**TECHNOLOGY ASSESSMENT REPORT COMMISSIONED BY THE NIHR HTA PROGRAMME ON BEHALF OF THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**FINAL PROTOCOL**

**Date**: 28 November 2012

# 1 TITLE OF THE PROJECT

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer

# 2 TAR TEAM AND PROJECT 'LEAD'

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# 3 PLAIN ENGLISH SUMMARY

Ovarian cancer is a common gynaecological cancer affecting women in the UK. The outcome of ovarian cancer is generally poor, with an overall 5-year survival rate of less than 40%. Although ovarian cancer usually responds to first-line therapy, in a large proportion of patients the cancer eventually comes back. This is defined as recurrent ovarian cancer. There are several different treatment options for recurrent ovarian cancer on the market with the aim of controlling the disease for as long as possible.

The aim of this project is to review all technologies for treatment of recurrent ovarian cancer, in a multiple technology appraisal (MTA). This will include a review of TA91 (Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent

treatment of advanced ovarian cancer) and TA222 (Trabectedin for the treatment of relapsed ovarian cancer). In addition, this MTA will also cover gemcitabine. The medical benefit and risks associated with these treatments will be assessed and compared across the treatments and against available standard drug treatments for recurrent ovarian cancer. In addition, this project will include an assessment of whether these drugs are likely to be considered good value for money for the National Health Service (NHS).

# 4 DECISION PROBLEM

### *4.1 Purpose*

Ovarian cancer is the fifth most common cancer in women in the UK.[(1)] Almost 7,000 women are diagnosed with ovarian cancer each year.[(2)] The risk of developing ovarian cancer increases with age, and most women are post-menopause when they develop the disease.[(1)] Ovarian cancer comprises a group of tumours in different tissues within the ovary. The most common type is epithelial ovarian cancer, which is the diagnosis for almost 9 out of 10 ovarian cancer tumours.[(1)] Ovarian cancer often spreads from the ovary to any surface within the abdominal cavity and eventually to other parts of the body. Symptoms of ovarian cancer are usually vague and can be related to other much less serious conditions. The symptoms can include abdominal pain and bloating, loss of appetite, and irregular bleeding.[(1)] Most women are therefore not diagnosed until they have advanced stage disease, that is, the disease has spread away from the ovary to other parts of the body. The outcome is generally poor with an overall 5-year survival rate of around 40%.[(2)]

Although a significant proportion of women with ovarian cancer respond to the initial chemotherapy, many of these women relapse within 2 years of completing treatment. Recurrent ovarian cancer may be classified based on the time from initial chemotherapy to recurrence of disease into: platinum-sensitive, when the cancer responds to initial chemotherapy but recurs 6 months or more after completion of the regimen; and platinum-resistant, when the cancer recurs within 6 months of completion of initial chemotherapy. Platinum-sensitive ovarian cancer can be further divided into fully platinum-sensitive (when the recurrence-free interval is 12 months or more) and partially platinum-sensitive (when the interval is between 6 and 12 months). Patients may also have refractory disease, which does not respond to first-line therapy. However, in practice there is a time-dependent continuum of platinum sensitivity, and categorisation by level of platinum sensitivity is not rigid.

This MTA will appraise the clinical and cost-effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine within their licensed indications for the treatment of recurrent or refractory ovarian cancer.

### *4.2 Interventions*

The five pharmaceutical interventions that are the focus of this MTA all have marketing authorisations in the UK for the treatment of several types of cancer, including ovarian cancer. Paclitaxel (various manufacturers) is licensed for first-line treatment of ovarian cancer in combination with cisplatin (platinum-based chemotherapy), and as second-line treatment of ovarian cancer after failure of standard platinum-based therapy.[3] PLDH (Caelyx, Janssen-Cilag) and topotecan (various manufacturers) are licensed for the treatment of advanced ovarian cancer after failure of first-line platinum-based therapy.[4;5] Gemcitabine (Gemzar, Lilly) is licensed in combination with carboplatin (platinum-based chemotherapy), and trabectedin (Yondelis, PharmaMar) is licensed in combination with PLDH, as second-line treatment of ovarian cancer in patients with relapsed platinum-sensitive disease.[6;7] All the interventions are administered by intravenous infusion.

