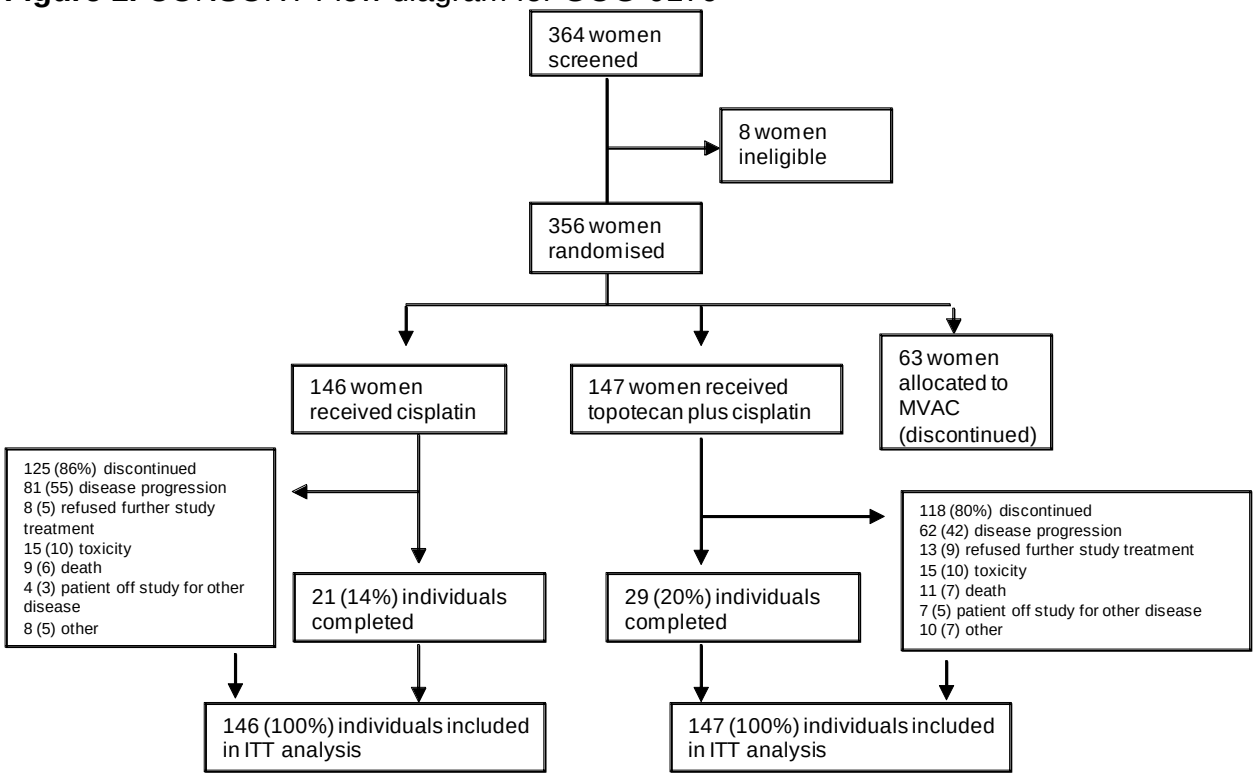
Reason for study conclusion	Cisplatin (n=146)		Topotecan/cisplatin (n=147)	
	n	%	n	%
Completed study[a]	21	14	29	20
Withdrawal reason				
Disease progression	81	55	62	42
Refused further study treatment	8	5	13	9
Toxicity	15	10	15	10
Death	9	6	11	7
Patient off study for other disease	4	3	7	5
Other	8	5	10	7
Total withdrawn	125	86	118	80

[a] Completed as defined by completing six courses of treatment as described in the protocol
ITT: Intent-to-treat

As specified in the clinical study protocol, patients were monitored every 6 months and vital status, medical history and physical examination, disease status, evidence of long term AEs and cancer therapy were documented. The Gynecologic Oncology Group did not provide data on patients followed up 2-5 years following study completion.

Figure 1 presents the CONSORT flow chart for GOG-0179, based on the data presented in Table 11.

Figure 1. CONSORT Flow diagram for GOG-0179



A9. Please provide results from the interim analysis performed after 56 deaths were observed in the cisplatin arm. Please also clarify what the 'multiplicity issues' were that are referred to on page 44 of the MS and the reason for adjustment of significance level for the final analysis from 0.05 to 0.044.

The Gynecologic Oncology Group did not share detailed analysis results from interim analysis with GSK. The adjustment of significance level to 0.044 in the final analysis is the penalty for the privilege of taking two analyses of the data (interim and final analysis) instead of a single data analysis. As described in section 5.8.2.1 of the CSR: "Conversely, in the event of a dramatic difference in the number of deaths as determined by the z-score the control regimen was to be considered for early closure. The critical region during interim analysis was z >=2.57 and, at the final analysis, z >=2.02. The tail probabilities associated with these z-scores were 0.01 and 0.022. This stopping rule maintained the type I error for each hypothesis at 0.0251."

A10. Please provide the survival data reported in Tables 4 and 5 to 2 decimal places. Please provide similar tables for progression free survival.

Table 12 provides revised data to two decimal places for the original Table 4 of the main submission.

Table 12. 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	6.54	9.40
95% confidence interval for median survival time	5.78 - 8.80	7.85 - 11.93
Log-rank p-value	0.03*	
Hazard Ratio (95% confidence interval)†	0.76 (0.59, 0.98)	

*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.

Table 13 provides revised data to two decimal places for the original Table 5 of the main submission.

Table 13. 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	5.90	7.85	8.77	15.74
95% CI for median survival time	4.73 - 8.80	5.52 – 10.87	6.41 – 11.47	11.93 – 17.74
Log-rank p-value	0.36		0.01	

CI = confidence interval

Equivalent data for progression free survival to two decimal places are presented below.

Table 14. Progression free 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	2.91	4.57
95% confidence interval for median survival time	2.56 – 3.48	3.55 – 5.72
Log-rank p-value	0.03	
Hazard Ratio (95% confidence interval)[†]	0.76 (0.60, 0.97)	

Table 15. 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	2.69	3.81	3.24	7.03
95% CI for median survival time	1.74 – 3.29	3.06 – 4.53	2.37 – 5.26	5.68 – 10.15
Log-rank p-value	0.88		0.00	

CI = confidence interval

A11. Please provide hazard ratios and 95% confidence intervals for Figure 12 on page 53 of the MS that details the subgroup analyses.

The hazard ratios and 95% confidence intervals for Figure 12 of the main submission are presented below.

