National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Cochrane Gynae Cancer Group	Appropriate as being used via Cancer Drugs fund and on principle I feel that agents are either proven to be effective, and should be recommended, or not effective, in which case their use should not be supported.	Comment noted. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	*[Would it be appropriate to refer this topic to NICE for appraisal?]* Yes -this patient population have high rates of recurrence even after good response to initial treatment and anything which may prolong time to relapse must be considered	Comment noted. No changes to the scope are required.
	National Cancer Research Institute/Royal College of Physicians/Royal College of Radiologists/Association of Clinical Pathologists/ Joint Collegiate	Very appropriate as improvement in treatment of platinum resistant ovarian cancer is great unmet need. Should be referred to NICE	Comment noted. No changes to the scope are required.

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	Council for Oncology (NCRI/RCP/RCR/ ACP/JCCO)		
	Royal College of Obstetricians and Gynaecologists (RCOG)	This is an appropriate topic for NICE as effectiveness of this therapy in recurrent setting needs to be evaluated.	Comment noted. No changes to the scope are required.
	Roche Products	No comment	Noted
	Target Ovarian Cancer	There are few treatment options for women with platinum resistant ovarian cancer (Drugs. 2011 Jul 30;71(11):1397-412. Efforts to improve outcomes by combining different chemotherapies have failed to improve survival and led to greater toxicity (Gynecol Oncol. 2014 Jun;133(3):624-31). New treatment options are urgently needed.	Comment noted. No changes to the scope are required.
Wording	Cochrane Gynae Cancer Group	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?]* Yes	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR/ ACP/JCCO	Reflects the issues	Comment noted. No changes to the scope are required.
	RCOG	The wording does reflect the clinical issue of difficulty in managing recurrent platinum resistant ovarian cancer	Comment noted. No changes to the scope are required.
	Roche Products	The wording is appropriate	Comment noted. No changes to the scope are required.

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	Target Ovarian Cancer	The wording needs to clarify that the proposed use of Bevacizumab is in combination with one of the three approved chemotherapy regimes.	Comment noted. Bevacizumab will be appraised within its marketing authorisation (that is, in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin hydrochloride); this is specified in the 'intervention' section.
Timing Issues	Cochrane Gynae Cancer Group	Urgent as being used in this context via the CDF and need data on clinical and cost effectiveness to justify the high costs of this treatments	Comment noted. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	Urgent	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR/ ACP/JCCO	Urgent as current therapies of very limited value	Comment noted. No changes to the scope are required.
	RCOG	Timely, the drug is in use in the primary treatment setting already	Comment noted. No changes to the scope are required.
	Roche Products	EMA granted a marketing authorisation for bevacizumab in this indication on 31st July 2014.	Comment noted. No changes to the scope are required.
	Target Ovarian	High, as overall survival for platinum resistant patients is around 12 months (Drugs. 2011 Jul 30;71(11):1397-412) and there are very	Comment noted. No changes

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	Cancer	limited treatment options.	to the scope are required.
Additional comments on the draft remit	NCRI/RCP/RCR/ ACP/JCCO	Although the approved treatments are correctly listed, they actually benefit so few patients that weekly paclitaxel is most commonly used standard of care despite lack of comparative phase 3 trials as it has proven activity related to response and symptom control.	Comment noted. Paclitaxel is included as a comparator. No changes to the scope are required.
	Roche Products	None	Noted

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Cochrane Gynae Cancer Group	Accurate	Comment noted. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	Agree with this information	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR /ACP/JCCO	Adequate	Comment noted. No changes to the scope are required.
	RCOG	The information appears accurate	Comment noted. No changes to the scope are required.
	Roche Products	No comment	Noted

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	Target Ovarian Cancer	Recent research indicates the majority of High Grade Serous (the most common subtype of ovarian cancer) originates from the epithelium of the distal fallopian tubes and not the epithelial cells on the surface of the ovaries (Am J Obstet Gynecol. 2013 Nov;209(5):409-14).	Comment noted. No changes to the scope are required.
The technology/ intervention	Cochrane Gynae Cancer Group	*[Is the description of the technology or technologies accurate?]* Yes - but need to consider need for on-going maintenance treatment with Bevacizumab until clinical progression in terms of QoL and cost effectiveness	Comment noted. Attendees at the scoping workshop discussed the duration of bevacizumab therapy in clinical trials and clinical practice; this may be considered by the Committee during the appraisal. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR /ACP/JCCO	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted. No changes to the scope are required.
	RCOG	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted. No changes to the scope are required.
	Roche Products	No comment	Noted