### *4.3 Place of the interventions in the treatment pathway*

For patients with relapsed, recurrent or refractory ovarian cancer NICE has issued guidance that encompasses PLDH, paclitaxel, and topotecan,[8] and it has appraised evidence on trabectedin.[9] The recommended options for patients with platinum-sensitive or partially platinum-sensitive advanced ovarian cancer are paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin), or single-agent PLDH (only for partially platinum-sensitive ovarian cancer). Trabectedin in combination with PLDH is not recommended.[8] The recommended options for patients with platinum-resistant or platinum-refractory ovarian cancer are single-agent paclitaxel, PLDH, or topotecan (for patients for whom PLDH and paclitaxel are considered inappropriate). At present there is no published guidance regarding the use of gemcitabine for treatment of ovarian cancer. However, combined with carboplatin, gemcitabine is licensed for the treatment of relapsed ovarian cancer in patients with platinum-sensitive or partially platinum-sensitive disease.[6]

### *4.4 Relevant comparators*

For patients with platinum-sensitive ovarian cancer the relevant comparators are:

- the interventions licensed for platinum-sensitive disease in comparison with each other;
- bevacizumab in combination with platinum-containing chemotherapy;
- single-agent platinum chemotherapy.

For patients with platinum-resistant or platinum-refractory ovarian cancer the relevant comparators are:

- the interventions licensed for platinum-resistant or platinum-refractory disease in comparison with each other;
- etoposide alone or in combination with platinum chemotherapy;
- best supportive care.

For patients with ovarian cancer, who are allergic to platinum-based chemotherapy the relevant comparators are:

- the interventions licensed as single agents, without platinum-containing chemotherapy, in comparison with each other;
- etoposide;
- best supportive care.

### *4.5 Population and relevant subgroups*

The population of interest to the current appraisal is women with ovarian cancer that has recurred after treatment with, or that did not respond to, first-line (or subsequent) platinum-based chemotherapy. If the evidence allows, the use of the interventions will be considered separately in the subgroups of:

- patients with platinum-sensitive disease: who respond to first-line platinum-based chemotherapy but relapse after 6 months or more;
- patients with platinum-resistant disease: who respond to first-line platinum-based chemotherapy but relapse within 6 months and/or patients with refractory disease who do not respond or whose disease progresses on first-line platinum-based chemotherapy;
- patients with relapsed ovarian cancer, for whom platinum-based chemotherapy is not suitable because of allergy or intolerance.

### *4.6 Outcomes to be addressed*

Evidence on the following outcome measures will be considered:

- overall survival;
- progression-free survival;
- response rate;
- adverse effects of treatment;
- health-related quality of life (HRQoL);
- cost-effectiveness.

# 5 REPORT METHODS FOR SYNTHESIS OF EVIDENCE OF CLINICAL EFFECTIVENESS

This MTA will include a review of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer. It will include a review of TA91 and TA222.[8;9] The MTA will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[10]

### *5.1 Search strategy*

To update the literature search on topotecan, PLDH, and paclitaxel from TA91, the search for these interventions will be carried out from April 2004.[8] As trabectedin and gemcitabine were not included in the scope of TA91, a second search will be carried out with no restriction on search date to identify randomised controlled trials (RCTs) evaluating these interventions. Should the randomised evidence base be insufficient to inform the decision problem that is the focus of this MTA, a search for non-randomised trials will be conducted. Any non-RCT evidence identified will be considered for suitability and recommended methods[11] used to minimise the introduction of bias.