Table 16. Hazard ratios and 95% confidence intervals for Figure 12 of the main submission

	Hazard Ratio	Lower 95% CI	Upper 95% CI
Age			
<65 years (n=274)	0.75	0.58	0.96
>=65 years (n=19)	0.77	0.25	2.35
Race			
White (n=213)	0.74	0.55	1.00
Black (n=52)	1.00	0.55	1.81
Other (n=28)	0.53	0.23	1.19
Perf. Status			
0 (n=137)	0.73	0.50	1.06
1 (n=132)	0.86	0.59	1.24
2 (n=24)	0.56	0.21	1.46
Cell Type			
Squamous (n=249)	0.82	0.62	1.07
Adenocarcinoma (n=44)	0.60	0.30	1.18
Prior RT Sensitization			
No RT (n=38)	0.74	0.36	1.51
RT with no Sensitizer (n=74)	0.66	0.39	1.10
Non Cisplatin Sensitizer (n=16)	0.18	0.04	0.79
Cisplatin Sensitizer (n=165)	0.90	0.65	1.25
Time from Diagnosis to study			
<16 months (n=172)	0.89	0.64	1.23
>=16 months (n=121)	0.52	0.34	0.79
Overall (n=293)	0.76	0.59	0.98

CI: Confidence interval

A12. Please clarify whether the following sentence on page 80 is taken from reference 34 or is the opinion of GSK: "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".

This sentence is the opinion of GSK.

A13. Please clarify whether the reference cited on page 19 is correct: "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]". (Reference 14 is a report of GOG-0169 comparing cisplatin with or without paclitaxel.

This sentence was incorrectly referenced in the original submission dossier. The correct citation is: EMEA - Periodic Safety Update Report (PSUR) for topotecan- May 2008 to November 2008.

A14. Please confirm whether the reference in section 5.1 of the SmPC to a 180 day cisplatin free interval reflects a specific restriction in the marketing authorisation, and therefore that the use of topotecan for the treatment of women with less than 180 day cisplatin free interval would be regarded as outside of the marketing authorisation. Please provide the evidence that informed the specification of a 180 day cut point.

Patients with persistent cervical cancer and those without a sustained cisplatin-free interval were included in the study but are not covered by the licensed indication. This reflects a specific restriction in the marketing authorisation, and therefore the use of topotecan for the treatment of women with less than 180 day cisplatin-free interval would be regarded as outside licensed indication.

Evidence for specification of 180 day cut point:

At the time of marketing authorisation, the CHMP acknowledged the fact that the intensity of prior therapy is likely to affect activity of later lines of therapy. In patients not administered cisplatin containing chemoradiotherapy, treatment benefit is considered robust both from a statistical and clinical perspective. The CHMP also noted that the add-on of cisplatin to radiotherapy increases the risk of resistance to next-line chemotherapy and it is well known that early recurrence after cisplatin-based therapy in patients with, e.g. ovarian carcinoma is associated with poor prognosis and platinum resistance.[31]

In patients with prior cisplatin chemoradiotherapy (n= 141), the median survival in cisplatin vs. cisplatin + topotecan groups was 5.9 vs. 7.9 months respectively (HR 0.97, 95% CI 0.69, 1.38).

In an attempt to reduce the level of heterogeneity and gain understanding, data were further explored through unplanned sub-set analysis.

The median survival in the cisplatin vs. cisplatin + topotecan groups was 4.5 vs. 4.6 months for patients (n=39) with recurrence less than 180 days after chemo-radiotherapy with cisplatin (HR 1.15, 95% CI 0.59, 2.23). In those with recurrence after 180 days (n=102), the median survival in the cisplatin and cisplatin + topotecan groups was 6.3 and 9.9 months respectively (HR 0.75, 95% CI 0.49, 1.16).
From an efficacy perspective the CHMP therefore considered a restricted indication appropriate:

"Treatment, in combination with cisplatin, of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination (see section 5.1 of the SPC)."[31]

Indirect comparison

A15. Please provide a tabulation of the patient characteristics for patients compared in GOG-0179 and GOG-0169 (including data on median time from diagnosis to study entry, prior radiotherapy, prior chemoradiation, and site of disease for GOG-0179, and details on cell type for patients included in GOG-0169, if available).

The median time from diagnosis to study entry for GOG-0179 was 13.11 months. Prior radiotherapy and cisplatin use data for GOG-0179 are presented below.

Table 17. Prior radiotherapy and cisplatin use data for GOG-0179, ITT population

	Cisplatin (n=146)		Topotecan/cisplatin (n=147)	
	n	(%)	n	(%)
No prior radiotherapy	20	14	18	12
Prior radiotherapy, no prior sensitizer	37	25	37	25
Prior non-cisplatin radiotherapy sensitizer	7	5	9	6
Prior cisplatin radiotherapy sensitizer	82	56	83	56

The Gynecologic Oncology Group did not provide disease site information. GSK does not have access to GOG-0169 data that are not in the public domain.

A16. Please provide further justification for not including study GOG-0204 in the indirect comparison. Monk et al (ASCO Annual '08 Meeting) reports response rates, adverse events, overall survival and progression free survival.

GOG-0204 was closed early and the trial data were highly summarised and presented in a poster, therefore this trial was not included in the indirect comparison presented in the original submission. However, it should be noted that data from GOG-0204 were included in a sensitivity analysis of the topotecan health economic model.

For completeness, data from the cisplatin + topotecan and cisplatin + paclitaxel arms from GOG-0204 were included in a meta-analysis alongside the indirect comparison presented in the original submission. The direct comparison in GOG-0204 was favourable to the cisplatin + paclitaxel arm (hazard ratio 1.27 (0.96,1.69)). When the indirect and direct evidence was pooled, it resulted in the overall comparison being slightly (but not significantly) favourable towards the cisplatin + topotecan arm. In this case, the hazard ratio was 0.98 and confidence intervals 0.73 to 1.23.

A17. Page 33 of the MS reports an HR of 1.268 for overall survival for topotecan + cisplatin versus paclitaxel + cisplatin, however 1.268 appears to be the HR for the progression fee survival. Please re-run the analysis using an HR of 1.255.

The HR of 1.268 was incorrectly reported on page 19 and this was then duplicated on pages 33 and 81. The correct value of 1.255 was incorporated in the indirect comparison sensitivity analysis, presented on pages 140 and 141 of the main submission.

Section B. Clarification on cost effectiveness

General issues

B1. Please provide additional justification for employing a patient-level approach to the primary cost-effectiveness analysis as opposed to using a decision-analytic approach.

Justification for the patient-level approach has previously been requested by NICE and a paper has been provided by GSK setting out our reasons for this approach. A copy of this response is included in Appendix 1.

Specific issues

B13. The All-Wales Medicines Strategy Group reported that, in Wales, cisplatin was used in only 7.5% of patients and paclitaxel / cisplatin not at all. Table 18 (p90 of MS) shows cisplatin monotherapy is the most common option, used in 39% of cases, based on IMS Oncology analysis. Please clarify whether the numbers reported are based on UK data only or include data from the 5 key European markets. If the data are not UK specific, please report the % of patients from the UK. In addition, please provide data for the period Q3 2006 to Q3 2008.

