GDG feedback on issues arising from the appeal hearing report and the specification for further modelling

The osteoporosis GDG welcomes the opportunity to give some feedback to the Appraisal Committee following publication of the appeal hearing report and the recent publication of the DSU project specification. We hoped that there would be some direct communication between the NICE advisory bodies, particularly on the further modelling carried out, but in the absence of this, the GDG is giving its response on some issues we believe are pertinent to the development of both appraisals and the guideline.

Before the appeal of the osteoporosis FADs, there was demarcation between the appraisals and the guideline, some of which was stated in the FADs:

- guideline covering: osteopenia, steroid-induced osteoporosis, 2nd line therapies and treatment for those contraindicated to alendronate
- appraisals covering osteoporosis only and initiation of treatment).

However, since the appeal, some areas have definitely been re-assigned to the appraisal, and it is unclear on the other areas. The DSU project specification does not really clarify this.

The purpose of this document is to pass on some of the thoughts of the GDG on how they would have tackled these areas, in the hope that this may be helpful to the Committee and will enable a smoother way forward for these concurrent pieces of NICE guidance.

A) What are the populations of the appraisals, post-appeal?

1. It is unclear which population groups are to be included in the appraisals post-appeal: the report of the Appeal panel states that '*an appraisal that does not as a minimum examine all significant patient groups within the scope, and make recommendations where the evidence permits this, is very likely to be rejected on any appeal*'.

The appraisal scope for primary prevention (2002) states that the population is '*post-menopausal women at risk of developing osteoporosis or having a related fracture. Risk factors include: low bone mineral density, smoking, low body mass index, early menopause, family history of osteoporosis, untreated hypogonadism, corticosteroid therapy, other diseases which affect bone metabolism*'. In addition, drugs should only be recommended for their licensed indication. Therefore, for at least some of the drugs (see Appendix), this includes women with osteopenia, and those taking corticosteroids. It may also include postmenopausal women who have chemotherapy-induced bone loss. The population groups to be considered are not clarified in the DSU specification, but the GDG notes that both osteoporosis and osteopenia populations are included in the economic model's net benefit analyses (see point 4).

2. The appeal report also noted that it '*did not consider that it would be appropriate for any part of a TA to defer to or be delegated to the production of a clinical guideline. This might deny patients the benefit of the funding direction*'. The further point is that, if linking statements to the guideline are inappropriate or ineffective, restriction of the FAD to women with osteoporosis would mean that those with a T-score above -2.5 SD would be denied the benefit of the funding direction, despite treatment being cost effective and within the licensed indication.

3. The GDG's interpretation of the appeal report is that women with osteopenia should be included in the appraisal and not left to the guideline. A number of the drugs are licensed for 'the prevention of osteoporosis' (i.e. must be for people with osteopenia or normal BMD). In addition, the cut-off T-score of -2.5SD contradicts the evidence that BMD is a continuum and that there are risk factors for osteoporotic fracture which are independent or partially independent of BMD. This principle is clearer if absolute risks of fracture are calculated: there are contributions from both BMD and other risk factors. It is essential that clarification is provided on whether the appraisals will cover osteopenia.

4. The GDG notes that the cost effectiveness analyses determine the net benefit for the whole spectrum of post-menopausal women (osteoporosis and osteopenia). It is possible that if this calculation were restricted to the women with osteoporosis, the strategy (DXA plus treatment) would no longer be cost effective. This would not be an issue if the patients with osteopenia are included in the appraisal.

5. Osteoporosis induced by glucocorticoids (GIO) and chemotherapy induced osteoporosis could arguably be treated separately by the guideline, but the GDG is not sure whether they are excluded from the appraisals' scope. The GDG notes that GIO was excluded from the scope by a previous appeal (2004), but it is unclear if the present appeal report over-rides the previous appeal's ruling. The GDG believes that the appraisals also need to specify whether or not postmenopausal women with chemotherapy induced bone loss are similarly excluded.

B) Possible inconsistencies at the boundaries of guideline and appraisals

6. The GDG notes that if osteopenia is to be covered by the guideline and osteoporosis by the appraisals, there may be inconsistent recommendations around the T= -2.5SD boundary if the GDG uses different model assumptions or efficacy data to the Committee (see section C).

