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]

Name of your organisation Royal College of Pathologists

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?

1. 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.

Response

1. These remarks are confined to patients with multiple myeloma who have failed at least one line of therapy, including those who have proved intolerant of one therapy. Currently, several therapies are available to treat these patients, including high dose dexamethasone, bortezomib (with Dexamethasone), Thalidomide-containing regimens, and the more traditional alkylating agents and anthracyclines. The choice is dictated by patient response to last treatment (whether refractory, or responded then relapsed), duration of response, co-morbidities (renal failure, neuropathy), and other patient specific factors and preference, and access. Because therapies for myeloma are evolving rapidly, with novel agents being recently licensed, geographical differences in current practice are inevitable, dictated by access to new agents (usually dictated by the local PCT's approach to their provision), and physician experience gained from participation in trials. Opinion is also evolving as physicians learn about new agents, and how to use them safely and effectively. This is the reality of myeloma therapy today. The current alternatives to the technology in this group of patients are outlined above, and each is associated with particular disadvantages and advantages. Thalidomide for example has a toxicity profile including somnolence, constipation and neuropathy which increase with cumulative exposure, but it has the advantage of being an oral medication. In contrast, bortezomib is administered intravenously twice weekly every 3 weeks, but which is unlikely to cause somnolence, and is associated with a lower incidence of constipation. Compared with Thalidomide, the overall incidence of neuropathy is lower with bortezomib, however the incidence of Grade 3/4 neuropathy is higher. In contrast, neuropathy is a rare side effect with the technology. The technology will provide a real and important alternative treatment for particular groups of patients, for example those with pre-existing neuropathy. A table is appended to illustrate the important differences between these therapies. Because of the different safety profiles and the heterogeneity in disease- and patient- specific factors, it is vital that

this technology is available, alongside the stated alternatives, so that physicians can select a therapy that is effective but tolerable for each patient.

2. Myeloma is a heterogeneous disease, and subgroups with poorer prognosis are defined by lack of response to frontline therapy, and the existence of particular genetic features. Evidence is not yet available to inform whether particular genetic subgroups are more likely to benefit from the technology, however recent trials suggest that patients who do not respond to more traditional regimens employing alkylating agents and/or anthracyclines may respond better to the technology. As indicated above, particular subgroups of patients are more likely to benefit from the technology. Peripheral neuropathy is a significant cause of morbidity in this patient group, either due to the disease or to previous treatment. Such patients would not be suitable for Thalidomide or bortezomib-containing regimens, and would particularly benefit from this technology. There is no evidence that the type and number of prior treatment lines influences the ability to benefit from this technology. In the Phase III trials, patients who had received Thalidomide therapy, even if they were resistant to Thalidomide, still benefited from the technology. Thus, prior treatment line/s per se does not identify any subgroup with a lesser or greater chance of benefiting from this technology. Patients with a history of spontaneous thromboembolism may be put at higher risk by the technology, unless appropriately anti-coagulated. In addition, patients with cytopenias and poor bone marrow reserve may be put at higher risk by this technology because of its myelosuppressive effects. The relative advantages and toxicities of these alternative are given in a table form (Appendix).

Although subgroups that may particularly benefit from the technology can be broadly defined, this technology should not be restricted to particular patients. Our understanding of the technology and how to use it most effectively continues to grow, and insights from longer follow up of trials may identify hitherto unrecognised patient- or disease-specific factors that affect long term outcomes. Thus, the technology, along with the range of other effective treatments for this group of patients should be made available, so that the selection of an effective but tolerable treatment for each patient can be made according to the current body of knowledge and experience.

3. The technology should be prescribed in Consultant-led specialist clinics, and patients should have access to other specialist practitioners, eg. clinical nurse specialists to advise on particular side effects. Patients should have regular blood counts. Such clinical services and professional input are routine standard of care for this patient group.

4. The technology is generally used within its licensed indication.

5. Guidelines – The 2005 Joint UKMF and Nordic BCSH guidelines on Diagnosis and Treatment of Multiple Myeloma (Smith, A et al. Guidelines on the diagnosis and management of multiple myeloma 2005, Brit J Haematol 2006; 132:410) are being updated and are due to be published by the end of 2008. They will include a section on the use of the technology. This is based on the data in the Phase III trials published in the New England Journal of Medicine, as well as more recent data in the public arena, on updated results of these trials. A position statement on the technology from the UKMF is under review and will be published shortly.