The IMS analysis is based on UK data only. Data incorporate responses from 41 UK doctors reporting cervical cancer cases covering the period Q3 2004-Q3 2008. Of these 5 are in Wales.

An updated analysis has been gathered for the period Q3 2006 to Q3 2008 as requested by NICE. The number of doctors reporting cervical cancer cases covering the period Q3 2006-Q3 2008 is 36 doctors in the UK of which 2 are in Wales. The total number of cervical patients collected during this period in the UK is 229 patients, of which 30 patients fell under Hycamtin targeted population.

The ages of the 30 patients identified in the period Q3 2006 to Q3 2008 and the chemotherapy regimens they received at point of eligibility for topotecan are presented in Tables 18 and 19, respectively.

Table 18. Age distribution of 30 patients at point of eligibility for topotecan in combination with cisplatin

Age	Number of patients	Percentage
26-30	4	13
31-35	5	17
36-40	1	3
41-45	4	13
46-50	1	3
51-55	2	7
56-60	3	10
61-65	4	13
66-70	3	10
71-75	2	7
76-80	1	3
Total	30	100

Table 19. Chemotherapy regimen at point of eligibility for topotecan in combination with cisplatin

Next line of therapy	Number of patients	Percentage
5-FU	1	3
5FU/CISP	1	3
5FU/MMC	1	3
CARB	3	10
CARB/GEM	1	3
CARB/PAC	7	23
CISP	8	27
CISP/ETOP	1	3
CISP/MTX	2	7
CISP/PAC	2	7
CISP/TOPO	1	3
DOC/GEM	1	3
TOPO	1	3
Total	30	100

5-FU: 5-fluorouracil; bleo: bleomycin; carb: carboplatin; cisp: cisplatin; doc: docetaxel; epi: epirubicin; etop: etoposide; fa: folinic acid; gem: gemcitabine; mitox: mitoxantrone; mmc: mitomycin C; mtx: methotrexate; pac: paclitaxel; topo: topotecan

B14. Please provide the time horizons employed for all subgroups considered in the direct comparison with cisplatin (p91 of the MS).

The time horizon for the sustained cisplatin-free interval patients was 18 months. For all other subgroups the horizon was 36 months.

B16. Please clarify whether the % side-effect data used for paclitaxel + cisplatin have been taken directly from study GOG-0169 or whether these have been adjusted (p94 of MS).

The percentage of patients experiencing side-effects has been taken directly from study GOG-0169 and has not been adjusted. This is a conservative assumption as patients had a longer exposure to topotecan in the GOG-0179 study than patients had to paclitaxel in GOG-0169.

B18. Please clarify which clinical events resource utilisation was contingent on (p98 of MS). Please provide the resource utilisation assumptions employed.

It was considered that haematological AEs account for the majority of resource utilisation attributable to AEs, and these were costed as shown in the table below, using the relevant HRG codes. It was assumed that only grade 3 and 4 episodes of neutropenia, thrombocytopenia and anaemia would result in resource use. If two events occurred simultaneously, only the more expensive was included in the resource use analysis. 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 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. For grade 3 haematological events, the number of interventions (G-CSF, platelet transfusions, red blood cell transfusions, and erythropoietin) influenced costs.

Adverse event	**Circumstances of AE**	**Relevant HRG code**	**Specific value taken from HRG code**
Anaemia / neutropenia / thrombocytopenia	Grade 1 or 2 with or without interventions	None applied	None applied
	Grade 3, no intervention	None applied	None applied
Anaemia	Grade 3, single intervention	HRG SO5 Red Blood Cell Disorders, age >69 or with complication	Day case, mean
	Grade 3, two interventions	HRG SO5 Red Blood Cell Disorders, age >69 or with complication	Day case, upper value
	Grade 3, >2 interventions. All Grade 4	HRG SO5 Red Blood Cell Disorders, age >69 or with complication	Inpatient
Thrombocytopenia or neutropenia	Grade 3, single intervention	HRG SO7 other haematological or splenic disorders age >69 or with complications	Day case, mean
	Grade 3, two interventions	HRG SO7 other haematological or splenic disorders age >69 or with complications	Day case, upper value
	Grade 3, >2 interventions. All Grade 4	HRG SO7 other haematological or splenic disorders age >69 or with complications	Inpatient

B20. Page 98 of the MS states 'the model extrapolates beyond the last observed deaths in each treatment arm.' Please discuss the implications of this for the analysis, and whether this assumption is required to implement the Lin method.

The predefined analytic horizon for the trial-based analysis was 36 months, the maximum period of trial follow-up. Although the last observed deaths occurred before 36 months, the Lin method was implemented over the full 36 month period for consistency with our K-M survival estimates to 36 months. Use of the word 'extrapolation' in our submission was incorrect. We did not extrapolate, but simply used all data up to the 36 month horizon. With respect to the few patients surviving beyond 36 months in both arms, which numerically favoured cisplatin + topotecan, we did not attempt to include any estimates of remaining survival or costs beyond 36-months for these few patients. The impact of this decision was to understate total estimated survival and costs and to introduce a small bias against cisplatin + topotecan. We judged that it would be preferable to provide a conservative estimate of the cost-effectiveness of cisplatin + topotecan using actually observed data, rather than to introduce uncertainty by modelling additional survival for a few patients."

B25. The submission describes two ways in which missing HRQL data were handled. In some circumstances, missing data were imputed using LOCF. In other cases, an adaptation of Lin method was used for estimating QALYs where data are censored. Please clarify in what circumstances was LOCF used to impute missing data, and when was the Lin method used to adjust?

Our imputation strategy distinguished between missing data and censored data. Where no QoL data were recorded at a known follow-up visit for an individual patient, these data were considered missing, and the LOCF assumption was applied. Where no further follow-up visits were recorded, cases were considered censored. The Lin method was applied to the entire dataset to account for censoring in estimating costs and QALYs.

B27. Table 25 (p111 of MS) indicates that the unit cost of 25 ml paclitaxel (generic) is higher (£532.95 versus £521.73) than the unit cost of 25 ml paclitaxel (Taxol®). The BNF indicates that 25 ml paclitaxel (generic) costs £500.86. Please confirm whether this is an error in the submission and if it effects the calculation of paclitaxel drug costs.

The 25 ml price is not used in the analysis and so does not affect the results of the submission. The indirect comparison assumes 2*16.7ml doses at a cost of £639.54.

B32. In Table 46 (p141), please clarify whether the last row should read "paclitaxel + cisplatin".

This was an error for which we apologise. The label for the last row of Table 46 should read "paclitaxel + cisplatin".