7. However, there is a further issue that has come to light. The guideline is bound by its scope to include the newer drugs, zoledronic acid, ibandronic acid and parathyroid hormone 1-84 (Preotact) as licensed interventions. The GDG's systematic reviews of these drugs suggest that zoledronic acid is the most promising of these. In addition to being in the guideline's scope, zoledronic acid's manufacturer, Novartis, has been informed by the NICE topic selection project manager that zoledronic acid will be included in the guideline rather than being subject to a

technology appraisal. The systematic review shows that zoledronic acid is highly efficacious, compared with placebo, for the prevention of both vertebral and hip fractures. There is also anecdotal evidence that some patients prefer the annual IV infusion of zoledronic acid over oral tablets of alendronate and that compliance may be higher for the former,

Preliminary cost effectiveness analyses have been carried out using the same assumptions for zoledronic acid as used in the FADs (for comparative purposes), with the exception of 100% compliance for zoledronic acid).This includes the 10x multiplier for adverse effects (unlike for raloxifene and strontium ranelate), which would give an estimate of side effects associated with zoledronic acid. The GDG notes that the true side effects profile would be very different from alendronate and would need to be reviewed. Pooled bisphosphonate relative risks have been used for alendronate and the January 08 price. Preliminary results suggest that:

- zoledronic acid is more cost effective first line than alendronate for postmenopausal women with lower T-scores (e.g. for 70 year old women with a fracture it becomes more cost effective to use zoledronic acid at T= -3.5SD and for those without a fracture at T= -4SD)
- zoledronic acid is more cost effective than risedronate as a second line treatment.

Therefore, the T-score threshold at which those intolerant of alendronate can receive 2nd line treatment will be higher for zoledronic acid than risedronate or strontium ranelate. In practical terms, women who are intolerant of alendronate would not have to wait as long to receive treatment with zoledronic acid as they would if risedronate was the alternative (waiting until their T-score had dropped to the threshold).

The GDG believes the guideline would have to insert additional recommendations on zoledronic acid into those from the appraisals. This would be expected to cause confusion when recommendations from two pieces of NICE guidance differ, and we would expect the manufacturers to exploit these differences with active marketing at the least. A possible outcome is that preferential uptake of the mandatory funded drug would result in the less cost-effective option being implemented.

Alternatively, if the wording of the appraisal recommendations is such that zoledronic acid cannot be inserted, or the process dictates that insertions are not possible, then the guideline would have to report its findings on zoledronic acid, stating why it is not recommending the most cost effective treatment for some groups of women. This could be grounds for appeal of the FADs by Novartis.

C) Methodological considerations

8. Pooling of alendronate and risedronate for clinical efficacy – this was done in the FADs, with the rationale that pooling would give more precise estimates of effect, and that this was said to be acceptable because a class effect applied. The GDG does not consider it valid to combine alendronate and risedronate because they are different drugs having different pharmacological effects (illustrated by differences in their efficacy).

9. The FADs already pool across different absolute risk levels (i.e. the meta-analyses take into account osteoporosis and osteopenia populations). The basis for this assumption is that the relative risk is independent of the absolute risk. Part of the rationale was that there is insufficient evidence for primary prevention alone, therefore the pooled results should be used for both primary and secondary prevention. The GDG has applied the same principles to how they will deal with GIO and men. This means that each of these population groups (including postmenopausal women) should use the meta-analyses across all three population groups. The GDG has carried out systematic reviews for the pharmacological interventions, also including updates over the past 2-3 years since the ScHARR systematic reviews have been completed, and is very happy to share the results with the Committee. The GDG recommends that the Committee use the efficacy estimates from these reviews.

10. The GDG notes, as before, that it is still unhappy with some of the assumptions used in the model, notably the use of 10x multiplier for adverse effects. The appeal hearing (points 98 and 99) notes that '*the adverse effects… did not substantially influence the calculations of cost effectiveness'*. Whilst this is true for the side effects as used in the base case (1x), the increase to 10x did have a big influence. Point 99 states that there was a typographical error at 4.2.21 (of the secondary prevention FAD), but does not state what this error was. Point 100 states that no multiplier had been used for raloxifene and strontium ranelate, but was unclear whether the multiplier had been used for risedronate. The GDG would like clarification on whether a 10x multiplier was used for risedronate, raloxifene and strontium ranelate.

11. With regard to 2nd line therapies or initiation for those people contraindicated for alendronate, the GDG would like clarification on the assumptions used on side effects for these drugs. The GDG considers that the use of a 10x multiplier for risedronate implies there are similar side effects for risedronate and alendronate, which brings into question whether risedronate should be used 2nd line following alendronate.

12. The GDG has concerns that the categories of 'opportunistic assessment' and 'self identification' have not been determined correctly. The GDG believes it is incorrect to treat all patients who do not have a fracture as 'opportunistically assessed'. It is clear that patients who have been taking corticosteroids should be treated as self identifying, but so too should patients with rheumatoid arthritis and medical conditions associated with low BMD. Women with untreated premature menopause, patients who have conditions that result in prolonged immobility and those with an established high risk of falling should also be included in this category. The guideline's risk factors review identifies which groups this should apply to.

