Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)
Bevacizumab for the treatment of recurrent
Ovarian cancer

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], Royal College of Physicians on behalf of the following organisations

Name of your organisation: NCRI Gynaecological CSG, Royal College of Physicians, Association of Cancer Physicians, Royal College of Radiologists, Joint Collegiate Council for Oncology, British Gynaecological Cancer Society

Comments coordinated by Professor Jonathan Ledermann and Professor Charlie Gourley

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? √
- other? (please specify)

Please note that Professors Ledermann and Gourley have research collaborations with Roche and have sat on advisory boards for Roche to discuss the use of bevacizumab in ovarian

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients with 'platinum-sensitive' first recurrence are defined as a group of patients in whom tumour relapse has occurred more than 6 months after completing first-line chemotherapy. These patients will have achieved at least a full biochemical remission (CA125 normalisation) and often complete resolution of any abnormalities on the CT scan after first-line therapy. The term 'platinum-sensitive' is an internationally recognised definition referring to tumours that have a high probability of responding to further treatment with platinum-based chemotherapy. The group is subdivided into those who have 'partially-platinum' sensitive recurrence, relapsing 6-12 months after primary chemotherapy) and 'fully platinum-sensitive' recurrence, relapsing more than 12 months after treatment. These definitions are empirical, based on old cohort studies in the early 1990s and used as a guide to the probability of further response to platinum-based treatment.

There is agreement within the NHS that both groups of patients would normally be retreated with platinum-based drugs, commonly platinum in combination with another drug, or single-agent platinum therapy. There is an option (NICE T91) to treat with single agent pegylated liposomal doxorubicin (PLD) but this drug is not commonly used as a single agent in this group; more commonly it is combined carboplatin following the publication of the CALYPSO trial.

The key treatments used in above group of patients are:
Carboplatin and paclitaxel; carboplatin and gemcitabine; carboplatin and PLD; single agent carboplatin; cisplatin (in patients with allergy to carboplatin); PLD alone, or in combination with trabectedin [partially-platinum sensitive group]- particularly relevant to those with allergy to platinum.

Carboplatin and paclitaxel is internationally regarded as a standard of care following the publication of the ICON 4 trial, the only study to show a survival benefit for combination chemotherapy (compared to single agent platinum) following relapse. It has the disadvantage of toxicity- neuropathy and hair loss and for this reason carboplatin-gemcitabine or carboplatin-PLD are often chosen as alternatives. Randomised trials have shown that the magnitude of PFS benefit for carboplatin-gemcitabine compared with single agent carboplatin is similar to that seen in ICON4 for combination carboplatin and paclitaxel [OVAR2.5 study for example showed a PFS advantage of 2.8 months for carboplatin-gemcitabine compared to single agent carboplatin (p=0.003) but this study was not powered for overall survival]. Carboplatin-PLD is at least as good as carboplatin-paclitaxel but has lower toxicity.

Carboplatin-gemcitabine is a commonly used regimen. It has the advantage that it avoids the early re-use of paclitaxel and delays the introduction of PLD. Both PLD and paclitaxel may then be given at a later stage in the treatment pathway as many patients receive several lines of chemotherapy.

There is some geographical difference across the UK with regard to therapies used to treat relapsed platinum sensitive ovarian cancer. In some areas, funding is only available for the use of PLD, rather than combination with carboplatin. Similarly there is variation in the availability of access to carboplatin and gemcitabine in spite of the license (The license was granted after NICE T91 Appraisal). In areas where access to these combinations is more difficult there is more use of combination carboplatin-paclitaxel and single agent platinum.

There is little difference of opinion between professionals as to what current practice should be (the evidence is fairly clear with respect to relative efficacy and toxicity). As stated above, the main deviation from this is a reflection of local funding arrangements.

The current technology really represents an additional treatment rather than an alternative treatment as it is delivered concomitantly with chemotherapy (which is currently used) and is then continued as a maintenance therapy (for which there is no current standard treatment option).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Apart from the subdivision of partially-platinum sensitivity, the key prognostic variable in these patients is tumour histology. Tumours with clear cell or mucinous histology respond less well to chemotherapy However, it should be noted that these tumour histologies were not excluded from entry into the OCEANS trial, and conclusions about the effectiveness of the technology in relation to histology cannot be drawn. Furthermore, the subgroup analysis in the OCEANS study suggested that the progression free survival (PFS) advantage was independent of progression-free interval (PFI), cytoreductive surgery for recurrent disease, age or baseline ECOG performance status.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The chemotherapy regimens are familiar to all those specialising in the chemotherapy of ovarian cancer and do not require any special facilities. Experience with the use of bevacizumab is growing; it is licensed in a number tumours and many physicians have experience using this drug. Participation in the ICON 7 trial in the UK and the recent licensing of bevacizumab in first-line therapy of ovarian cancer means

that many clinicians are familiar with its use. Clinicians and nurses need to be familiar with the specific side effects of the drug (hypertension, proteinuria and hypersensitivity) and to exercise some caution in not selecting patients with extensive bowel involvement as they are at greater risk of bowel perforation with bevacizumab. The technology can be delivered in any environment set up for the delivery of chemotherapy.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