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Appendix 1. Cost-utility analysis of topotecan in advanced cervical cancer: description and rationale for method

Purpose of this document

GlaxoSmithKline is preparing a submission to support a Single Technology Appraisal of topotecan (Hycamtin®) for the treatment of recurrent and stage IVB carcinoma of the cervix. Recent discussion between representatives of NICE and GSK on the decision problem prompted questions from NICE about the proposed methods for the cost-utility analyses to be included in the submission. GSK has indicated that it proposes to submit as the primary item of economic evidence a report of a trial-based analysis of topotecan plus cisplatin vs. cisplatin alone, as opposed to a model in executable form. GSK does, however, plan to provide secondary evidence comparing topotecan plus cisplatin vs. paclitaxel plus cisplatin as an Excel-based model. The view was expressed that as the Evidence Review Group is accustomed to running its own analyses with submitted models, all other things being equal it prefers to receive economic evaluations in executable form. This would not be straightforward for the proposed trial-based analysis, as the main analyses of the patient-level dataset have been programmed in SAS.
NICE requested GSK to provide a description of the trial-based analysis and a rationale for the selection of this method. It is hoped this document will help to illustrate the issues arising in this particular instance of the frequently occurring conflict between the methodological appropriateness and user accessibility.

Data available and issues arising

The principal clinical evidence supporting topotecan is a phase III trial, GOG-0179, which demonstrated that the combination of topotecan plus cisplatin provides a significant increase in overall survival over cisplatin alone. At the time of designing the economic study this clinical trial, conducted independently by the Gynaecological Oncology Group (GOG), was the only study comparing the two regimens directly.
The selection of an appropriate method for the economic evaluation was influenced by the available clinical data for chemotherapy regimens in general and for GOG-0179 in particular.

Comparative data

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 clinical 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.

The availability of a high-quality trial of topotecan plus cisplatin vs. cisplatin alone (GOG-0179) suggested the possibility of an internally valid economic evaluation between these two agents, in which the principle of randomisation would be preserved. Single-agent cisplatin had been the standard of care until recently, and although trials and off-label use of various combinations had been reported, it was considered that an economic evaluation of topotecan plus cisplatin vs. cisplatin alone would be desirable.
An indirect, modelled comparison between topotecan plus cisplatin vs. paclitaxel plus cisplatin was considered to be potentially possible, since each combination had been studied compared to cisplatin alone in separate trials. In fact, as mentioned earlier, our GSK submission will provide secondary evidence comparing topotecan plus cisplatin vs. paclitaxel plus cisplatin as an Excel-based model. Potential limitations of this analysis will be highlighted (e.g. as the study populations were poorly matched, an indirect comparison between the two combinations would lose the benefit of randomisation).

Study and licence populations

It was considered not appropriate to use the full GOG-0179 dataset in the economic evaluation, because the study population did not correspond exactly to the population defined in the Product Licence (PL) for Hycamtin®. Specifically, the trial included subjects who had received prior cisplatin less than 180 days before entry to the trial, and subjects with persistent disease, both of which categories fall outside the scope of the PL. These subjects accounted for 71 of the ITT population of 293. It was considered at the outset that a CEA based on the full ITT population would be criticised by health technology assessment agencies such as NICE.

Accuracy of estimation

Cost-utility analysis (CUA), the form of economic evaluation required by HTA agencies in the UK, requires the estimation of utility-adjusted survival. In modelled CUAs, this is done by assigning utility values to the modelled health states. Utility may be affected in advanced cervical cancer by the stage of disease itself, clinical response to treatment and the impact of treatment toxicity. Similarly, costs are assigned to each health state in decision models, such that expected costs and expected quality-adjusted survival can be estimated contingent on the uncertain occurrence of events. 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.

Follow-up time and censoring

In GOG-0179, some subjects survived beyond the 36-month maximum period of follow-up. The numbers of these survivors differed between groups. There was also some loss to follow-up during the 36-month period. Hence, regardless of whether the analysis was to 36 months horizon or extrapolated to a more distant horizon, there remained some censored observations of outcomes and costs to be dealt with.

Chosen solution

Given the data available and issues described above, we describe below the study method and provide a rationale for its choice.

Synopsis of study method

The primary economic evaluation is a cost-utility analysis of topotecan plus cisplatin vs. cisplatin. This was an analysis of individual patient-level data from trial GOG-0179, as opposed to a modelled approximation. This is described more fully in the formal submission. The portion of the GOG-0179 population reflecting the licensed indication for topotecan and its two subgroups, the cisplatin-naïve population and the sustained cisplatin-free interval (SCFI) population, were included in the analysis. The analytic horizon was up to 36 months, with no extrapolation beyond trial follow-up.

The primary outcome measure is quality-adjusted life years (QALYs). The GOG-0179 dataset was reanalysed to generate Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) for the Licence population and its subgroups. Mean OS was computed as the area under the OS curve (AUC) to 36 months (18 months for the SCFI population). As EQ-5D data were not collected in GOG-0179, an alternative means was required for the utility adjustment of the survival estimates. Utility values were calculated from FACT-G data prospectively collected alongside GOG-0179, using a proposed algorithm for conversion from FACT-G to time trade-off (TTO) utilities. These were assigned to time spent in defined health states for each patient and quality-adjusted survival computed. An alternative set of utility values relating to metastatic breast cancerv and advance cervical cancer was also identified and will be evaluated as part of sensitivity analyses.

Costing is performed at patient level. However, the trial protocol of GOG-0179 had made no specific arrangements to record resource utilisation prospectively for a "piggyback" economic evaluation. Therefore, the costing was carried out retrospectively from an NHS perspective. The costs considered include 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 (AEs). Unit costs are 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, is based on expert opinion of oncologists with experience of working in the NHS. Unit costs are derived primarily from the NHS National Reference Costs 2008. All costs and outcomes were discounted to present values at a rate of 3.5% per annum.

Although resource utilisation during trial follow-up was derived from individual patient data, observations for many patients were censored, so that subsequent resource utilisation and costs were unknown. Rather than using a full-sample estimator or an uncensored-cases estimator of costs, which would introduce bias, we estimated mean costs using the "without cost histories" variant of the method described by Lin et al, which is appropriate when the time of resource utilisation is not completely known. The trial follow-up period was divided into several intervals (the present study used 36 intervals each of one month). The mean total cost per patient was 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. The Lin method was adapted to estimate quality-adjusted survival (personal communication: Professor Alistair McGuire, London School of Economics). 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.

The distributions of estimated costs and effects reflect the sampling uncertainty in trial data. To propagate this uncertainty through the analysis, bootstrap estimates of incremental costs and effects will be generated. Up to this point, all analyses of the patient-level data are executed by SAS programs. The bootstrap output will be exported from SAS to Microsoft Excel, which is used to generate the final probabilistic estimates of the ICERs. These are presented as scatter plots on the cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs).

Scenario analyses will be carried out to explore alternative sub-groups of the trial population. Sensitivity analyses will be carried out to test the effects of the alternative set of utility values derived from FACT-G, of alternative assumptions regarding wastage and of the utilisation of pre-treatment medication for topotecan plus cisplatin.