To identify relevant RCTs, a comprehensive search strategy will be designed and used to search multiple electronic databases including MEDLINE, EMBASE, CENTRAL, and DARE. Bibliographies of retrieved studies (RCTs and systematic reviews) identified as relevant will be manually reviewed for potentially eligible studies. Ongoing clinical trials will be identified by searching clinical trial registries, including ClinicalTrials.gov and the EU Clinical Trials Register. The Index to Scientific and Technical Proceedings will be searched to identify relevant conference proceedings. Appropriate organisational websites, databases, and registers will also be searched. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, submissions provided by manufacturers will be assessed for unpublished data.

No language restrictions will be applied to the search strategy. Full details of the terms used in the scoping search are presented in Appendix 9.1. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

### *5.2 Study selection criteria and procedures*

Two reviewers will independently screen all titles and abstracts according to the inclusion criteria (see Table 1). It is anticipated that relevant manufacturers will provide submissions that may include unpublished data that will be considered. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each

study assessed. Discrepancies will be resolved by consensus, with involvement of a third reviewer when necessary.

Table 1. Inclusion criteria

| | **Inclusion criteria** |
|---|---|
| Study design | Randomised controlled trials |
| Population | People with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy |
| Interventions | For people with platinum-sensitive ovarian cancer:<br>• paclitaxel as monotherapy or in combination with platinum-based chemotherapy;<br>• PLDH as monotherapy or in combination with platinum-based chemotherapy;<br>• gemcitabine in combination with carboplatin;<br>• trabectedin in combination with PLDH;<br>• topotecan monotherapy.<br>For people with platinum-resistant or platinum-refractory ovarian cancer:<br>• paclitaxel as monotherapy or in combination with platinum-based chemotherapy;<br>• PLDH monotherapy;<br>• topotecan monotherapy.<br>For people with ovarian cancer who are allergic to platinum-based chemotherapy:<br>• paclitaxel monotherapy;<br>• PLDH monotherapy;<br>• topotecan monotherapy. |
| Comparators | For people with platinum-sensitive ovarian cancer:<br>• the interventions listed above in comparison with each other;<br>• bevacizumab in combination with platinum-containing chemotherapy (subject to NICE appraisal);<br>• single-agent platinum chemotherapy.<br>For people with platinum-resistant or platinum-refractory ovarian cancer:<br>• the interventions listed above in comparison with each other;<br>• etoposide as monotherapy or in combination with platinum-based chemotherapy;<br>• best supportive care.<br>For people with ovarian cancer who are allergic to platinum-based chemotherapy:<br>• the interventions listed above in comparison with each other;<br>• etoposide monotherapy;<br>• best supportive care. |
| Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; NICE, National Institute for Health and Clinical Excellence | |

### *5.3 Subgroups*

If the evidence allows, the use of the interventions in the subgroup of patients with relapsed ovarian cancer that is platinum-sensitive will be considered separately from that of patients who are platinum-resistant or refractory, or who are allergic to platinum-based compounds.

### *5.4 Outcomes*

Data on the following outcome measures will be assessed:

- overall survival;
- progression-free survival;
- response rate;
- adverse effects of treatment；
- HRQoL.

### *5.5 Data extraction strategy*

Full paper manuscripts of any included reference will be obtained where possible. Data will be extracted independently by two reviewers using a standardised data extraction form (see Appendix 9.2). Information extracted will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events reported. Where there is incomplete information the study authors will be contacted to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

### *5.6 Quality assessment strategy*

The quality of the clinical effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The study quality will be assessed according to recommendations by the NHS Centre for Reviews and Dissemination[10] and *Cochrane Handbook for Systematic Reviews of Interventions*.[12] This will include assessing the following factors:

- random sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other bias.