See above: used in ovarian and other cancers. There is variation in access to bevacizumab within its licensed first-line indication; much of England can access this through the Cancer Drugs Fund but it is not possible to access the agent in the devolved nations.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Current international guidelines include the use of carboplatin and gemcitabine as a choice of therapy for patients with platinum-sensitive recurrent ovarian cancer as discussed above. The evidence for the use of this chemotherapy is derived from phase III randomised controlled trials. The inclusion of bevacizumab with this chemotherapy is derived from a single randomised controlled trial. However, there is evidence of the effectiveness of bevacizumab as a single agent in the treatment of advanced ovarian cancer (response rate and disease stabilisation), benefit in combination with carboplatin and paclitaxel (first-line therapy [ICON7 and GOG 218 trials]) and in platinum-resistant disease (in combination with either PLD, weekly paclitaxel or topotecan [AURELIA trial – presented at American Society of Clinical Oncology 2012].

Bevacizumab has been shown to be active at all stages of the treatment of ovarian cancer and the particular strengths of its use in platinum-sensitive recurrent ovarian cancer are in extending the progression-free survival of patients and increasing the percentage of tumours that respond to treatment, so reducing tumour-related symptoms more effectively.

The Scottish Collegiate Guidelines Network (SIGN) guidelines for the management of ovarian cancer are currently being reviewed. This is a structured process including prioritisation and ranking of evidence. The role of bevacizumab is being considered in this review.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

All patients with recurrent ovarian cancer will eventually relapse or progress following second-line therapy. The aim of second (and subsequent-line) therapy is to control disease-related symptoms and extend the time that patients remain free of disease (and symptoms). Thus, prolongation of progression-free survival (PFS) is a key measure of the success of treatment. In the OCEANS trial the PFS for the bevacizumab arm was superior to that for the placebo arm (hazard ratio [HR], 0.484; 95% CI, 0.388 to 0.605; log-rank P <0.0001); median PFS was 12.4 v 8.4 months, respectively [J Clin Oncol (2012) 30:2039-2045]. Some patients have significant symptoms from recurrent disease. It is particularly relevant in these patients to use treatments that have a high probability of producing a good tumour response. The combination of bevacizumab with carboplatin and gemcitabine has been shown to increase the response rate (control with agents that produce a high response rate. The objective response rate (78.5% v 57.4%; P <0.0001) and the duration of overall response was (10.4 v 7.4 months; HR, 0.534; 95% CI, 0.408 to 0.698). At the time of publication a second interim survival analysis with 48.6 % deaths did not show and improvement in overall survival (median 35.2 months control v 33.3 months experimental; HR 1.027 [0.792-1.331]). Final outcome data are not yet available.

A second large randomized controlled trial (AURELIA: 361 patients; presented at ASCO, June 2012) was performed in the setting of relapsed platinum resistant ovarian cancer. Although this is outside of the remit of the current assessment, we feel that these data should be considered as it highlights the apparent independence of the bevacizumab-associated improvement in outcome from the chosen concomitant chemotherapy regimen. AURELIA randomized patients to chemotherapy (a choice of paclitaxel, topotecan or pegylated liposomal doxorubicin) with or without bevacizumab until progression. The median PFS in the bevacizumab arm was 6.7 months cf 3.4 months in the control arm [HR 0.48 (95% CI 0.38-0.60)]. The response rate in the bevacizumab arm was 31% cf 13% in the control arm (p<0.001).These differences are of major clinical significance as the options for standard treatment in this group of patients is small and the benefits rather modest.

