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: Prof Jon Tobias

Name of your organisation: North Bristol NHS Trust/University of Bristol

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.)? Yes (member of the British Society for Rheumatology and President elect of the Bone Research Society).
- other? (please specify)

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

How is osteoporosis treated currently?

The great majority of postmenopausal women receiving treatment to prevent osteoporotic fragility fractures are managed in primary care, using drugs recommended by NICE TAG 160/161 (these appraisals cover treatment of those without and with previous fragility fractures respectively). Several drugs are available which broadly equivalent anti-fracture efficacy (eg alendronate, risedronate, ibandronate and strontium). Alendronate is currently the only one of these that is generic (risedronate will follow in approximately 12 months), and since initial selection is on the basis of drug cost, alendronate is by far the commonest agent used in this context. The main disadvantage of these agents, which are all administered orally, is their poor tolerability mainly due to GI side effects, leading to problems with long term adherence (rates typically below 50% after 12 months). Another limitation is that these agents only have partial anti-fracture efficacy (eg vertebral fracture relative risk reduced by approximately 50% and evidence of anti-fracture efficacy at other sites largely based on subgroup analyses).

A relatively small number of patients are treated with teriparatide by daily sc injecton or zoledronate by annual IV administration. Because of their parenteral route of administration, the latter agents are better tolerated and long term adherence rates are probably higher than with conventional oral agents. In addition, anti-fracture efficacy of these two agents is probably greater than with oral therapies (eg relative risk of vertebral fracture reduced by approximately 70%). These drugs are generally restricted to patients with more severe osteoporosis and/or difficulty in tolerating conventional oral agents, and their use is largely limited to secondary care.

The main sources of geographical variation in the treatment of osteoporosis relates to the numbers of patients identified with osteoporosis as defined above. Variation in numbers of patients being offered treatment is largely due to how much resources are invested locally in terms of case finding strategies. There are differences in professional opinion in terms of what constitutes a case of osteoporosis, particularly in borderline instances where bone mineral density (BMD) as measured by DXA scans is only moderately reduced.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient and might need to be treated differently?

Osteoporosis represents a very broad clinical spectrum. For example, an early postmenopausal woman with a low trauma fracture after a fall and mild reduction in BMD is at higher risk of having another fracture over the following ten years and as such might merit preventative treatment for osteoporosis. This type of relatively low risk patient is generally treated in primary care. An example of the other extreme is a patient with multiple vertebral fractures coming on spontaneously, who is found to have an extremely low BMD. In such cases, further multiple fractures associated with severe height loss and progressive pain and morbidity over the next few years is likely to follow if left un-treated.

Arguably, all patients at risk of osteoporosis will benefit from more effective therapies. However, while newer agents like teriparatide and zoledronate are probably more effective they are also more expensive. Therefore, use of the latter agents is generally restricted to higher risk individuals (eg individuals with very low BMD and/or vertebral fractures), in whom they are more likely to be cost effective. As discussed above, patients intolerant of oral agents are another important subgroup of patients

with osteoporosis, in whom parenteral agents like zoledronate in particular are being used increasingly frequently.

Denosumab will be more expensive than conventional oral agents, but is likely to be better tolerated by virtue of its parenteral route of administration, as well as being more effective (eg reduction in risk of vertebral fractures by approx 70%). Therefore, this agent would appear to have a role in treating similar patients to zoledronate and teriparatide, ie higher risk patients in whom it is more likely to be cost effective and/or patients intolerant of oral agents.

In what setting should/could the technology be used?
There is no reason why denosumab can't be managed in primary care. For example, it is administered by six monthly sc injection which does not require any additional expertise or training in primary care and is not currently thought to require specific monitoring. However, though denosumab is suitable for use in a primary care setting, it may be that initial case selection needs to be by secondary care since GPs do not currently have sufficient expertise or training for identifying high risk sub-groups of osteoporosis.

The advantages and disadvantages of the technology
The main evidence base for the technology is the FREEDOM trial (SR Cummings et al 2009, NEJM 361:756). The main outcomes were a reduction in relative risk of new radiographic vertebral fracture (risk ratio 0.32, 95% confidence interval (CI) 0.26, 0.41), and a decrease in the relative risk of hip fracture (risk ratio 0.60, 95% CI 0.37, 0.97). These are both the most important end-points for interventional studies in osteoporosis. To my knowledge IV zoledronate is the only other agent to have achieved both these end-points in a single study based on analysis of the whole study population. Moreover, the relative risk reduction for vertebral fracture is probably greater than that observed with comparators such as alendronate. For example, in the FIT trial, risk ratio for new radiographic vertebral fracture with alendronate in those with vertebral fracture at entry was 0.53 (95% Cl 0.41, 0.68) (Black et al Lancet 1995 348:1535-41).

Patients in the FREEDOM trial were older postmenopausal women (mean 72 years) with a BMD in the range of osteoporosis. These characteristics are similar to the patients I envisage receiving denosumab in normal clinical practice, with the exception that only 23% had a prevalent vertebral deformity, suggesting that overall they represent somewhat lower risk individuals compared to those likely to be considered suitable for denosumab in the UK. That equivalent efficacy is observed in higher risk patients, such as those with prevalent vertebral fractures at baseline, may be confirmed in sensitivity analyses published subsequently.

