Appendix D – Clinical specialist statement template

Denosumab for the treatment of bone metastases from solid tumours

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: Dr Stephen Harland

Name of your organisation University College, London, UCL Hospitals Trust

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)? Yes
- 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.)? No
- other? (please specify) Chairman of the Advanced Prostate Cancer Subgroup of the NCRI Prostate Cancer Clinical Studies Group.
- I have been asked to represent Prostate Action, the prostate cancer charity.

What is the expected place of the technology in current practice?

The proposal is for the use of denosumab for the prevention of skeletal related events in patients with metastatic prostate cancer in progression after androgen suppressive therapy.

How is the condition currently treated in the NHS?
The standard treatment of metastatic bone disease is systemic hormone- or chemotherapy, radiotherapy. No prophylaxis of bone disease is recommended in the NHS. Zoledronic acid is recommended in many healthcare systems for the prevention of skeletal-related events (SREs). Zoledronic acid is recommended (NICE guidelines) for the treatment of bone pain after other treatments have failed.

Is there significant geographical variation in current practice? Yes. Within the NHS, some institutions are able to prescribe prophylactic zoledronic acid, particularly palliative care establishments.

Are there differences of opinion between professionals as to what current practice should be? Yes. Some feel that prophylactic zoledronic acid should be given. I am not convinced of its benefit. The NNT for the prevention of the need for radiotherapy, the commonest SRE is about 16-17. This would not matter if zoledronic acid did not have drawbacks:

- It needs to be given every three to four weeks by intravenous infusion. This means that it is usually administered in a cancer treatment centre (though sometimes in a hospice) with frequent patient journeys and staff costs.
- It commonly produces symptomatic side effects such as fever, joint pain, muscle aches, leg swelling and malaise. No one of these symptoms is common, but taken together they are.
- Rarely, renal damage can occur and this requires patients to have had a blood creatinine test prior to each treatment.
- It causes osteonecrosis of the jaw in about 1% of cases, or more commonly when the dental hygiene is poor.

Additionally, zoledronic acid has never been shown to improve the quality of life, nor to reduce pain/analgesic requirements, in prostate cancer.

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? There probably are but they are not known. Only about 30-40% of metastatic prostate cancer require radiotherapy. If there is a high risk group, zoledronic acid could be given to these patients with a lower NNT.

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)? These are pertinent questions. For zoledronic acid which can be nephrotoxic, a plasma creatinine has to be checked before each monthly treatment. Also it has to be given by intravenous injection over 15 min. In practice this means that it is given in a hospital chemotherapy suite or in a palliative care institution.

If the technology is already available, is there variation in how it is being used in the NHS? For zoledronic acid, yes, see above. I don't know of anywhere in the NHS that denosumab is being used.
Is it always used within its licensed indications? If not, under what circumstances does this occur? No answer

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.

The advantages and disadvantages of the technology

Please see below

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?

Bone prophylaxis with denosumab: Denosumab is a monoclonal antibody which also inhibits bone resorption , but by a different mechanism form that of zoledronic acid. A large study has demonstrated that denosumab is superior to zoledronic acid in terms of efficacy – both in postponing the time to first SRE, and in reducing the number of SREs. The difference however is small. The drug does not have quite the same number of drawbacks as zoledronic acid:

- It needs to be administered once every four weeks, but it is given subcutaneously, so can be given by (GP) practice nurses.
- Symptomatic side effects appear to be as common as with zoledronic acid but the initial febrile response is not seen.
- Renal damage does not occur, so preliminary blood tests are not necessary.
- ONJ seems to occur with the same frequency, so checking on dental hygiene remains important.
- Neither increase in the quality of life nor pain reduction is claimed for denosumab.

Prospects for denosumab use in patients with CRPC: Denosumab is of similar efficacy to zoledronic acid but has some advantages. It is a little more efficacious and, being non-nephrotoxic, preliminary blood tests are avoided. This, together with the ability to administer it near the patient's home, makes it more convenient for patients and hospital departments. The NNT is still high, though if a high risk group can be identified, this may fall to an acceptable level.

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)?
The relative simplicity of denosumab administration is unlikely to require sources additional to the cost of the drug. There will be some diminution of radiotherapy for bone pain.