Advantages of patient-level analysis

Advantages specific to the dataset

The availability of the patient-level dataset of GOG-0179x circumvents the problems cited in paragraphs 0, 0 and 0 above. This solution would not have been possible in a modelled analysis. Patient-level data allowed restriction of the analysis to the populations consistent with the PL. Patient-level FACT-G data were available, which allowed mapping to utility values, notwithstanding some concerns about the published algorithm used to perform the mapping. Nevertheless, the availability from GOG-0179 of patient-level incidence of clinical events and toxicity enabled the use of an alternative method in which externally-sourced utility values were assigned to each patient's health state. While we are obliged to set a tariff of values derived from non-cervical cancer states, this limitation is not specific to our trial-based CUA; it will have similarly affected a modelled analysis. The availability of patient-level incidence of clinical events and toxicity also enables estimation of resource utilisation and costs at a patient level, while taking into accounting the timing of these costs. The problem of censoring was addressed as follows. First, the time horizon of the analysis was restricted to 36 months, the maximum period of trial follow-up, thus ignoring any differential survival benefit between treatments. Second, the Lin method described above allowed us to account for censored observations, so that unbiased mean total cost and quality-adjusted survival for each patient could be estimated to the 36-month analytic horizon.

Analysis of uncertainty

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.

Disadvantages of patient-level analysis

Programming requirements

The patient-level CUA of GOG-0179 required SAS programming to execute the analyses. These consisted of the initial sorting of relevant cases from the total trial population, then the assignment of resource utilisation, unit costs and utility values to individual cases according to their clinical histories, the imputation of costs and utilities for censored cases and missing values and finally the bootstrapping of costs and survival curves. The final CUA was carried out in Excel once the bootstrapped data had been imported from SAS output. Performing the CUA as specified and running sensitivity and scenario analyses therefore requires the use of SAS and subsequent manipulation of SAS output. It is recognised that this is more time consuming than analysis of an executable model programmed in Excel or TreeAge, and requires the availability of SAS skills. It would not have been practical to carry out the whole analysis in Excel using similar methods. Had the use of Excel been an overriding requirement, this would have necessitated building a simpler decision-tree or Markov model with consequent loss of information.

Generalisability

The CUA of the patient-level data, while achieving high internal validity, cannot necessarily be generalised to other settings. It certainly can accommodate alternative populations whose characteristics are known baseline characteristics within the trial, for example populations that include or exclude patients with stage IVB disease, cisplatin-naive populations or cisplatin-experienced populations with a sustained-cisplatin free interval. However, this non-modelled analysis can generate ICERs only between the trial comparators: topotecan plus cisplatin and cisplatin alone. Comparisons between topotecan plus cisplatin and other chemotherapy regimens would require modelling, with the caveat that the studies on which these models are based should be well-matched in terms of prognostic patient characteristics.

Rationale

It was concluded that the advantages of patient-level CUA of topotecan plus cisplatin vs. cisplatin outweighed the disadvantages. It was felt that a modelled analysis would inevitably be less faithful to the data available and that it would be poor science not to make full use of these data. Although this required the use of SAS and some complex programming to account for censoring, use of appropriate methods is generally held by health economics thought leaders to outweigh convenience factors such as the user-friendliness of the software. All the necessary programs will be provided to external assessors and we can run scenarios as required.

An analysis against alternative comparators used in England and Wales, particularly paclitaxel, will be attempted. It was therefore decided to present the comparison with paclitaxel as a secondary, modelled analysis, in which the shortcomings are clearly acknowledged (e.g. population matching was imperfect and the common follow-up period between the available sources of clinical evidence was only 24 months).

In conclusion, based on the contemporary data available, we believe that it is entirely appropriate to use patient-level data from GOG-0179 to estimate the cost-utility of topotecan plus cisplatin compared to cisplatin alone, and the advantages of this approach outweigh any disadvantages.

In future, further head-to-head clinical data including other chemotherapy regimens may be reported. Since the time of designing the study described here, an abstract describing a phase III trial (GOG-0204) of four cisplatin-containing doublet combinations, including topotecan plus cisplatin, has appeared. This raises the possibility of further economic evaluations once full data from this study is available, either using similar trial-based methods to maximise internal validity, or by constructing of model based on a network of summary data from GOG-0169, GOG-0179 and GOG-0204.

For the purpose of this submission the current available results from study GOG-204 will be explored as part of our sensitivity analyses.

Appendix 2: Search strategies replicated by the ERG

The manufacturer's submission described the search strategy used to identify published studies of Topotecan and comparator products in the treatment for recurrent or stage IVB carcinoma of the cervix. The submission stated that a general search strategy was presented in Appendix 2. Unfortunately complete search strategies were not provided in the initial submission and had to be requested by the ERG. The submission explained that searches were undertaken to update an existing systematic review by Cancer Care Ontario[7]. The submission also made it clear that this strategy was used to identify comparator studies (RCTS of platinum-based chemotherapies for treatment of women with recurrent or stage IVB cervical cancer) (6.6 Indirect/mixed treatment comparisons).

The Cost-effectiveness section of the report (7.1.1 Identification of Studies) referred to the search strategy details presented in Appendix 3. A description of the databases and date spans searched were detailed in Appendix 3, however no search strategies were provided. Reference was made to the cost-effectiveness searches being undertaken in tandem with the clinical-effectiveness searches. The submission referred back to the general search strategy table presented in Appendix 2 (MS, pp.171-172).

Clinical-effectiveness searches

The submission described the resources searched and was designed to meet NICE requirements (6.1 Identification of Studies). The methods section included the specific databases searched; the service providers used; the dates when searches were conducted and the date spans of the searches.

The databases searched for the clinical-effectiveness literature included Medline and Embase as required by NICE, but also Embase Alerts, ASCO, EMSO and CMA Infobase which are not required.

From the original submission, it was unclear whether Medline In-Process, another resource required by NICE, has been searched. Following a query from the ERG, the manufacturer confirmed that Medline In-Process had been searched (MR, pp1-9).

As the clinical effectiveness searches acted to update an existing CCO systematic review[7], all clinical-effectiveness searches undertaken by the manufacturer were limited to the date span 2006-2008. Language limits were not applied to subsequent searches, however the CCO review[7] did apply an English language limit to literature upto 2006. Therefore, a language bias may have been introduced.
The three internet searches were limited to the date span 2005-2008.

In the original submission by the manufacturer, a table illustrating a general search strategy was provided (MS, 10.2 Appendix 2, pp.170-172). This general strategy appeared to act as a summary outlining the search facets, rather than an actual search strategy comprising of search terms. Unfortunately exact search strategies were not supplied and the ERG was unable to replicate the search methods from the original table. The number of records retrieved for each search set and the final result number for each strategy was also not supplied.

There were a considerable number of limitations and omissions with the original reporting the search methods.

The table did not include a complete search strategy in consistent search syntax. The table presented a 'general search strategy' comprising of sections in the syntax of upto three different database hosts.

The 'therapy' search facet (line #18) appeared to come from the OVID host, however the search string did not work due to the absence of truncation or parentheses to express the search logic.

