Professional organisation statement template

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] **submitting on behalf of:**

Name of your organisation: NCRI Breast Clinical Studies Group/RCP/RCR/ACP/JCCO

Comments coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- 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)

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?

Although the majority of women present with early breast cancer (EBC), around 10% present with metastatic disease and a further 30-40% of those with EBC go on to develop metastatic breast cancer (MBC) despite optimal treatment at the time of initial diagnosis. At present MBC is not curable but treatment can result in improved quality of life (QoL) and prolonged survival.

Treatment options for MBC include, local therapies such as radiotherapy, and systemic therapies such as chemotherapy, endocrine therapy, bisphosphonates and trastuzumab. The choice of therapy is individualised but takes into account a number of factors including : patient choice, previous therapy received, age, performance status (PS), comorbidity, hormone receptor status and the predominant disease being visceral or soft-tissue (the latter being more indolent).

Chemotherapy schedules for the treatment of MBC that have been approved by NICE include: docetaxel, paclitaxel, vinorelbine and capecitabine as single agents, and the combinations docetaxel/capecitabine and paclitaxel/gemcitabine. Combination therapies are believed to be more active and result in higher response rates. Furthermore, in addition to these chemotherapy agents, anthracyclines are widely used, especially in the adjuvant treatment of high-risk EBC. As a result, most patients with MBC have already received an anthracycline. Given the many factors outlined above that are taken into account in the choice of systemic therapy for MBC some variation in practice may occur but there is no evidence that this occurs in a systematic way leading to geographical variation.

There is general agreement amongst oncologists that anthracyclines and taxanes are the most active agents we currently have for the treatment of MBC. Current alternatives to the paclitaxel/bevacizumab combination for the treatment of MBC include:

1. **docetaxel (3-weekly)**
2. **paclitaxel (weekly or 3-weekly)**
3. **combination docetaxel/capecitabine**
4. **combination paclitaxel/gemcitabine**
5. **vinorelbine**
6. **capecitabine**

Vinorelbine and capecitabine are generally used after taxane failure. Where a taxane is being considered the choice is currently between single agent docetaxel or paclitaxel and the combinations of docetaxel/capecitabine and paclitaxel/gemcitabine. Taxane monotherapy remains the commonest treatment option used in first line MBC. The combinations are considered when

a higher response rate is desirable as in the presence of aggressive visceral disease.

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?

Patients with HER2 negative MBC represent a wide-spectrum of disease with different symptoms, PS and life-expectancy. Patients with visceral metastases, poor PS and comorbidity have a poorer prognosis while those with indolent soft-tissue disease that is hormone receptor positive have a better outcome irrespective of treatment received. Patients with bone only metastases would be difficult to monitor for efficacy. The combination of paclitaxel/bevacizumab should be used within the groups that were used in the clinical trials and be restricted in patients who were excluded from these trials.

Patients with HER2 positive disease currently receive a taxane in combination with trastuzumab in the first line MBC setting and should continue to do so. There are no randomised trials that have reported that have combined taxanes, bevacizumab and trastuzumab although in phase II trial high response rates have seen, and a large multicentre randomised phase III clinical trial in this setting is ongoing. Until further data is available this group should continue to receive taxane/trastuzumab combination therapy.

It would not be appropriate to offer this combination to patients with uncontrolled hypertension and other cardiac disease.

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 paclitaxel/bevacizumab combination should only be used in specialist chemotherapy units that already have experience in the delivery of taxanes and biological therapies such as trastuzumab. This may be in both Cancer Centres or Cancer Units as long as the expertise exists. Taxanes are currently widely used, in both Cancer centres and cancer Units, and treatment protocols already exist both for their administration and management of side-effects. Many Centres/Units already have experience with bevacizumab from the treatment of metastatic colorectal cancer and also from involvement in clinical trials.

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?

Current use in the UK is restricted largely to the private sector where patients are already widely benefiting from this extra treatment option.

Bevacizumab is not currently licensed in the UK for the treatment of EBC.

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.

No guidelines exist for the treatment of MBC using paclitaxel/bevacizumab, since its use is currently restricted.

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?

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.

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?

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?

As mentioned above taxane monotherapy is the commonest treatment option used in this setting. Units are also well used to the delivery of biological therapies such as trastuzumab. As such introduction of this technology into the UK would be seamless with minimal additional difficulty. Many units are already using this technology in the colorectal cancer setting.

In the E2100 trial, which compared weekly paclitaxel with weekly paclitaxel/bevacizumab, the efficacy benefit seen was not defined to a particular subgroup of HER2 negative patients (only a tiny fraction of patients

in the trial were HER2 positive). For example the benefit was seen irrespective of hormone receptor status or delivery of previous adjuvant chemotherapy. This was confirmed in a second pivotal randomised placebo controlled trial, AVADO, which used docetaxel rather than paclitaxel, and has recently been presented and at the American Society of Clinical Oncology meeting May 2008.

Bevacizumab was given in combination with paclitaxel in the E2100 trial however it was continued as monotherapy to disease progression in the vast majority of patients unless discontinued due to toxicity. The issue of when to stop bevacizumab is an important one with clear efficacy, toxicity and resource implications and is being considered in ongoing clinical trials.

The patient population studied in the E2100 trial does reflect the circumstances under which patients are treated in current everyday UK clinical practice. In the trial two thirds of patients had received adjuvant chemotherapy including 20% having received a taxane. This is comparable with current UK practice although the latter figure will rise following recent NICE guidance for the introduction of taxanes in EBC. As such the trial results can be extrapolated to the UK setting. The primary outcome measure in the E2100 trial was Progression-Free Survival (PFS) which is appropriate. Overall Survival was a secondary outcome measure.

The paclitaxel/bevacizumab combination was well tolerated. The predominant side effect seen in the trial attributable to bevacizumab was hypertension which is relatively easily managed with standard anti-hypertensive therapy. Other regularly seen side effects/adverse reactions included proteinuria and minor bleeding events such as epistaxis. On a larger scale within the global clinical trial experience and global everyday usage adverse events such as severe haemorrhage or gastrointestinal perforation have been seen very rarely. Recent large scale studies such as ATHENA have now reported experience in using bevacizumab in everyday clinical practice in over 2000 pts confirming that the agent is well tolerated with the incidence of severe complications described above being incredibly rare.

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.

As mentioned above the international multicentre randomised placebo controlled trial of docetaxel +/- bevacizumab (AVADO) completed accrual in March 2007 with 763 patients randomised. It has recently been presented and like E2100 it met its primary endpoint confirming a benefit in favour of improved progression free survival for the doctaxel/bevacizumab combination.

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)?

Some education/training may be required to allow units to deliver the combination of paclitaxel/bevacizumab. Other than manpower there are no major additional resources needed. All these patients would be receiving taxane chemotherapy. As with the addition of any new agent extra chemotherapy chair usage and pharmacy preparation time will be required compared with current standard practice.

In summary this technology would be a very useful addition to the current treatment options available for patients with metastatic breast cancer. The magnitude of the PFS benefit seen in the E2100 trial and the tolerability of the paclitaxel/bevacizumab regimen compare very favourably with that seen in other combination chemotherapy trials.

As mentioned above there are important ongoing clinical questions relevant to UK everyday practice, such as the optimal duration of therapy, that remain unanswered. The UK clinical trials community would be well placed to perform a randomised trial, for example, assessing the impact of stopping bevacizumab at a specific time point versus continuing to disease progression. The results of such a trial would not just benefit the UK in terms of patient welfare and

appropriate use of resources but would have a significant impact internationally.