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	Target Ovarian Cancer	The dose is not defined. The AURELIA trial used both 15mg/kg every three weeks (when combined with topotecan) and 10mg/kg every two weeks when combined with paclitaxel or pegylated liposomal doxorubicin (J Clin Oncol. 2014 May 1;32(13):1302-8).	Comment noted. Bevacizumab will be appraised at the dosage specified within its marketing authorisation. No changes to the scope are required.
Population	Cochrane Gynae Cancer Group	Should consider sub-group of women with germline or tumour BRCA mutations who may have differing responses to PLD and PARP-inhibitors. Also consider sub-groups for HG and LG serous tumours.	Comment noted. Attendees at the scoping workshop considered that the suggested subgroups would not need to be considered separately in an appraisal of bevacizumab. Attendees agreed that consideration should be given to subgroups based on the chemotherapy drug with which bevacizumab is combined.
	National Forum of Gynae Oncology Nurses	*[Is the population defined appropriately?]* Yes it is - no groups to be considered separately	Comment noted. Attendees at the scoping workshop agreed that consideration should be given to subgroups based on the chemotherapy drug with which bevacizumab is combined.
	NCRI/RCP/RCR	*[Is the population defined appropriately?]* Yes	Comment noted. No changes

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	/ACP/JCCO		to the scope are required.
	RCOG	*[Is the population defined appropriately?]* Yes	Comment noted. No changes to the scope are required.
	Roche Products	We recommend that the wording be updated to exclude patients who have been previously treated with bevacizumab or other VEGF inhibitors or VEGF-receptor targeted agents. i.e. Adults with relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer, who have received no more than two previous chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF-receptor targeted agents Despite ongoing efforts, there is no evidence supporting the use of a biomarker to identify those patients predicted to benefit most from bevacizumab.	Comment noted. No changes to the scope are required.
	Target Ovarian Cancer	Does this need to be expanded to include some of the extensive exclusion criteria used in the AURELIA trial which excluded those with a risk of bowel perforation. These stringent criteria were credited for helping limit the incidence of bowel perforation observed in the trial (J Clin Oncol. 2014 May 1;32(13):1302-8).	Comment noted. Attendees at the scoping workshop agreed that the risk of bowel perforation may affect the decision to offer bevacizumab to individual patients in clinical practice, but considered that this did not need to be specified in the population section of the scope.

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Comparators	Cochrane Gynae Cancer Group	Best alternative depends on previous SE experienced by patient and previous treatments received. - Comparators seem appropriate	Comment noted. Attendees at the scoping workshop also noted that platinum-based chemotherapy is used in some people with platinum-resistant ovarian cancer, however this does not appear to be established practice in England. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	Treatment options are used in different orders depending upon choice of oncologist but are mainly very similar	Comment noted. Attendees at the scoping workshop also noted that platinum-based chemotherapy is used in some people with platinum-resistant ovarian cancer, however this does not appear to be established practice in England. No changes to the scope are required.
	NCRI/RCP/RCR /ACP/JCCO	Weekly paclitaxel is the standard treatment currently used and is best alternative care	Comment noted. Attendees at the scoping workshop also noted that platinum-based chemotherapy is used in some people with platinum-resistant ovarian cancer, however this does not appear to be established practice in

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			England. No changes to the scope are required.
	RCOG	*[Are these the standard treatments currently used in the NHS with which the technology should be compared? Can these be described as 'best alternative care'?]* Yes	Comment noted. Attendees at the scoping workshop also noted that platinum-based chemotherapy is used in some people with platinum-resistant ovarian cancer, however this does not appear to be established practice in England. No changes to the scope are required.
	Roche Products	The comparators listed are aligned to treatments in established clinical practice and current NICE guidance.	Comment noted. Attendees at the scoping workshop also noted that platinum-based chemotherapy is used in some people with platinum-resistant ovarian cancer, however this does not appear to be established practice in England. No changes to the scope are required.
	Target Ovarian Cancer	*[Are these the standard treatments currently used in the NHS with which the technology should be compared? Can these be described as 'best alternative care'?]* Yes	Comment noted. Attendees at the scoping workshop also noted that platinum-based chemotherapy is used in some people with platinum-

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			resistant ovarian cancer, however this does not appear to be established practice in England. No changes to the scope are required.
Outcomes	Cochrane Gynae Cancer Group	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes - should specifically look at bowel perforation and need to consider need for on-going maintenance treatment with Bevacizumab until clinical progression in terms of QoL and cost effectiveness	Comment noted. Bowel perforation has been added to the outcomes. Attendees at the scoping workshop discussed the duration of bevacizumab therapy in clinical trials and clinical practice; this may be considered by the Committee during the appraisal. Attendees also noted that bevacizumab may affect symptom control (such as ascites and the need for paracentesis), which may affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.
	National Forum of Gynae Oncology Nurses	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes - appropriate measures included	Comment noted. No changes to the scope are required. Attendees at the scoping workshop also noted that

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			bevacizumab may affect symptom control (such as ascites and the need for paracentesis), which may affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.
	NCRI/RCP/RCR /ACP/JCCO	No as lack of overall survival benefit due to crossover	Comment noted. No changes to the scope are required. Attendees at the scoping workshop also noted that bevacizumab may affect symptom control (such as ascites and the need for paracentesis), which may affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.
	RCOG	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. No changes to the scope are required. Attendees at the scoping workshop also noted that bevacizumab may affect symptom control (such as ascites and the need for paracentesis), which may

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			affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.
	Roche Products	No comment	Comment noted. No changes to the scope are required. Attendees at the scoping workshop also noted that bevacizumab may affect symptom control (such as ascites and the need for paracentesis), which may affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.
	Target Ovarian Cancer	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. No changes to the scope are required. Attendees at the scoping workshop also noted that bevacizumab may affect symptom control (such as ascites and the need for paracentesis), which may affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.