The 'treatment' facet (lines #19-#20) did not include any truncation. MeSH Indexing for Topotecan was not included and the search lines had insufficient synonyms to capture the different trade and generic names for Topotecan.

The facet intended to exclude references to animal studies (line #14-#16) had incorrect logic. Instead of exclude animal-only studies, the search statements would have omitted references to human studies. The ERG queried the search strategy in the Points of Clarification**.**

For this reason, the ERG requested full search strategies in the Point of Clarification, and the manufacturer supplied additional detail and full search strategies (MR, pp.1-9).

The ERG was unable to replicate the Medline, Medline In-Process Citations, Embase and Embase Alert searches, as the searches were undertaken in a host (Datastar) not readily available to the ERG. In the detailed searches, the animal/human facet is applied correctly. The logic appears to be adequate, however the search strategy has several spelling errors in it. For example, in the response document (MR, pp.2), Table 1, line 7, 'RANODMIZE$' should read *'randomize$'*. In Table 1, line 9, 'META-ANALASES' should read *'meta-analyses'*. These errors meant that the search strategy would fail to retrieve records by the terms *'randomize$'* or *'meta-analyses'*. Without re-running the searches in Datastar, it is not possible to gauge the impact the errors would have on the efficacy of the search and the number of references retrieved. The manufacturer states they retrieved 179 references for the clinical effectiveness search and 37 unique references for the cost-effectiveness search. The ERG was unable to reproduce the searches and confirm the numbers of records retrieved. The detailed search strategies appear to contain comprehensive subject indexing and free text search terms; and search facets were combined using appropriate Boolean operators. An RCT and Meta-analysis filter was used and the search results were restricted to humans.

The ERG was able to replicate the Cochrane Library, PubMed and HEED searches, using the same search interfaces.

The manufacturer's Cochrane Library search was undertaken on 18.12.08; the issue number of the Cochrane Library searched was not given. This search identified 26 references. The ERG reproduced the Cochrane Library (Issue 1:2009) search strategy on 1.4.09, and identified 21 records. This variation in numbers retrieved could be due to the ERG searching a subsequent version of the Cochrane Library. Unfortunately it is not currently possible to search archived issues of the Cochrane Library via the internet in order to explain this discrepancy (n=5).

The internet searches were conducted on 18.12.08 and were limited to the date span 2005-2008. Unfortunately the manufacturer did not give the number of records retrieved by the original searches.

Following clarification, the ERG was able to replicate the ASCO and CMA Infobase on 14.4.09. The ERG re-ran the ASCO search. The search was limited to annual meetings 2005-2008, using the term “cervical cancer” in the title field. The search retrieved 82 records.

The ERG re-ran the CMA Infobase search, using the term “cervical cancer” in the title, subject or abstract. The ERG’s search did not retrieve any records. The ERG conducted an additional test search on this resource, using only the term ‘cervical’ in the title, subject or abstract. This term retrieved 40 records, including the CCO review[7].

The ERG was unable to replicate the EMSO search, as the manufacturer appears to have sifted electronic conference abstracts 2005-2008, looking for abstracts on gynaecological cancers.

Cost-effectiveness searches

The cost-effectiveness searching was undertaken in tandem with the clinical-effectiveness searches. For this reason, both sets of searches were documented together in both the original submission (6.1 Identification of studies, p31-32) and the response to point of clarification.

The databases searched for the cost-effectiveness literature included Medline, Embase, HEED, NHS EED as required by NICE, but also Embase Alerts which is not required.

From the original submission, it was unclear whether Medline In-Process, another resource required by NICE, has been searched. Following a query from the ERG, the manufacturer confirmed that Medline In-Process had been searched (MR, pp.8).

As with the clinical-effectiveness searches, the ERG was unable to replicate the Medline, Medline In-Process Citations, Embase and Embase Alert searches, as the searches were undertaken in a host (Datastar) not readily available to the ERG. The logic appears to be adequate. The manufacturer states they retrieved 37 unique references for the cost-effectiveness search. As with the clinical-effectiveness searches, the ERG was unable to reproduce the searches and or to confirm the numbers of records retrieved. The detailed search strategies appear to contain comprehensive subject indexing and free text search terms; and search facets were combined using appropriate Boolean operators. An economics search filter was used.

The manufacturer did not provide a full search strategy documenting the NHS EED search. Therefore the ERG was unable to replicate the NHS EED search.

A detailed HEED strategy was not provided in the original submission. For this reason, the ERG requested full search strategies in the Points of Clarification. The manufacturer supplied a detailed HEED strategy in their response document to NICE (MS, pp.9). The full HEED strategy did not include terms to specifically identify ‘utilities’, as detailed in the original submission document (MS, Appendix 5, Appendix A, p10). The manufacturer’s search did not identify any references. The ERG reproduced the HEED search strategy on 1.4.09, and identified 11 references, none of which were relevant. As HEED does not state when the database is updated, it is not possible to know exactly which update of HEED was searched by the manufacturer. The variation in the number of records retrieved by the ERG could be due to the ERG searching a subsequent version of HEED.

The original submission described additional cost-utility searches (Appendix 5).

In the original submission by the manufacturer, a table illustrating a general search strategy was provided (MS, Appendix 5, Appendix A, pp.10). The strategy provided appeared to be a PubMed strategy.

According to the methods detailed in the main submission (MS, Appendix 5, Appendix A, pp.10), PubMed was searched on 19.12.08. The manufacturer did not apply language or date of publication limits.

The ERG was able to replicate the PubMed search for the cost-utilities PubMed strategy on 14.4.09, and identified 508 records. Unfortunately the manufacturer did not provide details of the number of records their original search retrieved.

Cochrane Library Issue 1:2009. Searched 1.4.09

ID	Search	Hits	Edit	Delete
#1	MeSH descriptor **Uterine Cervical Neoplasms**, this term only	1192	edit	delete
#2	(cancer*) or (carcinoma*) or (malignan*) or (tumour* or tumor*) or (neoplasm*)	65440	edit	delete
#3	(cervix or cervical)	7073	edit	delete
#4	(#2 AND #3)	2276	edit	delete
#5	(#1 OR #4)	2276	edit	delete
#6	(hycamtin or topotecan or evotopin or hicamtin or hycamtim) or (123948-87-8)	209	edit	delete
#7	(platinum chemotherapy) or (platinum-based chemotherapy) or (platinum based chemotherapy)	745	edit	delete
#8	(PLATINOL OR Cisplatin OR D00275 OR D-0025 OR "D 00275")	4972	edit	delete
#9	(oxaliplatin OR Foloxatine OR Transplatin OR Eloxatin OR Eloxatine OR Elplat OR L-platin) or (DACPLAT OR I-OHP OR ACT-078 OR act078 OR "act 078")	335	edit	delete
#10	(PARAPLATIN OR Carboplatin OR SPERA OR Satraplatin OR D05807 OR d-05807 OR "D 05807") or (Triplatin Tertranitrate OR BBR3464 OR bbr-3464 OR "bbr 3464")	1619	edit	delete
#11	(AQUPLA OR Nedaplatin OR C2H6N2O3Pt OR CCRIS4088 OR "CCRIS 4088") or (CCRIS-4088 OR "NSC 375101D" OR NSC-375101D OR NSC375101D)	8	edit	delete
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	6568	edit	delete
#13	(recurr* OR stage IVb stage 4b)	23652	edit	delete
#14	(#5 AND #12 AND #13)	92	edit	delete
#15	(#14), from 2006 to 2008	21	edit	delete
#16	(#14), from 2006 to 2008	21	edit	delete