### *5.7 Methods of analysis/synthesis*

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Should sufficient comparable data be identified, standard pair-wise comparisons and mixed-treatment comparisons will be performed to evaluate the clinical effectiveness. Treatment effects will be presented as odds ratios for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. Mixed-treatment comparisons will be performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation.[13] Meta-analysis will be carried out using Comprehensive Meta Analysis software, with the use of fixed- and/or random-effects model appropriate to the assembled datasets. Statistical heterogeneity between included studies will be assessed by $I^2$ test. In the presence of heterogeneity ($I^2$ > 30%) possible sources will be investigated, including differences between individual studies in study populations, methods or interventions. Where feasible, the possibility of publication bias and/or small study effects will be investigated using funnel plots and Egger's tests.

# 6 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST-EFFECTIVENESS

The purpose of this MTA will be to assess the cost-effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine within their licensed indications for second-line or subsequent treatment of relapsed ovarian cancer in the UK. These interventions will be compared with each other and with routine and best practice or supportive care currently used in the NHS. This overarching objective will be met through identification and appraisal of:

- published economic evaluations from the literature or submitted economic evaluations from manufacturers' submissions (MSs);
- HRQoL studies of people with ovarian cancer including safety data.
- UK specific resource use data, non-UK sources will be considered if there is insufficient UK specific information;

Should the published or submitted economic evaluations prove insufficient to answer the review question; an independent *de novo* economic model will be developed.

### *6.1 Search strategy*

As outlined in Section 5, this MTA is, in part, an update of an earlier systematic review (search date of April 2004) that evaluated the clinical and cost-effectiveness of topotecan, PLDH, and paclitaxel.[8] The cost-effectiveness search will aim to identify full economic evaluations, costing studies and HRQoL studies. The following electronic databases will be

searched in order to identify economic evaluations and quality of life studies for the interventions considered:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- Database of Reviews of Effects (DARE);
- NHS Economic Evaluations Database (NHS EED).

Databases will be searched from inception for evidence on trabectedin and gemcitabine, while searches for evidence on topotecan, PLDH, and paclitaxel will be carried out from April 2004 onwards.

The details of the search strategy are presented in full in Appendix 9.1. The search strategy will combine terms capturing the interventions or comparators of interest and the target condition (ovarian cancer). Health economic and quality of life search terms will be applied to capture the study designs of interest (cost-effectiveness, cost and quality of life, health state utility values [HSUVs]). No language (to assess volume of foreign language studies available), setting or country restrictions will be applied to the search strategy. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and manufacturers' submissions will be searched for additional references. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

### *6.2 Inclusion and exclusion criteria*

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

*Inclusion criteria:*

- all economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost minimisation);
- any setting (to be as inclusive as possible);
- intervention or comparators as per the final scope;
- study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
- full publications in English (numbers of relevant non-English studies will be reported);
- quality of life studies in ovarian or gynaecological cancers.
- costing/resource use studies in ovarian cancer (for resource use review)

*Exclusion criteria:*

- abstracts with insufficient methodological details;

- systematic reviews.

### *6.3 Data extraction strategy*

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion, however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. Tables 2 and 3 show the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (Table 4).

Table 2. Health economic evaluation data extraction table

| **Author, year, country** | **Perspective, discounting & cost year** | **Model type** | **Patient population** | **Intervention/ comparator** | **Outcomes** | **Results ICER (per QALY gained) incl uncertainty** |
|---|---|---|---|---|---|---|
| | | | | | | |
| Reviewer's comments: | | | | | | |
| Abbreviations used in table: QALY, quality adjusted life year | | | | | | |

Table 3. Quality of life data extraction table

| **Author, year, country** | **Sample size** | **Patient population** | **Instrument (Valuation)** | **Utility results** |
|---|---|---|---|---|
| | | | | |
| Reviewer's comments: | | | | |
| Abbreviations used in table: | | | | |

Table 4. Data exclusion table

| **Bibliographic reference** | **Reasons for exclusion** |
|---|---|
| | |
| Abbreviations used in table: | |

### *6.4 Quality assessment strategy*

All published economic evaluations identified within the review and any economic evaluations submitted by manufacturers to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against NICE's reference checklist for economic evaluations[(11)] together with the Philips checklist[(14)] on mathematical models used in technology assessments (see Appendix 9.3). Each economic

evaluation will be assessed by one health economist and the details of the assessment checked by a second health economist.

