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
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	4453

No.	Database	Search term	Results
		COST-UTILITY OR COST ADJ UTILITY	
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
	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

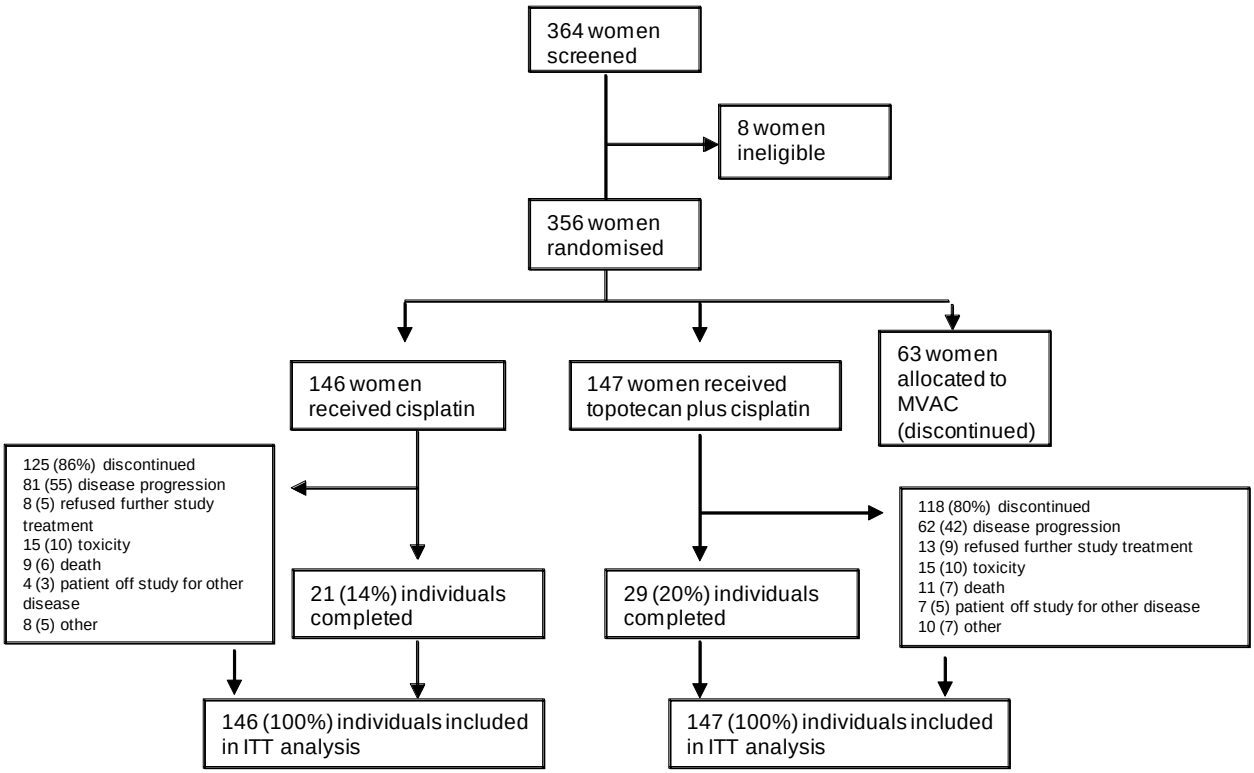
Reason for study conclusion	Cisplatin (n=146)		Topotecan/cisplatin (n=147)	
	n	%	n	%
Completed study[a]	21	14	29	20
Withdrawal reason				
Disease progression	81	55	62	42
Refused further study treatment	8	5	13	9
Toxicity	15	10	15	10
Death	9	6	11	7
Patient off study for other disease	4	3	7	5
Other	8	5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

B2: Please clarify the rationale for restricting the time horizon of the indirect comparison with paclitaxel to 24-months instead of using 36-months which reflect the duration of the topotecan clinical trial. Please discuss the implications of using a shorter time horizon, with reference to the comparisons using data from both the GOG-0169 and GOG-204 studies.

24 months of follow-up data were the longest follow-up available for GOG-0169 and therefore it was decided that it would not be appropriate to consider an analysis beyond this period. The implication of using a shorter time horizon however are that the full survival benefits of topotecan compared to paclitaxel are not reflected. This is probably a conservative assumption as the majority of costs have probably been incurred within 24 months and there may be additional survival benefit for topotecan plus cisplatin that is ignored by a 24 month time horizon.

