NICK SLEVIN

Clinical specialist statement

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

NICK SLEVIN

Name of your organisation (if applicable)

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)?

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 in 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?

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?

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)?

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.

This application concerns the treatment of Stage 3 and 4 head and neck cancer using a combination of radiotherapy and Cetuximab. Head and neck cancer constitutes 4% of all cancers in the UK and of those approximately 60% present with Stage 3 or 4 disease. Approximately half of Stage 3 and 4 patients are treated with surgery +/- (chemo) radiotherapy. The standard non surgical treatment for Stage 3 and 4 head and neck cancer is synchronous chemoradiotherapy. However, this increases the normal tissue toxicity compared to radiotherapy alone. Acute toxicity due to mucositis leads to feeding problems, pain, weight loss and increased susceptibility to infection. Late toxicity is particularly problematic in relation to chronic dysphagia and longterm dependence on tubal supplementation of nutrition. As a consequence, clinicians select fitter patients for chemoradiotherapy protocols. Anecdotally the proportion of patients considered unfit for chemoradiotherapy is about 1 in 3. These less fit patients currently receive radiotherapy alone.

Addition of synchronous chemotherapy to radiotherapy improves overall survival by approximately 10% compared to radiotherapy alone. Most centres use platinum (Cisplatinum 3 weekly or weekly; Carboplatin 3 weekly) given intravenously. The variation is accounted for by concern for increased mucositis as well as logistics.

Some patients with Stage 3 and 4 disease in the UK are also treated with neoadjuvant chemotherapy but this group is usually younger and fitter than the average head and neck cancer patient.

It is likely that Cetuximab would be delivered in specialist clinics on the same site as the radiotherapy provision. Patients should be observed during the first infusion as there is the possibility of a hypersensitivity reaction (approximately 2% of patients).

A large Phase 3 trial (Bonner et al NEJM February 9th 2006) has demonstrated significant improvements in both local regional control and overall survival. At three years there was a 13% difference in local regional control and a 10% difference in overall survival, both differences being statistically significant. This survival benefit is of the same order as that seen with synchronous chemoradiotherapy. Importantly, however, there is no increase in acute adverse events and in particular no exacerbation of mucositis, pain or weight loss seen in the Cetuximab plus radiotherapy arm.

Although there is a clear therapeutic gain from adding Cetuximab to radiotherapy, the above trial has been criticised for not using chemoradiotherapy in the standard arm. One could argue that Cetuximab should replace chemotherapy as a standard for all patients based on the lack of increased toxicity; however, most practitioners feel that it should be reserved for less fit patients until further clinical trial evidence is available.

Trials are currently in progress examining whether Cetuximab added to chemoradiotherapy improves outcomes.. There are no trials directly comparing chemoradiotherapy versus radiotherapy and Cetuximab.

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 in clinical practice reflects that observed under clinical trial conditions. 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?

Cetuximab is given intravenously in an initial dose of 400 milligrams per metre squared one week before radiotherapy and infused over 2 hours. Subsequent weekly doses are delivered during radiotherapy in a reduced dose of 250 milligrams per metre squared over one hour. There is limited experience of the safety of these doses in patients over the age of 75 (the median age of patients in the Bonner was 56, range 34 to 81). Treatment is generally well tolerated with 2% discontinuing because of hypersensitivity and 4% because of grade 3 rash. Fewer than 5% of patients in the Bonner study reduced a dose reduction of Cetuximab. No deaths in the Phase 3 study were directly attributed to Cetuximab.

Patients in the Phase 3 study were generally representative of those seen in our routine non selected practice. The Karnofsky performance status ranged from 60 to 100 but was most commonly 90. One therefore has to extrapolate the clinical benefit from a clinical trial fitter group to the less fit patients for which this application is being made.

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 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 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)?

Staff Costs

Most centres would not see more than one new patient per week. The Pharmacy time would be half an hour per week, the nursing time two to three hours per week. There is no specific haematological or biochemical monitoring. Cetuximab is not a vesicant; it does not cause significant vomiting; it can be given through a peripheral vein as a day case.