Clinical Specialist 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: Professor Roger Michael Francis

Name of your organisation: Musculoskeletal Unit, Freeman Hospital, Newcastle upon Tyne and Institute for Ageing and Health, Newcastle University.

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) ✓ **I am a Trustee of the National Osteoporosis Society and Chair of their Medical Board.**

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?

Oral bisphosphonates are generally used in the treatment of osteoporosis, but annual intravenous zoledronate or three monthly intravenous ibandronate are used when patients are unable to take, tolerate or absorb oral treatment. Intravenous bisphosphonates are also used where there is poor compliance and persistence with daily or weekly medication or where there is a failure to respond to oral bisphosphonates. Strontium ranelate is used where patients are unable to take or tolerate bisphosphonates or when there is a failure to respond to other treatments. Teriparatide is generally only used in patients with severe osteoporosis, who fail to respond to other treatments. There is considerable variation in osteoporosis assessment and treatment after fragility fractures in the UK (secondary prevention), which is also likely to be the case in primary prevention.

The main alternatives to denosumab currently are oral and intravenous bisphosphonates and strontium ranelate. These are effective at reducing the risk of fractures, but variation in bioavailability and poor compliance and persistence with oral treatments may reduce their anti-fracture efficacy.

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?

Patients with recent vertebral fractures or those with multiple vertebral fractures are at particularly high risk of further vertebral fractures.

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)?

Denosumab treatment will probably be initiated in specialist clinic in secondary care, but I envisage that it could subsequently be administered in primary care in a 'shared care' arrangement.

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?

Denosumab is not currently used in the NHS.

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.

I am unaware of any clinical guideline on the use of denosumab.

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?

The administration of denosumab by subcutaneous injection is more convenient than oral treatments, so may be preferred by some patients. This is likely to result in improved compliance and persistence with medication. This and avoidance of potential problems with absorption of oral treatments is likely to enhance the anti-fracture efficacy of medication. The improvement in bone density appears larger than seen with bisphosphonates and there is an impressive reduction in vertebral and non-vertebral fractures.

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.

As this is a novel biological agent, I suspect its use initially will be restricted to patients with severe osteoporosis at high risk of fragility fractures, who are either unable to take or tolerate or fail to respond to bisphosphonate treatment. I envisage that the efficacy of treatment could be monitored by repeat bone density measurements after 2-3 years, or by the use of biochemical markers of bone turnover after 3-6 months' treatment.

Treatment is initially likely to be discontinued after three years, because of uncertainty about the longer term safety and efficacy. Although the safety of denoumab in clinical trials is reassuring, I envisage that the appropriateness of further treatment would be reviewed if a patient developed malignancy, unusual or recurrent infections.

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 major clinical trial of denosumab recruited women between the ages of 60 and 90 years, with a range of bone density measurements (T-Score -2.5 to -4.0). This study included women with more severe osteoporosis, who I anticipate would be offered denousumab. The most important outcome in osteoporosis is fragility fracture and these were assessed as the main outcome measure.

Denosumab is also likely to be effective in men with osteoporosis, as it has been shown to improve bone density in men on androgen deprivation therapy.

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?

Although denosumab is a biological agent, the major clinical trial showed no evidence of an increased risk of cancer of infection. There was also no evidence of hypocalcaemia or delayed fracture healing. No cases of osteonecrosis of the jaw were reported in this study, but I understand that a case has now been reported in a patient on denosumab treatment. As the agent leads to marked suppression of bone turnover, there may theoretically be an increased of sub-trochanteric fractures with longer term treatment, as described with prolonged treatment with alendronic acid.

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.

No, not at this time.

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)?

As I envisage that treatment would be initiated in specialist centres, I suspect only limited training would be necessary, but wider education in primary care would be necessary for 'shared care' arrangements to be implemented.