When comparing against the GOG-204 study the opposite effect is expected. The (non-significant) point estimate of the OS hazard ratio for Paclitaxel compared to topotecan favours paclitaxel. Therefore shortening the time horizon in this analysis overestimates the benefit of topotecan.

B3: Please provide further justification for not quality-adjusting the overall survival estimates employed in the indirect comparison based on the aggregate data. Please discuss whether it is possible to use the aggregate data available for PFS and OS (as well as side effects) to provide these quality-adjustments. Please also discuss the implications of using the data this way.

The life gains in the indirect analysis were not quality adjusted as it was felt that the available quality of life data were not suitable of being used in a way that would be sufficiently robust and could not provide meaningful interpretation. The FACT-G mapped values from the GOG-0179 are relevant to the Topotecan arm of the trial, but are recorded at 4 time points which would not be relevant to the aggregate data from the GOG-0169 study as we do not have the individual patient level data to ensure that the utilities are correctly applied.

An estimate could be performed using the PFS and OS figures from the GOG-169 study and the time points from the trial shown in table 20, but averaged for the cisplatin naïve population; however these results would need to be interpreted with caution. We are unable to disaggregate the times and frequency of adverse events from the GOG-169 study and so these would have to be estimated from the rates. We would also have to assume that the timings of the utility values from the GOG-0179 arm we're applicable to the GOG-169 arm, event though the disease progression is different. This is likely to overestimate the utility gain

of patients in GOG-169. It was our opinion that there were too many uncertainties in this approach and that as the analysis was only intended as a secondary analysis to the main direct analysis, the cost per life-year gain would be more a robust approach and sufficient to support the submission.

B4: It is stated in the submission that PFS is not reported in GOG-0169. Please clarify why the PFS data reported in figure 1 of Moore et al (2004) is not suitable for the purpose of informing the indirect comparison.

This statement in the submission was made in error for which we apologise. What was meant here was that although PFS is reported in the Moore paper, the approach we are taking to model life-years gained instead of quality adjusted life years gained, means that only the overall survival results from Moore et al are required.

B5: Please provide an Excel file with the calculations used to estimate the ICER based on the indirect comparison using results from GOG-204

This is provided in the file 'Topotecan Indirect Comparison – GOG204.xls' that has been sent with this response

B6: Please clarify the difference between the HR (crude) and the HR (cox) estimates reported in Cells B50 and B51 (Sheet GOG169 – GOG179). Please report the source for the HR (Cox) estimate.

The hazard ratio labelled as 'crude' in the model is calculated using methods suggested by Parmar et al (1998) using the calculations shown in the model spreadsheet. The hazard ratio labelled 'cox' is calculated by processing the Moore et al data using SAS survival analysis functionality to fit a Cox hazard function. The HR calculated using the Parmar method is used in the analysis.

B7: Please supply an Excel file with equivalent OS data to that presented in the range F21:J45 (Sheet GOG169 – GOG179) for the full 36-months for both cisplatin and topotecan + cisplatin arms – for both the whole licensed population and the cisplatin naïve populations.

This is provided in the file 'Topotecan 36 month survival tables.xls' that has been sent with this response

B8: Please supply an Excel file with the PFS data for the full 36-months for both cisplatin and topotecan + cisplatin arms – for both the whole licensed population and the cisplatin naïve population.

This is provided in the file 'Topotecan 36 month survival tables.xls' that has been sent with this response

B9: Please undertake an additional sensitivity analysis based on applying the hazard ratio approach for paclitaxel and cisplatin to the 36-month cisplatin OS data.

The requested analysis has been performed, the results of which are shown in Table 18 below.

Table 18. Cost effectiveness results for the indirect comparison with paclitaxel.

	Mean cost per patient	Incremental cost	Mean life years	Incremental life years	ICER: cost per life years gained
Cisplatin	£2,395		0.90		
Topotecan + cisplatin	£7,310	-£4,915	1.18	0.28	£17,781 (vs. Cisplatin)
Paclitaxel + cisplatin	£7,587	£277	0.98	-0.19	Dominated (by Topotecan +Cisplatin)

B10: Please provide and Excel file with equivalent estimates for PFS derived from Figure 1 in Moore 2004.

