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 Sarcoma CSG, RCP, RCR, ACP, JCCO

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? √
- 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?

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.

Osteosarcoma (OS) is a rare primary malignant bone tumour, classically affecting children and young people, though not confined to this age group. There are approximately 120 new cases per year in England and Wales. This tumour typically arises in a long bone causing pain and swelling. Metastases occur principally to the lung. Surgical removal of the tumour is essential usually involving complex reconstruction and lifelong functional cost. Less than 20% of those affected will be cured by surgery alone, all others succumbing to metastatic disease. Chemotherapy was introduced in the early 1970s and now more than half of all those with localised extremity disease will achieve long term survival. OS arising in the pelvis or other axial skeletal sites or in older patients has a worse outlook. Bone sarcomas, of which OS is the most common, remain the second commonest cause of death from cancer in young people.

Standard treatment comprises intensive combination chemotherapy given before and after surgical resection of the primary tumour. Excision of lung metastases may also be undertaken. Clinical research over the past 20 years has been aimed at improving the proportion of patients to survive. There is little evidence of a significant shift in survival over that period and no significant advances in systemic chemotherapy.
As for other cancers of children and young people, considerable emphasis is placed on treatment within clinical trials. Chemotherapy regimens are reasonably well standardised outside of trials although some variation may occur for patients treated in smaller centres by medical oncologists. This is especially true for older teenagers and adults where the intensity of treatment required for OS may be unfamiliar to clinicians treating the occasional patient. The current standard chemotherapy regimen is a triplet comprising doxorubicin, cisplatin and methotrexate (MAP).

There is clearly a need to identify new treatments that can improve survival. Mifamurtide has been proposed on the basis of one randomised trial to improve survival for patients with resectable OS when added to combination chemotherapy. This agent has not been used outside of this population and has not been available for patients since completion of the study in 1997. There is no information to support

its use for patients with OS outside of the eligibility criteria of this trial (limited to those under 30 without metastastic disease). A further question has arisen as to whether specific chemotherapy drugs are required to ensure activity of mifamurtide. In the initial report the benefit appeared to be confined to those randomised to receive mifamurtide in addition to ifosfamide, as well as the standard MAP chemotherapy. As stated above, outside of clinical trials, this 3 drug combination would be widely regarded as standard treatment ie without the addition of ifosfamide.

There has been considerable discussion amongst oncologists familiar with treating OS as to interpretation of the published reports of the trial (Meyers et al, JCO 2005;23:2004 and Meyers et al JCO 2008;26:633), most recently illustrated in correspondence (see Bielack et al DOI: 10.1200/JCO.2008.17.1108; Hunsberger et al, DOI: 10.1200/JCO.2008.17.3484). The concerns centre on the presence of an interaction or otherwise between arms of the trial. This uncertainty about the results would reasonably be resolved by a further clinical trial, for which there would likely be considerable support.

As mifamurtide is currently unlicensed some assumptions must be made about the detail of a marketing authorisation should it be granted. As stated above the clinical trial evidence would only support its use in conjunction with chemotherapy in the adjuvant first line treatment of patients with localised resectable osteosarcoma. Currently such patients are eligible for an international randomised trial, EURAMOS 1 (see www.euramos.org). This trial uses MAP as the standard treatment and randomises patients after resection of the primary tumour to receive test or standard treatment on the basis of whether the resected primary tumour has undergone a greater or lesser degree of chemotherapy-induced necrosis. In localised OS, histological response to pre-operative chemotherapy is the strongest and most consistently observed prognostic factor. The trial tests a) the addition of pegylated interferon as post-chemotherapy maintenance treatment in those with good histological response and, b) for those with poor histological response, the addition of other chemotherapy drugs to MAP. The trial is being conducted in 14 countries including the United States. As of September 2008, over 1100 patients have been recruited with accrual to the planned 2,000 patients anticipated to be complete in June 2010. Since September 2005, 154 patients in the UK have been entered through 26 participating centres, estimated to be about 60% of those eligible.

No guidelines currently exist that include mifamurtide but it would only be used in specialist clinics.

There is much to recommend the further evaluation of mifamurtide through rigorous clinical trials to define more clearly a survival advantage for localised OS and especially any role in those with metastatic disease, recurrent disease, older patients and other osteosarcomas such as craniofacial tumours. The obstacles preventing such trials being undertaken are formidable and it seems more likely that, given marketing authorisation for localised disease, there would be a considerable pressure from clinicians and patients to use mifamurtide outside of its licensed indication.

In summary, mifamurtide may represent a significant advance in improving survival from a rare cancer predominantly affecting children and young people. Its use will be confined to specialist paediatric oncology or sarcoma centres. Confirmatory clinical trial evidence of its benefit on survival for localised disease is highly desirable. In the event of marketing authorisation for this indication, guidelines would be required to direct its use in other settings for OS, for which there are currently no trials either

completed or being undertaken but for which there may be some clinical rationale and certainly likely considerable pressure for its use.

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?

Evidence from clinical trials suggests that this is a safe and well-tolerated treatment. It will add to the duration of treatment. Standard MAP chemotherapy is completed in approximately 30 weeks. A further 18 weeks of weekly administration of mifamurtide would be needed to be consistent with the schedule in the trial, INT0133 (Meyers et al, JCO 2005;23:2004). The inconvenience and toxicity would be minor compared with chemotherapy. It is worth noting that a significant proportion of patients are teenagers and young adults who may resist prolongation of treatment. The commonest cause for declining randomisation in EURAMOS 1 is believed to be a desire not to prolong therapy.

There has been no measurement of quality of life in patients with OS receiving mifarmutide.

This is an outpatient treatment involving a short intravenous infusion. For most centres, who treat only a few patients with OS, this is unlikely to be burdensome. Although some degree of initial familiarisation will be required, this treatment would become quickly assimilated into routine oncology practices in specialist centres.

The principle efficacy end point for this agent is to improve event free survival. For individual patients therefore there are no routine outcome measures of effect that will be appropriate. As the survival improvement, if any, is small and applicable to a proportion of patients with OS, the impact of its addition to standard treatment is

unlikely to be visible in population-based survival analyses, for example those that are anticipated to be more readily available through the National Cancer Intelligence Network. We do not anticipate that beyond the unlikely identification of unexpected adverse events that post marketing surveillance of any form will increase knowledge of the efficacy of mifarmutide.

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.

There is no additional information about the use or utility of Mifamurtide. A compassionate access programme has been commenced in 2008 in the US and is being activated in Europe.

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)?

The additional effect of availability of Mifamurtide on facilities, training and education would be minimal. As this is a rare disease, and the impact of NICE guidance on services for patients with sarcoma is to further centralise care in designated specialist centres, the planning for provision would be reasonably straightforward.