As discussed above, the main comparators for denosumab are teriparatide and IV zoledronate in respect of the treatment of patients at high risk of osteoporosis and/or who have difficulty in tolerating long term oral treatment. The relative merits of these three agents in the treatment of postmenopausal osteoporosis is as follows:-

Mode of action
-Unlike teriparatide which stimulates osteoblastic bone formation, zoledronate and denosumab both act to suppress osteoclastic resorption.

-Theoretically the anabolic action of teriparatide may have greater long term benefits in treating osteoporosis, but these are yet to be born out by clinical evidence.

-The anti-resorptive effect of zoledronate is more prolonged than denosumab, reflecting its prolonged retention within bone, but how this difference relates to anti-fracture efficacy or possible adverse effects is currently unclear.

Effectiveness

-Densoumab appears to have excellent all round anti-fracture efficacy which is similar to that of IV zoledronate.

-Densosumab also has similar anti-fracture efficacy to teriparatide at the spine, but unlike teriparatide was also found to be effective at reducing hip fracture risk.

Convenience and acceptability

- Recent experience of sc therapies such as teriparatide and biologics suggest that patients cope well in general with this route of administration. As denosumab is only twice a year this may increase patient acceptability as compared with teriparatide which requires daily injections.

-Densoumab represents a significant advantage over IV zoledronate since the requirement for IV drug administration for zoledronate means that this is generally given in secondary care.

Tolerability and adverse effects

-Denosumab appears to have been well tolerated in clinical trials, so as far as is known this is probably equivalent to zoledronate and teriparatide with the exception that denosumab injection lacks the tendency to provoke flu-like symptoms as commonly occurs after zoledronate.

- One possible safety issue specific to denosumab to emerge from clinical trials is an increase in the risk of cellulitis, but this was rare ie 0.3% of subjects receiving Denosumab in the FREEDOM trial. There was also a near-doubling noted in the incidence of eczema. The significance of these side effects, and in what way this might affect the use of denosumab, is currently unclear.

-There have been insufficient patients treated with denosumab to determine whether this also increases the risk of osteonecrosis of the jaw (ONJ), but more recent evidence suggests that this is linked to a specific effect of bisphosphonates on mucosal tissue suggesting that denosumab is unlikely to cause this.

-Atypical subtrochanteric fractures (STF) have recently been implicated as an adverse effect of prolonged treatment with bisphosphonates, and are thought to be related to prolonged suppression of bone resorption. Whereas densoumab may cause greater suppression of bone resorption that zoledronate, suppression is more rapidly reversible, and so on theoretical grounds it is not possible to predict whether denosumab is more or less likely to increase the risk of STF compared to zoledronate.

Scope and contra-indications

-Teriparatide and IV zoledronate are both licensed for use in postmenopausal women treated with steroids, in which the pathogenesis of osteoporosis may differ, whereas no results are currently available with regard to denosumab in this group.

-Zoledronate is contra-indicated in patients with significant renal impairment (GFR < 35 mls/min) due to instances of acute renal failure in this context, whereas there is no evidence that denosumab will need to be restricted in the same way.

-If the risk of cellulitis with denosumab is proven, there may be a need to limit use of this agent in patients at increased risk skin infections.

-There is evidence that unlike both teriparatide and zoledronate, denosumab is effective at preventing erosive progression in rheumatoid arthritis, and consequently denosumab may have added benefits when treating osteoporosis in this context.

Implementation issues

Would any rules be needed governing use of denosumab?

Criteria will be needed for defining high risk subgroups in whom denosumab is likely to be cost effective. These are expected to be broadly similar to those included in NICE TAG 160 and 161 for the selection of patients for teriparatide, which comprise a combination of low BMD below a threshold in-keeping with severe osteoporosis, and clinical features of more advanced osteoporosis such as a history of two or more low trauma fractures. Although NICE does not make this distinction, in clinical practice high risk patients are also generally selected on the basis of a history of low trauma fractures at sites associated with a particularly high risk of further fractures, such as vertebral fractures.

Alternatively, assessment of fracture risk using the FRAX tool developed by the WHO could be used to select high risk subgroups for denosumab [www.shef.ac.uk/FRAX/]. However, the FRAX tool includes several risk factors which may be insensitive to treatment intended to increase BMD, and in addition FRAX provides limited assessment of vertebral fracture risk.

Would any additional resources be required?

If the intention is to administer denosumab by sc injection every six months by the practice nurse, this would have limited resource implications. On the other hand, the plan may be for patients to be taught to inject themselves; though readily achievable in most cases based on experience with teriparatide and biologics, there would need to be some provision for patient training. If this was to involve the prescribing doctor/team there would again be limited resource implications. Alternatively, the company may be intending to include the cost of patient training (for example by 'Healthcare at Home' as used for teriparatide) in the price of the drug, in which case use of denosumab would not require any additional resources as far as the NHS is concerned.

If this drug were to replace IV zoledronate, there would be cost savings in relation to hospital day cases that would no longer be required.