This is provided in the file 'Topotecan 36 month survival tables.xls. that has been sent with this response

B11: Please consider undertaking an additional indirect cost-effectiveness analysis utilising both the PFS and OS data. Please apply separate utility weights to the progression free and progressive disease periods. Also include utility decrements for the major SAEs and present the assumptions employed regarding the duration of these decrements. Present results for comparisons with paclitaxel based on GOG-169 and GOG-204 employing both 24 and 36 month time horizons.

Analysis has been performed as requested. We have used the literature breast cancer utility rates for the analysis as these best fit to progression free survival and progression health states required in the adapted model.

We have used the percentage of trial population rates of neutropenia grade 3, neutropenia grade 4 and thrombocytopenia to calculate the expected proportion of patients that suffer lower utility and assumed these side effects are incurred in the first cycle and last for 1 month. The utility value for patients in progression free survival is estimated using the available utility scores for patients who achieve complete response and those that maintain a stable condition. These values are weighted by the reported trial rates for complete response. GOG-169 reports a 15% complete response rate and GOG-0179 reports a 10% complete response rate. The number of patients with progressed disease is estimated by calculating the difference in the area between the overall survival and the progression free survival curves.

Analysis has been performed for both studies GOG-169 and GOG-204. The PFS for the paclitaxel plus cisplatin arm in the GOG-169 analysis is calculated as described in question B10. PFS for the paclitaxel plus cisplatin arm in the GOG-204 analysis is calculated using the hazard ratio of 1.268 cisplatin, presented by Monk et al (2008) and is calculated from the topotecan plus cisplatin PFS data.

The utility values used in the model are shown in Table 19 below and the results of the cost effectiveness analysis shown in Table 20.

Table 19: Application of the breast cancer utilities to the updated indirect model.

Applies during model period *(Brown 1998 reference)*	**Brown 1998[49] Breast Cancer utilities**
Initial cycle *(Start 2nd line)*	0.64
Initial cycle. Neutropenia grade 3. *(Febrile neutropenia without hospitalisation)*	0.56
Initial cycle. Neutropenia grade 4. *(Febrile neutropenia with hospitalisation)*	0.30
PFS complete response *(2nd line response)*	0.81
PFS Non-complete response *(2nd line stable)*	0.65
PFS weighted utility Topotecan/Paclitaxel	0.666/0.674
Progression *(2nd line progression)*	0.39

Table 20: Results of the indirect cost-effectiveness analysis including progression free survival and utility values.

	Mean cost per patient	**Mean QALYs Gain**	**Incremental cost**	**Incremental QALYs**	**ICER: cost per QALY gained**
GOG-169 analysis – Branded Taxol price					
Topotecan + cisplatin	£7,310	0.67	-£277	0.12	Topotecan + Cisplatin Dominates Paclitaxel plus Cisplatin
Paclitaxel + cisplatin	£7,587	0.55			
GOG-169 analysis – 50% of Taxol price					
Topotecan + cisplatin	£7,310	0.67	£1,450	0.12	£12,213 (Topotecan vs Cisplatin)
Paclitaxel + cisplatin	£5,860	0.55			
GOG-204 analysis – Branded Taxol price					
Topotecan + cisplatin	£7,310	0.67	£277	0.11	£13,260 (Paclitaxel vs Topotecan)
Paclitaxel + cisplatin	£7,587	0.78			
GOG-204 analysis – 50% of Taxol price					
Topotecan + cisplatin	£7,310	0.67	-£1,450	0.12	Paclitaxel + Cisplatin Dominates Topotecan plus Cisplatin
Paclitaxel + cisplatin	£5,860	0.55			

B12: Please provide results using the literature based cancer utility estimates and alternative wastage assumptions simultaneously.

The analysis in B11 uses the breast cancer rates from the literature. Analysis is presented below for the GOG-169 base case scenario using utility values given in question B11 and

looking at different wastage scenarios described in section 7.2.9 of the main submission . These results are presented in table 21.

Table 21: Results of the indirect cost-effectiveness analysis for GOG-169, using different wastage assumptions.

Wastage assumption	Cost per QALY gained
Minimal wastage	
Branded Taxol	Topotecan dominates Paclitaxel
50% of branded Taxol	£7,997
Maximum wastage	
Branded Taxol	£1,884
50% of branded Taxol	£16,428

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 22 and 23, respectively

Table 22. 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 23. 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.