### *6.5 Methods of analysis*

*Published and submitted economic evaluations*

A narrative summary and accompanying data extraction tables will be presented to summarise evidence from published or submitted economic evaluations.

*Economic modelling*

Should the economic evidence identified prove insufficient to answer the review question; a *de novo* economic model will be developed. The structure of the *de novo* model will be informed by economic evaluations identified in the published literature and MSs; all structural assumptions will be documented and accompanying rationales provided. It is anticipated that the model used in the previous MTA will be the most informative in the development of any *de novo* economic evaluation.[8] However, in addition to the interventions considered by Main *et al*. trabectedin and gemcitabine will be considered in any *de novo* economic evaluation. The clinical effectiveness parameters required for the economic model will be informed by the review of clinical effectiveness discussed in Section 5. The clinical effectiveness section evaluates all the technologies for recurrent ovarian cancer, and includes a review of TA91 and TA222. In addition, parameters such as estimates of quality of life (utility data) will be informed by the published literature, identified in the review. In cases where parameters required to populate the model are not available from published studies or MSs, expert clinical opinion will be considered.

The cost-effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per LYG. As appropriate, cost data will be obtained from NHS reference costs[15], British National Formulary[16], Unit Costs of Health and Social Care[17], published sources or MSs. Costs will consist of direct medical costs (e.g. drug costs and cost of adverse events, monitoring and administering chemotherapy) and direct non-medical costs (e.g. healthcare professional's costs). Resource use and costs will be valued from the NHS and Personal Social Services perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guidance.[11] The time horizon for the economic analysis will be lifetime in order to reflect the chronic and advanced nature of recurrent ovarian cancer disease.

### *6.6 Methods for estimating quality of life*

The third Consensus Conference on Ovarian Cancer held in Baden-Baden in September 2004 stated that "the main goals of the treatment of patients with relapsing ovarian cancer are to provide disease control, i.e., survival prolongation, together with symptom palliation and an emphasis on *patient quality of life*".[18] Ideally, evidence of the impact of treatments included in this review on HRQoL will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related technology appraisals or clinical guidelines. In accordance with NICE methods guidance, utility values will be taken from studies that have been based on "public" preferences elicited using a choice-based method.[11] Utility data will also be adjusted for age using data from the Health Survey of England.[19]

### *6.7 Analysis of uncertainty*

As a standard, the model will be probabilistic; that is, all relevant input parameters will be entered as probability distributions to reflect their imprecision and Monte Carlo simulation will be used to reflect this uncertainty in the model's results. In addition, uncertainty will also be explored through one-way sensitivity analysis. The outputs of probabilistic sensitivity analysis (PSA) will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. One way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions. If data permits, the impact of patient heterogeneity (e.g. platinum sensitive vs. platinum resistant/refractory) on cost-effectiveness results will be explored in subgroup analyses.

# 7 HANDLING THE COMPANY SUBMISSION(S)

All data submitted by the drug manufacturers/sponsors will be considered if received by the TAR group on or before 20/03/2013. Data arriving after this date will not be considered. Data meeting the inclusion criteria for the review will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the manufacturer(s)'s submission(s), provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR group judges that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo* model.

Any 'commercial in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be highlighted in blue and underlined in the

assessment report (followed by an indication of the relevant manufacturer name, for example, in brackets). Any 'academic in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be highlighted in yellow and underlined in the assessment report.

# 8 COMPETING INTERESTS OF AUTHORS

None.