Cost-effectiveness

HEED: Inception to 1.4.09. Searched 1.4.09

1	AX= 'CANCER*' OR 'CARCINOMA*' OR 'MALIGNAN*'	4737
2	AX='tumor*' or 'tumour*' or 'neoplasm*'	1025
3	CS=1 OR 2	4979
4	AX='CERVIX' OR 'CERVICAL'	561
5	CS=3 AND 4	387
6	AX='HYCAMTIN' OR 'TOPOTECAN' OR 'EVOTOPIN' OR 'HICAMTIN' OR 'HYCAMTIM'	27
7	AX='platinum*' AND 'chemotherapy'	20
8	AX='PLATINOL' OR 'Cisplatin' OR 'D00275' OR 'D-0025' OR 'D 00275'	160
9	Ax='oxaliplatin' OR 'Foloxatine' OR 'Transplatin' OR 'Eloxatin' OR 'eloxatine' OR 'Elplat' OR 'L-platin'	25
10	AX='DACPLAT' OR 'l-OHP' OR 'ACT-078' OR 'act078' OR 'act 078'	0
11	AX='PARAPLATIN' OR 'Carboplatin' OR 'SPERA' OR 'Satraplatin' OR 'D05807' OR 'd-05807' OR 'D 05807' OR 'Triplatin Tertranitrate' OR 'BBR3464' OR 'bbr-3464' OR 'bbr 3464'	60
12	AX='AQUPLA' OR 'Nedaplatin' OR 'C2H6N2O3Pt' OR 'CCRIS4088' OR 'CCRIS 4088' OR 'CCRIS-4088' OR 'NSC 375101D' OR 'NSC-375101D' OR 'NSC375101D'	1
13	CS=6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	613
14	AX='recurr*' OR 'stage IVb' OR 'Stage 4b'	1118
15	CS=5 AND 13 AND 14	11

Cost-Utility

PubMed: Inception to 14.4.09. Searched 14.4.09

#12	Search **#11 AND utilit***	06:06:50	508
#11	Search **#1 OR #10**	06:06:42	81445
#10	Search **#8 AND #9**	06:06:32	81445
#9	Search **Cervix OR cervical**	06:06:23	169077
#8	Search **#2 OR #3 OR #4 OR #5 OR #6 OR #7**	06:06:10	2544027
#7	Search **Neoplasm OR neoplasms OR neoplasmic**	06:05:56	2079140
#6	Search **Tumor OR tumors OR tumorous**	06:05:46	2319178
#5	Search **Tumour***	06:05:34	159517
#4	Search **Malignan***	06:02:50	310074
#3	Search **Carcinoma OR carcinomas**	06:02:38	566937
#2	Search **Cancer OR cancers OR cancerous**	06:02:20	2262510
#1	Search **"Uterine Cervical Neoplasms"[Mesh]**	06:02:03	47401

Appendix 3: The ERG's critical assessment of the Cancer Care Ontario systematic review

Database of Abstracts of Reviews of Effects (DARE)

Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a systematic review
Hirte H W, Strychowsky J E, Oliver T, Fung-Kee-Fung M, Elit L, Oza A M

Bibliographic details	Hirte H W, Strychowsky J E, Oliver T, Fung-Kee-Fung M, Elit L, Oza A M. Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a systematic review. International Journal of Gynecological Cancer 2007; 17(6): 1194-1204
Authors' objectives	To investigate the effectiveness of chemotherapy for recurrent, metastatic, and persistent cervical cancer.
Searching	MEDLINE, EMBASE, CDSR and CENTRAL were searched through to February 2006. The Canadian Medical Association Infobase and the National Guidelines Clearinghouse were also searched. Only publications in English were eligible and search terms were reported. In addition, conference proceedings of the American Society of Clinical Oncology (1995-2005) and the European Society of Medical Oncology (2002-2005) were searched for new or ongoing trials, and references from retrieved and recent review articles were manually searched.
Study selection	Randomised controlled trials (RCTs), practice guidelines, systematic reviews, and meta-analyses comparing one chemotherapy regimen with another, or no treatment, in women with recurrent, metastatic, or persistent cervical cancer, were eligible for inclusion. Eligible studies were required to report one of the following outcomes: response rate, survival, toxicity, or quality of life (QOL). Studies of women with a range of disease stages were eligible if results were given separately for the relevant population. Studies evaluating radiotherapy in combination with chemotherapy were not eligible for inclusion. Included studies were conducted in the United States, Europe, Russia, Belgium, South Africa, Mexico, and Denmark. Studies compared single-agent cisplatin with combination cisplatin-based chemotherapy, cisplatin-based chemotherapy with other chemotherapeutic regimens, carboplatin with other chemotherapy, and non-platinum containing agents. Platinum doses ranged between 20 and 400mg/m2. Some patients had received prior chemotherapy, chemotherapy as a radiosensitiser, radiotherapy, or surgery, and the site of disease was reported as distant, in the pelvis, or both. QoL was assessed using various different assessment tools. The authors state that the evidence was selected and reviewed by members of the PEBC gynaecology Cancer Disease Site Group (DSG) and two methodologists, but no further information was given.
Validity assessment	The authors did not state how they assessed validity, but reported on blinding, method of randomisation, statistical power, comparability of participants, and intention-to-treat analysis.
Data extraction	The authors did not state how data were extracted. The number (%) of patients experiencing adverse events (toxicity), complete response, partial response, or complete plus partial response were extracted. Median survival and median progression-free survival (PFS) (in months) were also extracted, along with hazard ratios with their 95% confidence intervals (CIs), where this data were reported. QoL data were extracted in descriptive form.
Methods of synthesis	Data were presented as a narrative synthesis and in tables by outcome and comparison type. Meta-analysis was planned and undertaken, but not presented due to clinical heterogeneity.
Results	Fifteen RCTs (n=2538) were included in the review. Sample sizes ranged between 20 and 438 patients. The quality of the RCTs was deemed to be adequate; although none of the studies were blinded, only seven studies reported methods of randomisation, and only four trials were sufficiently powered. Baseline characteristics of participants were comparable between groups, and nine studies used ITT analysis. Three RCTs were terminated early. Significant improvements were reported in patients receiving combination cisplatin-based chemotherapy compared with single-agent cisplatin for overall response (complete response plus partial response) (four of 15 RCTs), median overall survival (one of 13 RCTs), and median PFS (three