B15: Please clarify whether the calculation of OS provides an estimate of mean OS or an estimate of the restricted mean OS. Please discuss the implication of using the approach employed with respect to the indirect comparison based on both GOG-169 and GOG-204.

The OS provides an estimate of the restricted mean, as it is calculated from the area under the curve up to 24 months. The implications of this approach are that we are likely to be underestimating the benefits of topotecan when comparing to GOG-169 as the better estimated long term survival for topotecan (assuming continuation of the HR) are not reflected, given that most of the costs have been incurred earlier on in the model. The reverse is true however in the comparison with GOG-204 as the point estimate of the survival HR for paclitaxel plus cisplatin versus topotecan plus cisplatin is in favour of paclitaxel.

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.

B17: *Please provide an estimate of the mean dose intensity index for the topotecan+cisplatin and cisplatin arms taking into account dose reduction due to AE (e.g. 83% of planned dose). Provide separated estimates for the licensed population and the cisplatin naïve population*

The mean dose intensity index's for the licensed and cisplatin naïve populations have been calculated and are presented in table 24 below.

Table 24: Mean dose index for licensed and cisplatin naïve populations.

Population	Cisplatin	Topotecan plus Cisplatin	
		Topotecan	Cisplatin
Licensed population			
N	113	101	
Mean dose	50	73.8	49.8
(sd)	(0.00)	(0.30)	(1.00)
Dose intensity index	1.00	0.984	1.00
Cisplatin Naïve population			
N	62	56	
Mean dose	50	74.2	49.9
(sd)	(0.00)	(0.03)	(0.40)
Dose intensity index	1.00	0.99	1.00

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. These data are summarised in table 25 below.

Table 25. Resource use relating to events in the analysis

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

B19: The Lin Method is normally appropriate for administrative censoring ie patients entering the trial at different dates, where data are missing completely at random Censoring due to loss to follow up is more problematic because data are likely to be missing at random or not missing at random. Please provide a table comparing baseline characteristics of patients who were completely followed up or died with those who were incompletely followed up.

Table 26. Baseline demographics of patients that were censored and those that were completely followed up in the direct analysis.

Characteristic	Not censored (n=247)		Censored (n=46)	
Age, years				
Median	46		53	
Range	22 - 84		29 – 76	
Race or ethnicity				
White	178	(72)	35	(76)
Black	44	(18)	8	(17)
Other	25	(10)	3	(7)
Performance status				
Performance status 0	110	(45)	27	(59)
Performance status 1	115	(47)	17	(37)
Performance status 2	22	(9)	2	(4)
Cell type				
Squamous	210	(85)	39	(85)
Adenosquamous	15	(6)	1	(2)
Adenocarcinoma	14	(6)	4	(9)
Mucinous	3	(1)	1	(2)
Clear Cell	2	(<1)	0	
Endometrioid	2	(<1)	1	(2)
Villoglandular	1	(<1)	0	
Tumour grade				
Tumour grade 1	14	(6)	3	(7)
Tumour grade 2	133	(54)	32	(70)
Tumour grade 3	96	(39)	8	(17)
Stage				
Stage IVB	25	(10)	5	(11)
Persistent	30	(12)	2	(4)
Recurrent	192	(78)	39	(85)
Cisplatin use				
Prior cisplatin	144	(58)	21	(46)
No prior cisplatin	103	(42)	25	(54)

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.”

B21: The submission identifies that the trial report for GOG 0169 only reports median, not mean survival page 99), and does not show the HR for the overall difference in rates between groups. The Parmar method for estimating the HR from a KM graph used in the submission makes assumptions about the number of patients who were censored based on minimum and maximum follow up time in each group. The spreadsheet GOG 0169 overall survival, column D seems to show that the submission assumed that no patients are censored (that is, column D is zero for all time periods). It is not clear how this assumption would affect the results (i.e. the estimated HR). Please confirm or explain further how the number at risk was calculated in this analysis

The censored points have not been included in the analysis as it was not possible to determine where they occurred in the survival curves. All exists from the study are therefore assumed to be deaths. However, examining the Kaplan-Meier curve in figure 2 of Moore et al, it appears that any censoring points appear in the tail of the survival and so would not be expected to have a significant effect on the hazard ratio. This approach will result in a very slight under estimate of the hazard ratio in favour of Topotecan.

