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Dear Dr Longson

NICE Osteoporosis Guideline Development Group comments on: ACDs on Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women and Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

The NICE Osteoporosis Guideline Development Group have considered the above ACDs and have the following comments as outlined below. These relate to both a) the process, and b) the content of the ACDs. A number of comments under 'B' below were raised in previous feedback on the Assessment Reports dated 2nd September 2005 but do not appear to have been addressed.

A. The process:

1. We understand that the TA process does not enable written responses to the comments on the Assessment Report or the ACD to stakeholders. However, the GDG are partners in a collaborative process, as minuted at a teleconference on 24th May 2004: '*there is substantial overlap in the scopes for the technology appraisal and clinical guideline, it is crucial that consensus is reached on the recommendations in the two pieces of NICE guidance*'. It is therefore necessary that a formal process for considering GDG feedback on TA Assessment Report or ACD, and for consulting with the GDG when changes are made, should be instituted for the remainder of this process. Such mechanisms are needed to achieve consistency, consensus and to develop clinically appropriate evidence based guidelines and guidance particularly when the processes are working interdependently.

Comment [e1]: Changes are made during TACommittee meetings and in that case the 2 GDG members are present.

2. The agreement, confirmed in writing, that the remit of the GDG included identification of the major clinical risk factors for osteoporotic fracture and development of the risk identification approach has been breached. This remit is outlined in the guideline scope and in Carole Longson's letter of February 20th 2004. No rationale for this infringement and the subsequent lack of consultation with the GDG has been provided. An example of this is the omission of some risk factors in the TA (see below).

   The scope also identifies that it is the remit of the GDG to cover all groups at risk of osteoporotic fracture and all pharmacological interventions. In line with the scope, the GDG have developed recommendations that are relevant to post-menopausal women, men, pre-menopausal women and glucocorticoid users. Since much of the GDG input has not been incorporated into the TAs, placing the TA recommendations into the guideline introduces large discrepancies between the two documents which will confuse the reader and reflect badly on the NICE process as a whole. Furthermore, the current wording of the TA guidance has implications for the development of treatment recommendations for men, pre-menopausal women and glucocorticoid users. This will alter the basis on which the GDG gives guidance for these groups or, if separate guidance is produced, will expose a large rift between the basis of the guidelines and the appraisals.

3. The TA committee have overlooked the systematic reviews produced to inform the evidence base of the guidelines. The risk factor systematic review is based on several published meta-analyses. This document was made available to the TA team in July 2004. The rationale for overlooking this evidence in favour of an unsystematic approach towards the selection of risk factors is required.

4. The GDG is concerned that at the TA Committee meeting on 6th September, the intervention thresholds were arbitrarily changed, apparently on the basis that side-effects and issues of compliance had been inadequately considered in the economic analysis. We are extremely concerned that the GDG only knew about this because Professor Juliet Compston and Dr. Peter Selby, were present at this meeting. This apparently arbitrary calculation undermines the credibility and transparency of the TA process. The reasons for such changes need to be made clear in the report. There was no excess of side-effects in bisphosphonate treated patients in the clinical trials and sensitivity analyses show that compliance only has a significant effect when it is very low (and lower than that shown for once-weekly bisphosphonate use in clinical practice

5. It is the view of the GDG that the modelling used in the TA reports as it currently stands requires further development. As part of good scientific practice, it is suggested that the modelling is rerun to undertake sensitivity analyses. The modelling so far provided only represents one part of the clinical scenario.

6. The NICE guideline development group for the osteoporosis guidelines should be listed in Appendix B, part B, page 43 as a consultee.

B. The content:

1. The cost-effectiveness of identification strategies depends critically upon the acquisition costs. Identification costs will not be uniform for all risk factors. For women with a prior fracture, this is reasonably set at 0, since patients will be self- evident. The same situation also pertains to women with rheumatoid arthritis or women taking glucocorticoids. Failure to recognise this disadvantages this segment of the population, particularly in younger individuals.

2. It is not possible at present to compare the results of the analysis with cost-effectiveness thresholds previously determined in the UK by Kanis et al.. Whereas direct comparisons may not be possible (as discussed in p110 of the previous TA draft), the analysis of Kanis expresses intervention thresholds as 10-year fracture probabilities. It is clear that the intervention thresholds differ by an order of magnitude. It is essential that the report gives 10-year fracture probabilities otherwise the credibility of the analyses will be undermined.

3. The hierarchical categorisation of interventions is inappropriate in the absence of direct comparator studies. It is claimed that alendronate is more cost-effective than strontium. There are slightly higher drug costs, but no significant differences in efficacy between the two agents and no direct comparator studies. It is unclear whether there are significant differences in the acceptability curves (Fig 9 and 10). The choice of treatment for individual patients requires consideration of other factors and is the remit of the GDG. The reality is that some of the scenarios that are most cost-effective in the TA reports are those that would be most unlikely to be recommended in practice, for example the use of HRT in women aged 80 years and over. However, there are other interventions that are less cost-effective but for which it is good clinical practice to recommend their use (this also applies to interventions for different groups of glucocorticoid users).