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Economic analysis	Cochrane Gynae Cancer Group	Need to consider need for on-going maintenance treatment with Bevacizumab until clinical progression in terms of cost effectiveness	Comment noted. Attendees at the scoping workshop discussed the duration of bevacizumab therapy in clinical trials and clinical practice; this may be considered by the Committee during the appraisal. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	Should also take account of time increase in comparison to time if not given	Comment noted. No changes to the scope are required.
	RCOG	This seems appropriate.	Comment noted. No changes to the scope are required.
	Roche Products	No comment	No changes to the scope are required.
	Target Ovarian Cancer	No further comments.	Comment noted. No changes to the scope are required.
Equality and Diversity	Cochrane Gynae Cancer Group	No change required	Comment noted.

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	National Forum of Gynae Oncology Nurses	No concerns treatment is appropriate for all groups, no exclusions.	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR /ACP/JCCO	No comment	No changes to the scope are required.
	RCOG	No	No changes to the scope are required.
	Roche Products	No comment	No changes to the scope are required.
	Target Ovarian Cancer	No further comments.	No changes to the scope are required.
Innovation	Cochrane Gynae Cancer Group	Current data suggest modest PFS change and no significant change to OS - so not step change	Comment noted. No changes to the scope are required.
	National Forum of Gynae Oncology Nurses	*[Do you consider the technology to be innovative?]* Yes	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR /ACP/JCCO	*[Do you consider the technology to be innovative?]* Yes	Comment noted. No changes to the scope are required.

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	RCOG	It can potentially significantly improve management of complex ovarian cancer relapse.	Comment noted. No changes to the scope are required.
	Roche Products	Bevacizumab is a step-change in the management of OC overall. VEGF-driven angiogenesis has been demonstrated to have a significant role in the development and progression of ovarian cancer, and it is the first in its class to target angiogenesis.	Comment noted. No changes to the scope are required.
	Target Ovarian Cancer	Whilst the progression free survival benefit is only 3.3 months (J Clin Oncol. 2014 May 1;32(13):1302-8) and no overall survival benefit was observed (the study was not powered to do so) this is an important development for women who have platinum resistant ovarian cancer where single agent chemotherapy is the only current option. The need is further highlighted by the recent failure of the PROCEED (EC145) Phase III trial of the folate receptor targeted drug, vintafolide, in this population.	Comment noted. No changes to the scope are required.
Other considerations	National Forum of Gynae Oncology Nurses	Ensuring that treatment will be available to all by specific recommendation	Comment noted. No changes to the scope are required.
	NCRI/RCP/RCR /ACP/JCCO	Be aware that many patients cannot receive weekly paclitaxel because of prexisting neurotoxicity	Comment noted. No changes to the scope are required.
	RCOG	None	No changes to the scope are required.
	Roche Products	No comment	No changes to the scope are required.

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	Target Ovarian Cancer	NA	No changes to the scope are required.
NICE Pathways	Roche Products	We believe bevacizumab will fit into the existing NICE pathway for ovarian cancer within the management of advanced (Stage II-IV) ovarian cancer/Second-line and subsequent therapy.	Comment noted. No changes to the scope are required.
Questions for consultation	NCRI/RCP/RCR /ACP/JCCO	Have all relevant comparators for bevacizumab been included in the scope? Yes Which treatments are considered to be established clinical practice in the NHS for relapsed, platinum-resistant epithelial ovarian, fallopian tube and primary peritoneal cancer? Paclitaxel usually weekly, PLDH, Topotecan and weekly cisplatin combined with etoposide. Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? No Where do you consider bevacizumab will fit into the existing NICE pathway, Ovarian cancer? Use in platinum resistant patients likely to be most cost effective as bevacizumab has greatest impact on progression free survival in this patient group NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people	Comments noted. Attendees at the scoping workshop noted that platinum-based chemotherapy (such as cisplatin combined with etoposide) is used in some people with platinum-resistant ovarian cancer, however this does not appear to be established practice in England. No changes to the scope are required. Attendees agreed that consideration should be given to subgroups based on the chemotherapy drug with which bevacizumab is combined. Attendees also noted that bevacizumab may affect

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		with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which bevacizumab will be licensed; No • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; No • could have any adverse impact on people with a particular disability or disabilities. No Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Questionnaire of those treating ovarian cancer and support groups Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes, improved response rate and symptom control in this patient group, reduces patients need for palliative care procedures such as	symptom control (such as ascites and the need for paracentesis), which may affect the costs of inpatient care; incidence of ascites and need for paracentesis have been added to the scope.

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		paracentesis and admission for bowel obstruction Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Aurelia trial results NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at Appropriate	

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer [ID684] (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Health Research Authority	NICE Secretariat		Removed	This organisation has requested to be removed from all technology appraisal matrices. Health Research Authority has been removed from the matrix of consultees and commentators, under 'Relevant research groups'.