	of eight RCTs). Cisplatin in combination with topotecan showed the greatest median overall survival benefits; HR 0.76 (95% CI: 0.59, 0.98, p=0.017). Fifteen treatment-related deaths were reported in five RCTs, the majority were receiving combination cisplatin-based chemotherapy. Greater haematologic toxicity was reported in patients receiving combination therapy compared to single agent cisplatin (six of seven RCTs). Results for non-haematologic toxicity were also reported in the review. There were no significant differences between the two treatment groups in QoL scores (two RCTs). Four RCTs showed that the greatest benefit in median survival was observed in patients who had not previously been treated with cisplatin as part of chemoradiotherapy.
Authors' conclusions	Cisplatin in combination with topotecan should be offered as a treatment option to appropriate patients who may be willing to maximise the response and survival benefits associated with combination chemotherapy. However, patients should be aware that prior chemoradiotherapy with cisplatin may reduce the benefits and that toxicity is greater. Further research is needed to investigate the treatment options.
CRD commentary	The review question and inclusion criteria were clear, and were supported by a comprehensive search of the literature for published and unpublished publications. However, only articles published in English were searched, which means that language bias may have been introduced. The authors report that the quality of included studies was adequate, but only limited data were reported by studies and it was unclear how the validity assessment process was performed. In addition, the process for study selection and data extraction was unclear, thus reviewer error and bias cannot be ruled out. Due to clinical and methodological heterogeneity, the authors' decision not to pool the results was appropriate, but such heterogeneity should be taken into account when considering the generalisability of the results. Further limitations include the small number of studies for treatment comparisons and the small study populations. Despite the above considerations, the authors' conclusions appear to reflect the evidence available and their recommendations for further research seems appropriate.
Implications of the review for practice and research	Practice: The authors state that there is concern that as more patients undergo cisplatin chemoradiotherapy, the median survival benefit with first-line combination cisplatin-based chemotherapy may reduce. Research: The authors state that further RCTs are required to investigate the effects of single and combination platinum and non-platinum chemotherapy regimens, particularly in patients with prior chemoradiotherapy. Further RCTs are also required to determine the generalisability of survival benefit to patient populations with a greater rate of prior chemoradiotherapy with cisplatin.
CRD summary	This review concluded that cisplatin plus topotecan should be offered as a treatment option to appropriate patients with recurrent, metastatic, or persistent cervical cancer, but further research is required. There were several considerations with the included studies, but the authors' conclusions appear to reflect the evidence available and their recommendations for further research seems appropriate.
Other publications of related interest	Hirte HW, Strychowsky JE, Oliver T, Fung-Kee-Fung M, Elit L, Oza AM. Chemotherapy for recurrent, metastatic, or persistent cervical cancer: a systematic review. Int J Gynecol Cancer. 2007; 17(6):1194-1204.
Funding	Not stated.

Appendix 4: Quality Assessment of Economic Model

Quality criterion	*Question(s)*	*Response (✓,× or NA)*	*Comments*
S1	Is there a clear statement of the decision problem?	✓	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	×	The decision problem is "the clinical and cost-effectiveness of topotecan in combination with cisplatin, *relative to platinum-based single and combination chemotherapy regimens*..." (MS p.10, emphasis added). Although a number of potential comparators are given (MS p.11), the model compares only topotecan plus cisplatin with paclitaxel plus cisplatin. The ERG was not convinced by the manufacturer's argument excluding potential comparators (ERG report, section 3.3); it is therefore not clear that the objective of the model is fully consistent with the stated decision problem.
	Is the primary decision-maker specified?	✓	
S2	Is the perspective of the model stated clearly?	✓	
	Are the model inputs consistent with the stated perspective?	✓	
	Has the scope of the model been stated and justified?	✓	
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	×	Results are given in terms of life-years-gained, not QALYs as would be expected given the perspective of the model.
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	
	Are the sources of data used to develop the structure of the model specified?	✓	
	Are the causal relationships described by the model structure justified appropriately?	✓	
S4	Are the structural assumptions transparent and justified?	×	The model does not consider dose reduction following adverse events (which potentially leads to inconsistencies in the costing between this model and that in the direct patient-level comparison also provided). This omission is not justified.
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the	✓	

	model?		
S5	Is there a clear definition of the options under evaluation?	✓	
	Have all feasible and practical options been evaluated?	×	See S1
	Is there justification for the exclusion of feasible options?	×	See S1
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	×	Only a 2 year time horizon is considered, whereas the main pivotal trial considered a 3 year time horizon and differences between treatments were observed during the final year.
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	
S9	Is the cycle length defined and justified in terms of the natural history of disease?	N/A	
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	✓	
	Where choices have been made between data sources, are these justified appropriately?	×	The manufacturer did not justify the preference for calculating overall survival with paclitaxel using a hazard ratio derived from an indirect comparison of GOG-0169 and GOG-0179 rather than adopting the hazard ratio directly from GOG-0204.
	Has particular attention been paid to identifying data for the important parameters in the model?	×	The results are sensitive to the costs of administering each treatment and the number of vials of topotecan required; the ERG is not convinced by the manufacturer's assumptions in this regard and particular attention does not appear to have been paid to identifying the most appropriate data to adopt.
	Has the quality of the data been assessed appropriately?	✓	
	Where expert opinion has been used, are the methods described and justified?	N/A	

D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓	
D2a	Is the choice of baseline data described and justified?	✓	
	Are transition probabilities calculated appropriately?	N/A	
	Has a half-cycle correction been applied to both cost and outcome?	N/A	
	If not, has this omission been justified?	N/A	
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	✓	
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓	
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	×	
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	×	
D2c	Are the costs incorporated into the model justified?	✓	
	Has the source for all costs been described?	✓	
	Have discount rates been described and justified given the target decision-maker?	✓	
D2d	Are the utilities incorporated into the model appropriate?	×	No utility weights incorporated
	Is the source for the utility weights referenced?	N/A	
	Are the methods of derivation for the utility weights justified?	N/A	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	

	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	✓	
	Is the process of data incorporation transparent?	✓	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	N/A	
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	N/A	
D4	Have the four principal types of uncertainty been addressed?	×	The model does not consider parameter uncertainty through PSA nor does it consider patient variability through subgroup analysis.
	If not, has the omission of particular forms of uncertainty been justified?	×	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	×	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	×	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	×	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	×	
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	×	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	✓	
C2	Are any counterintuitive results from the model explained and justified?	×	The resulting average costs for topotecan plus cisplatin are very different from those resulting from the accompanying direct patient-level comparison; the manufacturer made no attempt to justify these differences.
	If the model has been calibrated against independent data, have any differences been explained and justified?	N/A	
	Have the results of the model been compared with those of previous models and any differences in	×	

results explained?

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