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?

Response

1. The technology, when it becomes available, will be a significant advance in the treatment of this patient group, and has the potential to change the outlook for many patients with relapsed/refractory disease, or who are found to be intolerant of first line therapy. Oral administration makes this easy to use, provided regular blood tests are carried out to monitor for myelosuppression. Such blood tests are standard of care in any case, for this patient group. Due to the risk of thrombo-embolic disease, prophylaxis with low dose aspirin or low molecular weight heparin is required. Aspirin is already consumed by many in this patient group and poses little problem except in patients with a history of peptic ulceration. Low molecular weight heparin is given as a daily sub-cutaneous injection, which most patients can be successfully trained to self-administer. A risk management programme is required in view of the similarity to Thalidomide, but this is not onerous, and is already mandatory for Thalidomide prescribing.

2. Because the technology is potentially myelosuppressive, patients would need a blood test to check if their white blood cell and platelet counts are above a minimum, in order to initiate therapy. Blood tests of renal function are also required, so that dose adjustments can be made accordlingly. These investigations are part of routine care for this group of patients. The median number of cycles used in the Phase III trials was 11, which works out to about 8 per year. An informal stopping rule, based on clinical experience with the technology, and the disease in this patient group would be to stop after 2 cycles if disease progresses, and after 4 if at least a partial response (PR) is not achieved. The attainment of a PR is defined by EBMT critera as $\geq$50% fall in M-protein, and no appearance of new bone lesions. Assessments of disease response are by blood and/or urine tests performed at the start of each cycle, and the results are usually available within a week. No additional tests over and above what would be standard of care for this patient group, are required for these purposes.

3. The use of the technology under clinical trial conditions does reflect that observed in clinical practice, except perhaps that the dose of Dexamethasone is often reduced in clinical practice, due to patient intolerance and side effects. In the UK, we have recently had the opportunity to use the technology under an Expanded Access

scheme, and have confirmed the clinical responses and toxicity profile. This has been valuable in allowing access to, and experience of, the technology for UK physicians. The most important outcomes are TTP, response rates, OS and duration of response, which were all used in the Phase III trials, and reported. Another important measure of response is time to treatment failure, but a surrogate marker for this is the complete response rate (15% in test arm vs 2% in control arm), as depth of remission correlates with length of time before needing further therapy.

4. The risk of thrombo-embolic disease has already been mentioned, however, current thrombo-prophylaxis protocols are effective, and reduce the incidence to background levels. Fatigue and gastro-intestinal disturbance can occur and are sometimes troublesome, but can be effectively managed by dose reduction, and symptom-directed therapy. The adverse effect profile in UK experience hitherto reflects that reported in the trials. Experience gained in the Expanded Access protocol has meant that many UK physicians are now able to use the technology in a safe, appropriate and effective way.

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)?

Response
NICE guidance on this technology would undoubtedly mean that physicians and other healthcare professionals would need education and training, as is the case for most new technologies. Because this is an oral drug, there would be not requirement for staffing and facilities for intravenous administration, or hospital day care services.

Professional organisation (Royal College of Pathologists) statement on:

HTA – lenalidomide for multiple myeloma in people who have received at least one prior therapy.

Appendix. Comparison of the advantages/disadvantages of treatments for multiple myeloma

Toxicity, disadvantage or caution	TREATMENT				
	Dexamethasone	**Alkylating agents (Melphalan, cyclophosphamide)**	**Thalidomide**	**Bortezomib**	**Lenalidomide**
Neutropenia	No	Yes	No	No	Yes
Thrombocytopenia	No	Yes	No	Yes (transient, usually recovers at end of each treatment cycle)	Yes
Neuropathy	No	No	High risk, but less Grade 3/4	Lower risk, but more Grade 3/4	No
Constipation	No	No	Yes	Low risk	Low risk
Diarrhoea	No	No	No	Low risk	No
Somnolence	No	No	Yes	No	No
Fatigue	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate risk
Intravenous	No	No	No	Yes	No
Caution in Renal failure	No	Yes	No	No	Yes