B22: Please provide the coefficient used for the mapping of FACT-G to utility and the mean values of the FACT-G variables applied to these coefficients in each treatment group.

The coefficients used in the mapping of FACT-G to utility scores are shown in table 27 below. The values in the mapping are all categorical variables and so we show the spread of the data across the categories for each survey question.

Table 27. Coefficients used for the FACT-G mapping**.**

FACT-G Item and categories	Coefficient	Distribution across categories
PWB: Lack of energy		
0-1	–0.2222	0.32
2-3	–0.1137	0.58
4	0	0.10
PWB: Feel sick		
0	–0.1537	0.50
1-4	0	0.95
FWB: Able to work		
0-1	–0.0431	0.49
2-4	0	0.51
FWB: Able to enjoy life		
0-1	–0.1254	0.21
2-3	–0.0641	0.56
4	–0.0345	0.23

PWB = Physical Well-Being
FWB = Functional Well-Being

B23: Missing (utility) data were imputed in some cases as the last observation carried forward (LOCF). As HRQL is likely to be declining in many of these patients, this assumption might over-estimate the benefit of treatment. Please provide additional rationale for using LOCF as a method of imputation.

Analysis has been performed to show that whichever method of computation is used to estimate utility, there is little difference between the treatment arms. Three methods are analysed; using the raw utility data unadjusted, the LOCF assuming the last value is carried forward even after death and LOCF assuming death results in a carry forward of 0. The results of this analysis are shown in table 28.

The analysis also shows that using the LOCF method 2 where dead patients are assume to carry forward 0 utility, there is a marked decline in utility at 5 cycles and 9 months after randomisation which reflects progressing disease.

Table 28. Utility scores for Cisplatin and Topotecan plus Cisplatin patients using different methods of handling censored patients.

	Raw data		**LOCF method 1***		**LOCF method 2^**	
	mean	**(sd)**	**mean**	**(sd)**	**mean**	**(sd)**
Cisplatin (n=115)						
Prior to randomisation	0.79	(0.11)	0.79	(0.11)	0.79	(0.11)
Prior to cycle 2	0.77	(0.11)	0.78	(0.11)	0.73	(0.22)
Prior to cycle 5	0.77	(0.12)	0.76	(0.11)	0.58	(0.34)
9 months after randomisation	0.79	(0.13)	0.78	(0.12)	0.32	(0.39)

Topotecan + Cisplatin (n=107)						
Prior to randomisation	0.79	(0.12)	0.79	(0.12)	0.79	(0.12)
Prior to cycle 2	0.78	(0.11)	0.77	(0.11)	0.72	(0.22)
Prior to cycle 5	0.80	(0.10)	0.78	(0.11)	0.66	(0.31)
9 months after randomisation	0.80	(0.10)	0.80	(0.10)	0.45	(0.40)

* : Method does not imputes values where the information is missing due to death
^ : Method imputes the value of 0 where the information is missing due to death

B24: Table 20 reports higher utilities in the topotecan + cisplatin group prior to cycle 5 and 9 months after randomisation. Please provide additional discussion on these results, given the overall conclusions reported on page 52 for FACT-G and toxicity data (i.e. "no statistical evidence suggesting that reported QoL and adverse effect scores changed over time across regimens"). Please confirm whether the same imputation approach was employed for the data presented in figure 11 and table 20. Also please confirm whether an adjustment for baseline scores was undertaken for the utility estimates.

The quality of life scores in figure 11 are the FACT-G quality of life scores, but are not generic utility scores. The values presented in table 20 are based on FACT-G scores mapped onto time trade off utility scores. The difference seen in the two sets of data are driven by the sensitivity of the mapping regression equation. Although there is not a significant difference shown in the quality of life of patients on different treatment regimens, the values used in the analysis are based on the patients scores recorded in the GOG-179 and thus reflect the experience of patients in the trial. Different methods of imputation were also used in Table 20 compared to Figure 11. The data presented in Figure 11 shows the mean scores at each of the time points, using LOCF. The data in Table 20 uses utility values, mapped from the FACT-G questionnaire, again using LOCF. The difference between the way these two have been calculated is the addition of an extra piece of information in Table 20. Where the questionnaire was not completed due to the patient dying, a utility value of 0 was imputed; this was not the case for the data in Figure 11.

