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?

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.

Osteoporosis is currently treated using a number of proven effective therapies that significantly decrease the incidence of osteoporotic fractures. The mainstay of treatment (first line) is oral bisphosphonate therapy with alendronate the commonest treatment prescribed in the NHS due to a combination of the cost of generic tablets and clinical effectiveness. Other oral bisphosphonates that are utilised in the NHS are risedronate and ibandronate. Both of these therapies have similar efficacy in reducing fractures of the vertebrae but there is some debate over the efficacy of ibandronate against non-vertebral fractures. Recent evidence has shown the effectiveness of intravenous bisphosphonate therapy in the form of yearly zoledronate (ACLASTA®) in the treatment of osteoporosis. This treatment significantly decreases all osteoporotic fractures in at risk populations of all ages studied as well as reducing osteoporotic fractures and providing a survival advantage in patients post femoral neck fractures. Regional variations in treatment exist depending on access to facilities where intravenous therapy can be safely given. Most physicians will prescribe oral therapy with many using intravenous therapy as an alternative when side effects or other problems such as gastro intestinal pathology prevent the use of oral bisphosphonates. Intravenous therapy requires a more invasive approach and the need to be located within a facility where the infusion can be monitored and safely prescribed/administered. The alternative to intravenous therapy when problems arise with bisphosphonate treatment is oral strontium ranelate. This is not as effective as bisphosphonate therapy in reducing fractures but there is some evidence of efficacy in the elderly population which is not available for all oral bisphosphonates. Femoral neck fracture reduction becomes significant during the second year of treatment so long-term treatment is required. The side effect profile of strontium ranelate is different from bisphosphonates but

significant gastro intestinal side effects are experienced in many patients limiting its use. The efficacy of bisphosphonate treatment persists beyond the treatment period as the bisphosphonate remains within the skeleton. This has not been proven for strontium ranelate.

There is a clear requirement for an alternative second line therapy to oral bisphosphonates and intravenous bisphosphonate with the efficacy of the best bisphosphonate therapy as not all patients are able to take bisphosphonate therapy. The Technology offers such a treatment and head to head comparisons have shown denosumab to be equally if not more effective than alendronate treatment. The additional advantage of the Technology is that it is administered by injection twice a year overcoming the significant problems of concordance/persistence associated with oral bisphosphonate treatment. The "off effect" following stopping denosumab treatment is observed to be quicker than with bisphosphonate therapy making subsequent treatment with expensive anabolic therapy (PTH (1-34) or (1-84), Teriparatide or Preotact) in patients failing to respond to the technology more likely to be successful in improving bone mass and reducing fractures.

The Technology will have a therapeutic advantage in any patients unable to tolerate oral or intravenous therapy, in particular any patients with incapacitation/ immobilisation as a result of a stroke or mental illness where the 6 monthly injection would have a clear advantage. The technology could be given by the patient, a carer, a nurse or a practitioner. The technology is based on antibody technology and so care will be required in any groups with known allergies to Ab treatments, mouse protein or in patients who are immuno-compromised. There is some evidence that the Technology may have an advantage in patients with inflammatory disease such as rheumatoid arthritis and patients receiving glucocorticoid treatment. There is debate about the effects in subgroups with cancer particularly breast cancer and further data needs to be collected in relation to co-existent diseases.

The treatment is most likely to be used in secondary care but could easily be prescribed by General Practitioners and given by doctors or nurses in local Health Centres/Primary Care Trusts. Facilities to ensure adequate response to therapy should be available including assessment of ongoing response using biochemical tests to ensure adequate calcium and vitamin D status and decrease of bone resorption markers.

The Technology is not yet available within the NHS but clearly has other applications outside of the indication being assessed in particular new results showing significant benefit in the use as an adjuvant therapy in patients with cancer/ cancer metastases and a possible role in treatment of hypercalcaemia of malignancy especially when resistant to bisphosphonate treatment.
There are no current guidelines incorporating the technology.

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?

The Technology will not be first/second line therapy especially as cost is likely to be a major factor in determining its initial use. The Technology is likely to be used in patients considered unsuitable for, or a non responder to, oral or intra-venous bisphosphonate therapy.

The published results suggest that it is as effective as oral bisphosphonate treatment whilst ensuring a greater degree of concordance/persistence with treatment due to the mode of administration.

The additional requirement will be the requirement to teach the patient, carer or nurse/health care practitioner how to give the treatment safely and effectively. There is evidence that the treatment can confer additional benefits in terms of decreasing bone turnover and increasing bone mineral density following a course of oral alendronate therapy.

There is some evidence that the Technology may make infection worse and that serious infections can arise with its therapeutic use. Screening of patients to exclude the presence of infection may be considered advisable and the technology should be considered with care in immuno-compromised patients. The technology significantly decrease bone turnover and decreases resorption of bone by osteoclasts. Its use in patients who already have very low bone turnover, as assessed by bone resorption markers should be considered with care.

The trial population used to assess the efficacy of the Technology was directly comparable to that employed in the vast majority of osteoporosis trials conducted to date. The exclusion criteria were very similar to those adopted in other clinical trials. This means that a significant proportion of the population who will be prescribed the Technology when licensed is liable to be different from those tested in the studies. Considerable vigilance and yellow card reporting of adverse events will be required when the Technology is available for prescription.

The most important outcomes of vertebral, non vertebral and hip fracture were assessed in the major trials (eg FREEDOM Trial) and shown to be significantly reduced by the Technology after 3 years of treatment versus placebo. Several trials have shown the significant effect on reduction of bone resorption assessed by bone markers (particularly plasma CTX) and increase in bone mineral density assessed by dual energy X ray absorptiometry. Some trials have suggested these effects are greater in patients treated with denosumab compared to alendronate.

Within the clinical trials there were no reports of increased adverse events with the Technology compared to current treatments. However as stated previously there is some concern expressed following meta–analysis of trial data suggesting an increased risk of infections/serious infections in patients receiving denusomab.

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.

See the following articles:

Toulis KA et al Osteop Int Epub 2009
Replies to NEJM article Nov 26 :361; 2189-2191
Taylor KH et al Br J Oral Maxillofacial Surg 2009 Epub
Dore RK et al Ann Rheum Dis 2009 Epub
Kendler DL et al JBMR 2009 Epub
Anastakilakis AD et al Horm Metab Res 2009 Epub

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)?

NICE approval for the technology would have some cost implications as the Technology would be significantly more expensive than bisphosphonate therapy.

NICE should seriously reassess the decision to shelve the osteoporosis guidance review and documentation which would include recommendations regarding intravenous bisphosphonates and their use in treating osteoporosis. The release of the clinical guidance at the same time as a review of the Technology would be of significant benefit to the population suffering from osteoporosis.

There would be some education of NHS staff required as this technology or similar has not been in widespread use in the treatment of osteoporosis. There would be minimal requirement for additional resources.