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]. My area of specialisation is gastrointestinal cancer.

Name of your organisation

NCRI/RCP/RCR/ACP/JCCO

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)?** I have participated in trials in advanced colorectal cancer and was formerly on the Data Safety Monitoring Board for the Roche AVANT study of bevacizumab and oxaliplatin with 5-FU or capecitabine in the adjuvant treatment of colorectal cancer (study completed)

- **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.)?** Member of the NCRI Colorectal Clinical Studies Group and Advanced Colorectal Cancer subcommittee

- 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?

Treatment of advanced colorectal cancer within the NHS involves a multidisciplinary approach integrating surgical, oncological, pathological and radiological expertise. Metastatic colorectal cancer is generally treated with systemic chemotherapy in the UK, although the performance status and co-morbidities of patients determine the specific regimen used. The FOCUS study has provided the rationale for using monotherapy with a fluoropyrimidine prior to combination chemotherapy (with either irinotecan and oxaliplatin) without adversely affecting prognosis (Lancet 2007;370:143-52). The agents oxaliplatin, irinotecan and fluoropyrimidines (5-fluorouracil, capecitabine and UFT) are widely available within the NHS. Improvements in duration of survival and quality of life are generally accepted with systemic chemotherapy.

There appears to be significant variation in PCT approval rates for the addition of bevacizumab to irinotecan-based chemotherapy and for the use of cetuximab in metastatic colorectal cancer.

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?

Metastatic disease confined to the liver may be treated surgically and there is evidence for the benefit of perioperative chemotherapy. A recently published NICE guideline deals with the potential addition of cetuximab to chemotherapy in this setting. However the role of neo-adjuvant therapy has been specifically excluded from this evaluation.

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)?

This technology would be used in specialist oncology clinics under the supervision of medical and clinical oncologists. No additional professional input would be required

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?

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.

Clinical guidelines for the treatment of colorectal cancer are currently being produced for NICE. No currently available guidelines deal specifically with the technology being discussed in this application.

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?

This technology, if introduced, would be readily integrated into clinical practice. Combination chemotherapy with oxaliplatin and 5-FU or capecitabine is in standard use and the additional administration of bevacizumab would not significantly increase the difficulty of administration. There would need to be greater awareness of the potential hazards in using bevacizumab (hypertension, thromboembolism, proteinuria) and understanding of algorithms for treatment of toxicities such as hypertension.

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.

There are currently no methods available for identifying patients who might benefit from treatment with bevacizumab

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 technology under review involves the addition of bevacizumab with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer (MCRC). The most compelling study suggesting the benefit of addition of bevacizumab to chemotherapy in MCRC is that of Hurwitz *et al.* (N Engl J Med. 2004;350:2335-42) in which the chemotherapy regimen was irinotecan and 5-FU (IFL). This combination resulted in improved survival of the combination arm with median duration of survival 20.3 months in the group given IFL plus bevacizumab as compared with 15.6 months in the group given IFL plus placebo. The median duration of progression free survival was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo; the corresponding rates of response were 44.8 percent and 34.8 percent (P=0.004). Although the study has been criticised for the chemotherapy regimen used which is not optimal for irinotecan, it has resulted in widespread adoption of this combination in the first-line setting. However, NICE Technology Appraisal 118 examined bevacizumab in combination with 5-FU, with and without irinotecan, and did not recommend use.

There have been two major randomised studies investigating the combination of bevacizumab and oxaliplatin-based chemotherapy. In the NO16966 study, 1401

patients were randomised to oxaliplatin + capecitabine (XELOX) versus oxaliplatin + 5-FU and leucovorin (FOLFOX-4) and then to these regimens with bevacizumab (J Clin Oncol. 2008;26:2013-9). This large study was for first-line treatment of MCRC. The baseline characteristics of patients reflect that seen in clinical practice with a median age of 60. The primary endpoint of progression-free survival (PFS) was significantly increased in the bevacizumab-containing arms (9.4 months) versus the placebo arms (8.0 months). Subgroup analysis showed this superiority in the XELOX subgroup while results did not reach significance in the FOLFOX4 subgroup. The secondary endpoints of overall survival (OS) did not reach statistical significance while the response rate (RR) was equivalent in both arms. There was minimal cross-over with only 5% in the placebo arm receiving bevacizumab subsequently, so this is unlikely to have confounded the result.

This study demonstrated a minor increase in PFS in the bevacizumab arms without any impact on OS or RR. The investigators point out that although patients were allowed to be treated until PD, this was true only for a minority of patients. Analysis of on-treatment progression (pre-specified) resulted in an increased PFS for the bevacizumab arm (10.4 months) as compared with placebo (7.9 months). This does suggest that continuation of bevacizumab and probably fluoropyrimidine may be critical in regard to maximising the benefit of bevacizumab. However the study as published shows only a small benefit for oxaliplatin in combination with bevacizumab.

The other randomised study (E3200) involved 829 MCRC patients randomised to 3 regimens; oxaliplatin, 5-FU, leucovorin (FOLFOX4) and bevacizumab, FOLFOX4 alone and bevacizumab alone (J Clin Oncol. 2007;25:1539-44). Dose of bevacizumab was higher than in the NO16966 study at 10mg/kg. This study involved previously treated patients and OS was a primary endpoint. Median duration of survival for FOLFOX4 + bevacizumab was 12.9 months versus 10.8 months in the FOLFOX4 group and 10.2 months in the bevacizumab alone arm.

The Bevacizumab Expanded Access Trial (BEAT) evaluated the safety and efficacy of bevacizumab + chemotherapy in a general cohort of patients with mCRC. The result of this study confirmed efficacy and safety profile of previous trials. The time to progression was similar in the group receiving oxaliplatin as compared with the irinotecan cohort. In this study the demographics were comparable with the previous trials with median age of 60 years. Around 25% of patients were above 70 years old.

In conclusion, results of these studies overall indicate benefit for bevacizumab combination with oxaliplatin and fluoropyrimidine in the second-line setting with a modest effect in the first-line setting. There may be advantages in continuing treatment with bevacizumab and fluoropyrimidine until disease progression.

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?

Toxicity of the addition of bevacizumab has been extensively studied with the main issues being thromboembolic events, gastrointestinal perforation and haematuria. In the NO16966 study there was an incidence of Grade 3/4 events felt to be potentially attributable to bevacizumab of 16% in the bevacizumab arms, versus 8% in the placebo arms.

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.

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)?

NICE guidance on this technology would result in some need for extra guidance in NHS staff on the recognition and treatment of toxicities resulting from bevacizumab treatment. Regular monitoring of blood pressure and urine for protein, together with prompt diagnosis and treatment of thromboembolism would be mandatory, although the burden of these would not be high.