# 9 APPENDICES

***Appendix 9.1. Draft search strategy***

***Clinical draft search strategy***

Database: MEDLINE (Ovid host); search run: 25/10/2012
Records retrieved: 2698
Limits:

- Date limit applied to update search run for previous NICE TAR for topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel (from April 2004)
- All years were searched for trabectedin and gemcitabine
- Animal-only studies excluded
- No limits applied for study design or language

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1 exp ovarian neoplasms/ (59446)
2 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, abstract, name of substance, mesh subject heading] (77917)
3 (adenexa$ adj4 mass$).mp. [mp=title, abstract, name of substance, mesh subject heading] (5)
4 or/1-3 (79681)
5 topotecan/ (1693)
6 topotecan.mp. [mp=title, abstract, name of substance, mesh subject heading] (2350)
7 (hycam$ or potactasol).mp. [mp=title, abstract, name of substance, mesh subject heading] (72)
8 or/5-7 (2353)
9 exp doxorubicin/ (40006)
10 (doxorubicin hydrochloride or doxorubicin hcl).mp. [mp=title, abstract, name of substance, mesh subject heading] (536)
11 liposomal doxorubicin.mp. [mp=title, abstract, name of substance, mesh subject heading] (1201)
12 liposome encapsulated doxorubicin.mp. [mp=title, abstract, name of substance, mesh subject heading] (85)
13 doxil.mp. [mp=title, abstract, name of substance, mesh subject heading] (256)
14 caelyx.mp. [mp=title, abstract, name of substance, mesh subject heading] (156)
15 or/9-14 (40342)
16 exp paclitaxel/ (17628)
17 paclitaxel.mp. [mp=title, abstract, name of substance, mesh subject heading] (21432)
18 taxol.mp. [mp=title, abstract, name of substance, mesh subject heading] (5750)
19 or/16-18 (22887)
20 limit 8 to ed=20040401-20121025 (1177)

21 limit 15 to ed=20040401-20121025 (13829)
22 limit 19 to ed=20040401-20121025 (12895)
23 trabectedin/ (0)
24 trabectedin.mp [mp=title, abstract, name of substance, mesh subject heading] (362)
25 (yondelis).mp. [mp=title, abstract, name of substance, mesh subject heading] (90)
26 or/23-25 (368)
27 gemcitabine/ (0)
28 gemcitabine.mp. [mp=title, abstract, name of substance, mesh subject heading] (8348)
29 (gemzar).mp. [mp=title, abstract, name of substance, mesh subject heading] (207)
30 or/27-29 (8359)
31 20 or 21 or 22 or 26 or 30 (34100)
32 4 and 31 (2764)
33 animal/ not (animal/ and human/) (3705460)
34 32 not 33 (2698)

***Health economics draft search strategy***

Database: MEDLINE (Ovid host); search run: 23/10/12
Records retrieved: 101

1 exp Ovary Cancer/ (59382)
2 (adenexa$ adj4 mass$).mp. (5)
3 genital neoplasms, female/ or ovarian neoplasms/ (67028)
4 exp Carcinoma/ (454999)
5 exp ovarian neoplasms/ (59382)
6 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ti. (26128)
7 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ab. (38904)
8 (ovar$ adj4 (oncolog$ or carcinoma$)).ab. (11836)
9 or/1-8 (516972)
10 Topotecan/ (1691)
11 topotecan.mp. (2348)
12 (hycamtin or hycamptamine).mp. (69)
13 or/10-12 (2350)
14 exp Doxorubicin/ (39977)
15 doxil.mp. (256)
16 (doxorubicin hydrochloride or doxorubicin hcl).mp. (536)
17 liposomal doxorubicin.mp. (1199)
18 (caelyx or adriamycin or rubex).mp. (13576)
19 liposome encapsulated doxorubicin.mp. (85)
20 or/14-19 (44024)
21 Paclitaxel/ (17606)
22 paclitaxel.mp. (21404)
23 docetaxel.mp. (7850)
24 taxol.mp. (5746)
25 taxotere.mp. (911)
26 or/21-25 (27636)
27 exp Trabectedin/ (0)
28 ecteinascidin 743.mp. (126)
29 ET-743.mp. (166)
30 or/27-29 (218)
31 exp Gemcitabine/ (0)
32 Carboplatin/ (8292)
33 (carboplatin or paraplatin).mp. (11106)
34 or/32-33 (11106)
35 Cisplatin/ (37564)