4. As acknowledged in the discussion, the proportion of patients entering nursing homes after hip fracture may be seriously underestimated. Also, the assumption that fractures other than those at the femur or pelvis never result in nursing home admissions is not credible. Nursing home costs are very important determinants of the cost-effectiveness. If they are underestimated in the current model, this should be corrected.

5. QALY's appear to be handled over a lifetime, but not costs. The rationale for this apparent inconsistency needs to be described.

6. There is the issue of different thresholds for primary prevention. The T-score thresholds used in the TA appraisal vary between -2.5 and -3.5 in women aged 70+; in the GDG recommendations these vary between -1.5 and -3.0 in women aged 70+. There are further differences between the guidance and the clinical guidelines as depicted in the tables below:

NICE *guidance (top line in each row)* and guideline recommendations: intervention thresholds (T-scores) in women without fracture or steroids

Number of clinical risk factors	0	1	2	3
70-74 yrs	*No strategy* No strategy	*-3.5* -2.8	*-3* -2.3	*-2.5* -1.7
75-80 yrs	*No strategy* -3.0	*-3.0* -2.3	*-2.5* -1.5	*Treat* Treat
80+ yrs	*No strategy* -2.3	*-3.0* -1.5	*-2.5* Treat	*Treat* Treat

NB: parental history of hip # scores 2 for guidelines

Intervention thresholds (T-scores) for secondary prevention in guidance and guidelines

	Guidance	Clinical guideline
50-59 yr	BMD ≤ -3 or ≤-2.5 + one or more CRF	No assessment or treatment
60-64 yr	BMD ≤ -3 or ≤-2.5 + one or more CRF	No Rx unless 1 CRF BMD≤-2.4, 2 CRF≤ -2.1, 3+ CRF≤-1.4
65-69 yr	BMD ≤-2.5	Rx if BMD ≤-2.6, or if 1 CRF -≤-2.1, 2 CRF ≤-1.7, 3+ CRF treat without DXA
70-74 yr	BMD ≤-2.5	Rx if BMD ≤2.0, or if 1 CRF ≤-1.3, 2+ CRF treat without DXA
75-80 yr	Treat without DXA	Rx if BMD ≤-1.5 or if 1+ CRF treat without DXA
80 + yr		Treat without DXA

The report needs to acknowledge that thresholds will only be approximations and will need to be guided by clinical information.

The implication that a women aged 60 with several fragility fractures should not be treated is clinically inappropriate. The presentation in parts of the report, for example Tables 27-40 and 41-54, is too complex to be useful in clinical practice and needs to be simplified with accompanying explanatory text. It also does not include all possible combinations of risk factors.

7. The update of the secondary prevention economic reanalysis has generated more conservative cost-effectiveness figures than the initial secondary prevention appraisal. This is because the estimates are now pooled from primary and secondary prevention studies resulting in lower cost-effectiveness. Reanalysis should be conducted using estimates of efficacy derived only from secondary prevention studies as in the initial appraisal.

8. A rationale should be provided for the definition of low BMI (which conflicts with that of the GDG) and for the exclusion of alcohol (supported by 1 meta-analysis) and smoking (supported by 3 meta-analyses), which are statistically significantly associated with an increased risk of osteoporotic fracture. Furthermore, the WHO data show that the smoking and alcohol RR's for hip fracture are of similar magnitude to those associated with rheumatoid arthritis and prior fracture

9. The WHO has developed a progressive and patient-centred approach involving absolute risk assessment based on a combination of critical risk factors and BMD. This moves the field forward beyond the RCP case-finding approach, where the detection of a risk factor takes the patient simply to BMD assessment, which determines subsequent management.

   There are fundamental differences between the primary prevention identification strategy used by the TA appraisal (which recommends the RCP approach for those over 70 years of age if more than one risk factor) and that recommended by the GDG (for those over 70 years, the WHO approach is recommended whereby risk factors are not required except for those in the age band 70-74 years).

10. The TA has now dropped raloxifene as an option for primary prevention because strontium ranelate is seen as an alternative to bisphosphonates. The GDG would prefer to keep raloxifene as an alternative to bisphosphonates for primary prevention because of it's other benefits.

11. In the guidance, intolerance of bisphosphonates is defined as oesophageal ulceration, erosion or stricture any of which is sufficiently severe to warrant discontinuation of treatment with a bisphosphonate. These diagnoses can only be made by endoscopy. Upper gastrointestinal symptoms should also be included as criteria for intolerance.

We understand that this letter will be circulated to the TA Committee ahead of the meeting on the 1st November. As previously requested, the GDG would appreciate a written response once the TA Committee have considered the issues set out within this letter. We also understand that the issues outlined above will be discussed at the meeting on 31st October 2005. The GDG believe that once these issues are addressed it will be possible to produce the much needed high quality guidance to the NHS.

Yours sincerely

Chair, Guideline Development Group on behalf of the Osteoporosis Guideline Development Group