13. The GDG recognises that DXA scanning large numbers of women who have not had a fracture and who are (relatively) healthy, may not be clinically workable and the GDG (in agreement

with the Committee) supports that DXA scanning should only be for those women with at least one clinical risk factor (with the exception of older women at higher risk). These risk factors should be one of: family history of fracture, high alcohol level and low BMI and not the risk factors used in the FAD.

14. The current FAD for primary prevention does not correctly subdivide the risk factors for case finding in order to accommodate the fundamental principles behind the recommendations. It would read better:

- 1.3 For the purpose of this guidance, clinical risk factors which self-identify postmenopausal women at risk of fracture are: oral glucocorticoid use (ever use); rheumatoid arthritis (not necessary to say long term); medical conditions that have an increased risk of osteoporosis, such as ankylosing spondylitis, Crohn's disease; conditions that result in prolonged immobility; untreated premature menopause; and established high risk of falling
- 1.4 For the purpose of this guidance, additional clinical risk factors used for case finding to be considered are: parental history of hip fracture, alcohol intake of 4 or more units per day, low body mass index (defined as less than 22 kg/m^2)
- Then the recommendation on younger women would read: postmenopausal women younger than 70 years with clinical risk factors which identify them at risk of fracture (section 1.3) **and** at least one additional case finding clinical risk factor (section 1.4).

15. Women who are intolerant of alendronate: the GDG notes that the guideline at least will have to provide a patient pathway for <u>all</u> the patients and it is unclear how much of this should be included in the appraisals. Having said this, for people intolerant of alendronate who have too high a T-score to receive 2^{nd} line therapies, consideration should be given to the need for extra GP consultations and repeat DXAs. It may be cost effective to treat some patients in this group rather than continuously assess them with the associated costs, and the GDG suggests that the Committee considers this point when making recommendations for 2^{nd} line therapies.

Recommendations by number of risk factors

16. To date, the FAD recommendations have not included the number of clinical risk factors when giving T-score thresholds for initiation with alendronate. This is because of the fortuitous cut-off at T-score = -2.5SD: patients with more clinical risk factors, for whom it is cost effective to treat at a younger age with alendronate, have T-score thresholds above -2.5 SD and so are excluded from the appraisal. This situation this may change when the lower price of alendronate is used.

However, when other drugs are taken into consideration, for 2^{nd} line treatment or for those contraindicated for alendronate, the T-score at which patients can be treated varies with the number of clinical risk factors (e.g. in patients aged 70 to 74 years, risedronate 2^{nd} line can be given when the T-score is below -3.0 SD for 1 CRF, -2.5 SD for 2 CRFs etc). This makes the recommendation longer and more complex.

The same type of situation appears for women with osteopenia, and the GDG's view is that a table of T-scores by age and number of clinical risk factors would be needed to allow clinicians to manage the woman in front of them. The GDG considers that a more user-friendly approach would be to develop an electronic tool based on such a table. Alternatively, absolute risks of fracture could be used to form recommendations.

17. The GDG notes that the WHO FRAX risk calculator tool has just been published (February 20th 2008); http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=1 . The tool calculates the 10-year absolute probability of fracture, for major osteoporotic fractures and hip fractures separately. This risk calculator is based on the same WHO data as used in the economic model and is freely available on the internet as an electronic calculator. The GDG's view is that the uptake of this long-awaited calculator by GPs is likely to be high and it is expected to be in widespread used before the publication of either the guideline or the appraisals. Furthermore, it is likely that patients will also use the calculator, either as directed by their GP or following press coverage via patient organisations.

18. The GDG notes that assessment of the FRAX tool would form part of the guideline's chapter on risk assessment tools. In the meantime, the GDG suggests that the Committee examines carefully the FRAX tool and advises that recommendations are given based on absolute risk thresholds, as well as T-scores and number of risk factors, so that there is alignment. Ideally, a single electronic tool would be produced that links the FRAX tool with the NICE recommendations.

APPENDIX

Licensed indications

	Alend-ronate	Etidronate PMO	Rised-ronate	Strontium ranelate	Ralox-ifene	Terip-aratide	zoledronic acid
Fracture status not specified							
Postmenopausal women - prevention of osteoporosis	Y	Y	Y		Y		
Postmenopausal women - treatment of osteoporosis	Y	Y	Y	Y	Y	Y	Y
Men - treatment of osteoporosis	Y	Y	Y			Y (not in BNF)	
Treatment of steroid induced osteoporosis	Y	Y	Y				
Prevention of steroid induced osteoporosis	Y	Y	Y				
Established osteoporosis (post fracture)							
Postmenopausal women - treatment of established osteoporosis			Y				