36 (cisplatin or platinol).mp. (48141)
37 or/35-36 (48141)
38 13 or 20 or 26 or 30 or 34 or 37 (111012)
39 animal/ not (animal/ and human/) (3703336)
40 38 not 39 (94456)
41 economics/ (26627)
42 exp costs/ and cost analysis/ (40236)
43 exp economics, hospital/ (18252)
44 economics, medical/ (8491)
45 economics, pharmaceutical/ (2377)
46 (economic$ or pharmaeconomic$ or pharmacoeconomic$ or pharmaco-economic$).tw. (126456)
47 (cost or costs or costly or costing or costed).tw. (268651)
48 value for money.tw. (778)
49 cost utility/ (0)
50 cost effectiveness/ (55464)
51 or/41-50 (430154)
52 limit 51 to yr=2004-2012 (184620)
53 40 and 52 (584)
54 9 and 53 (101)

***Appendix 9.2. Data extraction form***

***Data extraction form clinical effectiveness studies***

| **Study information** | |
|---|---|
| Study name | |
| Study references (insert citations from reference manager) | |
| Country(ies) where the clinical trial was conducted | |
| Multicentre trial (number, location) | |
| Trial sponsors | |
| Date the clinical trial was conducted | |
| Trial design (e.g. parallel, crossover, or cluster trial) | |
| Trial duration (treatment duration and follow-up) | |
| Inclusion criteria | |
| Exclusion criteria | |
| Concomitant medications | |
| Outcomes | |
| Subgroups | |
| Criteria for disease progression (e.g. CA 125, RECIST criteria or both) | |
| Abbreviations used in table: RECIST, Response Evaluation Criteria for Solid Tumors. | |

| **Patient characteristics** | **Intervention** | **Control** | **Total** |
|---|---|---|---|
| N randomised | | | |
| N withdrawals (%) | | | |
| Age (mean SD, or age range) | | | |
| Platinum sensitive ovarian cancer | | | |
| Platinum resistant ovarian cancer | | | |

| | | | |
|---|---|---|---|
| Refractory ovarian cancer | | | |
| Primary site (e.g. ovarian, fallopian tube, primary peritoneal | | | |
| Previous treatment (summary of drugs or other treatments) | | | |
| Ethnicity | | | |
| Abbreviations used in table: SD, standard deviation | | | |

| | **Intervention** | **Control** |
|---|---|---|
| Drug name | | |
| Delivery | | |
| Dose | | |
| Formulation | | |
| Number of cycles | | |
| Length per cycle | | |
| Note | | |
| Abbreviations used in table: | | |

| **Outcome** | **Risk of Bias** | **Low** | **Unclear** | **High** | **Comments** |
|---|---|---|---|---|---|
| | Random sequence generation | | | | |
| | Allocation concealment | | | | |
| | Blinding (who [participants, personnel], and method) | | | | |
| Overall survival | Blinding of outcome assessment | | | | |
| | Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up) | | | | |
| | Selective reporting | | | | |
| Response rate | Blinding of outcome assessment | | | | |
| | Incomplete outcome data | | | | |
| | Selective reporting | | | | |
| Adverse events | Blinding of outcome assessment | | | | |
| | Incomplete outcome data | | | | |
| | Selective reporting | | | | |
| Progression-free survival | Blinding of outcome assessment | | | | |
| | Incomplete outcome data | | | | |
| | Selective reporting | | | | |
| Quality of life | Blinding of outcome assessment | | | | |
| | Incomplete outcome data | | | | |
| | Selective reporting | | | | |
| Abbreviations used in table: | | | | | |