There are practical implications from the use of this technology that need to be considered.
1.Treatment times will be increased by 1 hour on average every 3 weeks. Initial infusions are often given over 90 mins with subsequent infusion times reduced to 1 hour.
2. Treatment continues every 3 weeks beyond the completion of chemotherapy until progression of disease, or toxicity intervene. In the OCEANS study treatment was

discontinued due to progression in 50 %, patient choice in 25 % and adverse events in 25 %. Hypertension as a reason for treatment discontinuation occurred in 3.6 %. The occurrence of fistulae was slightly higher in patients receiving bevacizumab (1.6 v 0.4 %) and there were no gastrointestinal perforations in the OCEANS study. The median number of infusions of bevacizumab in the trial was 10 (range 1-43) at the time of publication.
3. There a few medical/nursing extra interventions required (measurement of blood pressure every 3 weeks and testing urine for protein).

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

From the information known about treatment of ovarian cancer with bevacizumab it would be reasonable to consider the combination of platinum-based chemotherapy and bevacizumab as a choice of therapy in patients with platinum sensitive relapse. The OCEANS study only included patients in first relapse and used gemcitabine in combination with carboplatin. From experience in treating patients with bevacizumab in combination with carboplatin and paclitaxel (ICON 7 and GOG 218 trials, and subsequent GOG (unpublished studies – GOG 252, GOG 262) there is no reason to expect that bevacizumab in combination with carboplatin and paclitaxel at relapse would be any less effect than the combination with carboplatin and gemcitabine. As noted above, the benefit seen from the addition of bevacizumab to chemotherapy in relapsed platinum resistant ovarian cancer was independent of the chemotherapy regime chosen (AURELIA study).
The OCEANS study precluded patients who had received bevacizumab first line. The OCEANS trial excluded patients with known abdominal fistulae, abscess or intestinal obstruction and it would be sensible to avoid the use of bevacizumab in patients with extensive large bowel (recto-sigmoid) involvement as in the AURELIA study.

From studies to date it appears that the maintenance effect of bevacizumab is the largest contributor to benefit so that treatment should be continued as in the OCEANS trial until disease progression, patient choice or significant toxicity.

Currently there are no predictive factors for response to anti-angiogenic agents. This is an area of current research and it is important that every effort is made to define predictive factors that might select patients who are likely to benefit the most.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The use of 6 cycles of platinum-based chemotherapy is common practice in the UK. Most experience with bevacizumab in the UK has resulted from treating patients in the ICON 7 trial with 7.5mg/kg, half the dose on the label and half the dose in OCEANS. There are no data examining the effect of the lower dose to treat recurrent disease. Studies are needed to assess whether the effect of bevacizumab in this patients with platinum-sensitive recurrent ovarian cancer is similar using a lower dose (with half the cost).

There is currently little experience of using carboplatin, gemcitabine and bevacizumab in the UK so that outcome data are not available. However, the population studied in the OCEANS trial is applicable to the UK population. For example, 75% of patients with advanced ovarian cancer will experience a relapse and 50 % of all patients have a 'platinum-sensitive' relapse. Thus, there are approximately 5000 patients with advanced ovarian cancer diagnosed each year in the UK; 2500 will experience 'platinum-sensitive relapse' Not all of these would be sufficiently well to receive platinum combination therapy, so that not all of these patients would be considered for bevacizumab therapy. We would estimate that about 2/3 might be eligible for bevacizumab. However, one would need to take into consideration that some patients may have received bevacizumab in the first-line setting, or that in other patients a clinical decision might be made to use bevacizumab in the 'platinum-resistant' disease setting (see AURELIA above).

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There are relatively few side effects of treatment. However, prolonged periods of treatment may have some effect on patients' quality of life although the studies thus far have not identified this as a significant factor. Upset to the routine of life has to be balance against an extension in the period of disease control, a median of 4 months in the OCEANS study.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from

registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The newest emerging data are contained in the AURELIA study (for more details see p5 above) in which bevacizumab was given with chemotherapy in the platinum-resistant disease setting (Pujade Lauraine ASCO 2012). Highly significant prolongation in PFS was seen in a group of women who traditionally have a poor and short-live clinical response to chemotherapy. This raises the question as to when it is best to use bevacizumab in the treatment of ovarian cancer.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Drug cost is the main issue for the implementation of bevacizumab therapy. 3 weekly attendance in daycare units will also increase the nursing costs, 'chair' time and pharmacy workloads. From our perspective we have no doubt that bevacizumab is an active agent and valuable addition to the therapeutic options we have to treat ovarian cancer. Clinical trials have demonstrated good activity as a single agent, in combination with chemotherapy and as maintenance. Prolongation in PFS is seen in the first-line, platinum-sensitive and platinum-resistant groups of tumours. The difficulty currently is knowing where best to place active drug in the pathway of care.

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Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- 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;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.