No adjustment for baseline scores was undertaken for the utility estimates.

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.

B26: Please present comparable utility estimates to those in table 20 using alternative imputation approaches.

Alternate methods of imputation for the utility values presented in table 20 of the main submission have been examined in answer to question B23 and are shown in Table 23 above.

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.

B28: The analysis assumes GCSF following neurotoxicity is included in the NHS HRG cost. Please provide the usage rate of GCSF in the trial. Please estimate the cost of GCSF. Please conduct a sensitivity analysis assuming the cost of GCSF is not included in the HRG reference cost.

The usage rate of G-CSF is given in Table 29 below, which shows the number of patients that required G-CSF and the total courses of G-CSF used in the ITT population. An average dose of 40m units per course (0.5m units/kg) is estimated, assuming that the average person in the trial weighed 80kg. A 30m unit injection is priced at £68.41 (BNF) and so a 40m unit dose is assumed to cost £91.21. This is used to assess the additional cost that should be applied to each treatment arm. The analysis shows that Cisplatin patients use an average of 0.2 doses per patient and Topotecan patients require 2.88 doses. This results in an increased cost of £18.12 for the Cisplatin treatment arm and £263.10 for the Topotecan treatment arm. The effect on the ICER is a slight increase to £9,128 which also shown in table 29.

Table 29. G-CSF usage in the licensed population

	Cisplatin	Topotecan plus cisplatin
n	146	147
Number of patients requiring G-CSF (%)	5 (3%)	37 (25%)
Number of courses	29	424
Average number of courses per patient	0.20	2.88
Increased cost per patients	£18.12	£263.10
ICER including additional cost	£9128	

B29: The submission presents few descriptive statistics for the quantity of resource use in each arm. Please provide mean, SD, median and IQR for the key resource use items in both groups at each follow-up. Please also indicate the extent of missing data.

Table 30. Resource use in each treatment arm in the Licensed population.

	Cisplatin	**Topotecan plus Cisplatin**

	Total number of courses	Mean no. of courses (SD)	Total number of courses	Mean no. of courses (SD)
Drug use				
Cisplatin	550	49.9 (0.4)	628	49.8 (1.9)
Topotecan	-	-	628	0.74 (0.1)
Erythropoietin	466	4.8 (2.2)	1173	7.2 (4.9)
G-CSF	29	5.8 (2.2)	424	7.1 (5.8)
Platelets	6	6 (-)	147	5.9 (5.6)
PRBC	271	4.2 (2.7)	773	5.7 (4.7)
Thrombopoietin	-	-	5	2.5 (2.1)
Disease management resource use				
CT scans	213	1.5 (0.2)	230	1.6 (0.2)
MRI scans	146	1.0 (0.0)	147	1.0 (0.0)
Blood tests	546	3.7 (2.3)	622	4.2 (2.9)
Clinician 1st visit	146	1.0 (0.0)	147	1.0 (0.0)
OP visits	400	2.7 (1.3)	475	3.2 (1.9)

B30: The submission shows the overall costs per patients but does not show the cost of components such as chemotherapy costs, follow up costs ect. Please provide a table.

The direct analysis has not been constructed with the functionality of breaking down aggregated costs into the individual components that would be required to construct a summary table such as table 35 in the main submission. We have therefore estimated a breakdown of the cost results based on the indirect analysis results, assuming that the proportion of cost in each area would remain the same in the direct analysis.

Table 31: Breakdown of average cost per patient in the Licensed population direct analysis.

Mean values	Cisplatin	Topotecan plus cisplatin
Chemotherapy costs	£175	£2,295
Administration costs	£1,066	£1,751
Pre-treatment medication costs	£93	£346
Post-treatment medication costs	£8	£11
Follow-up costs	£482	£502
Adverse event costs	£128	£1,170
Total cost per patient	**£1,952**	**£6,074**

B31: Please explain the costs in the indirect comparison.

These construction of the costs are shown in the attached spreadsheet 'Indirect Comparison – 36 months.xls' that has been sent with this response

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.[1] 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.[2]

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.[iii,iv] 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 cancer[v] 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*,[ix] 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-0179[x] 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[xi] 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.

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