| Outcome | Intervention | Control |
|---|---|---|
| **N randomised** | | |
| Overall survival | | |
| Response rate | | |
| Adverse events | | |
| febrile neutropenia | | |
| thrombocytopenia | | |
| anaemia | | |
| palmar-plantar erythrodyesthesia (PPE) | | |
| nausea | | |
| diarrhoea | | |
| constipation | | |
| stomatitis | | |
| abdominal pain | | |
| leukopaenia | | |
| mucositis | | |
| rash | | |
| fatigue | | |
| asthenia | | |
| alopecia | | |
| anorexia | | |
| malaise | | |
| raised blood pressure | | |
| proteinuria | | |
| bowel perforation | | |
| peripheral neuropathy | | |
| Time frame (e.g. end of study, weeks) | | |
| Abbreviations used in table: | | |

| Outcome | Intervention | | | Control | | |
|---|---|---|---|---|---|---|
| **N randomised** | | | | | | |
| | **mean** | **95% CI** | **N** | **mean** | **95% CI** | **N** |
| Progression-free survival | | | | | | |
| Quality of life | | | | | | |
| Time frame (e.g., end of study, weeks) | | | | | | |
| Abbreviations used in table: | | | | | | |

### *Appendix 9.3. Health economic evaluation study quality assessment*

### *NICE reference case (11)*

| Attribute | Reference case | Reviewer's comments |
|---|---|---|
| Decision problem | The scope developed by NICE | |
| Comparator(s) | Alternative therapies routinely used in the NHS | |
| Perspective costs | NHS and Personal Social Services | |
| Perspective benefits | All health effects on individuals | |
| Form of economic | Cost-utility analysis | |

| | | |
|---|---|---|
| evaluation | | |
| Time horizon | Sufficient to capture differences in costs and outcomes | |
| Synthesis of evidence on outcomes | Systematic review | |
| Outcome measure | QALYs | |
| Health states for QALY | Described using a standardised and validated instrument | |
| Benefit valuation | Time-trade off or standard gamble | |
| Source of preference data for valuation of changes in HRQoL | Representative sample of the public | |
| Discount rate | An annual rate of 3.5% on both costs and health effects | |
| Equity | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | |
| Sensitivity analysis | Probabilistic sensitivity analysis | |
| Abbreviations used in table: NICE, National Institute for Health and Clinical Excellence; NHS, National Health Service; QALY, quality adjusted life year. | | |

***Philips checklist (14)***

| **Dimension of quality** | **Reviewers comments** |
|---|---|
| **Structure** | |
| S1 Statement of decision problem/objective | |
| S2 Statement of scope/perspective | |
| S3 Rationale for structure | |
| S4 Structural assumptions | |
| S5 Strategies/comparators | |
| S6 Model type | |
| S7 Time horizon | |
| S8 Disease states/pathways | |
| S9 Cycle length | |
| **Data** | |
| D1 Data identification | |
| D2 Premodel data analysis | |
| D2a Baseline data | |
| D2b Treatment effects | |
| D2d Quality of life weights (utilities) | |
| D3 Data incorporation | |
| D4 Assessment of uncertainty | |
| D4a Methodological | |
| D4b Structural | |
| D4c Heterogeneity | |
| D4d Parameter | |
| **Consistency** | |
| C1 Internal consistency | |
| C2 External consistency | |
| Abbreviations used in table: | |

**Additional information that is needed by NETSCC, HTA and NICE.**
**Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.**

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Please send all correspondences to the lead, Steve Edwards, and the main reviewer, Sam Barton.

**Timetable/milestones**

A Progress Report (to NETSCC, HTA who forward it to NICE within 24hr) will be submitted 27 March 2013

A draft Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted 22 May 2013

The Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted 1 July 2013

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