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Dear Cathryn,

Health Technology Appraisal

The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fractures in postmenopausal women
And
The clinical effectiveness and cost effectiveness of strontium ranelate for the secondary prevention of osteoporotic fractures in postmenopausal women

Thank you for providing ScHARR with this opportunity to comment on the Appraisal Consultation Documents (ACDs) for the above appraisals. Having reviewed the ACDs and the evaluation report, I would like to raise the following concerns.

ACD on primary prevention

1) T-Score thresholds for treatment with Bisphosphonates

In section 4.3.11 of the ACD it states that the Committee agreed that a simplified strategy is the only practical way forward. The Assessment Group had already considered the problem of developing a simplified strategy and had done so based on the modelling methodology and cost effectiveness estimates presented in the Assessment Report. This strategy was included in the evaluation report under the section, "Corrections and further analysis on Strontium Ranelate AR by Assessment Group, 12th August 2005", and was also summarised in the ACD in section 4.2.25. The strategy presented by the Assessment Group differs substantially from that recommended in section 4.3.15 of the ACD, where it states that the T-Score thresholds modelled by the Assessment Group were considered, but that the Committee decided to exercise caution. The reason given for this caution was that some of the assumptions underpinning the cost effectiveness results were associated with uncertainty and were optimistic. The conclusions of the Appraisal Committee are presented in section 4.3.15 without any explanation of how they adjusted the T-Score

thresholds to account for the fact that they considered the cost-effectiveness results to be too optimistic. The economic analysis carried out by the Assessment Group has evaluated the cost effectiveness of identification strategies to identify women at risk of fracture using the best available evidence. The uncertainty in the costs and benefits of implementing such a strategy is not reduced by restricting the group of women eligible for treatment. As the identification strategy relies on the net benefit of treating women to offset the costs of identifying those women, it is possible that restricting the group of women eligible for treatment will lower the overall net benefit of the strategy. A better way to proceed would be for the Assessment Group to calculate the optimum identification strategy using a lower cost maximum acceptable incremental cost-effectiveness ratio (MAICER).

2) Clinical risk factors

The methodology used by the Assessment Group to assess the cost effectiveness was based on the clinical risk factors defined in the WHO study, which included current smoking and alcohol intake of more than 2 units per day. These risk factors are not included in the clinical risk factors to be considered in section 1.3 of the ACD, despite being considered as risk factors for the initiation of statins treatment. (The assumption that women may answer falsely to obtain osteoporosis treatment, whereas men will not to obtain statins is questionable)

The reasons given for excluding these risk factors are that their effect on fracture risk is small and they are difficult to confirm reliably. The size of the effect on fracture risk has been considered within the economic analysis and the presence of these risk factors is not insignificant. The change in the threshold for cost-effective treatment for the excluded risk factors is similar to other risk factors that were included such as rheumatoid arthritis. These risk factors have been established to be associated with fracture risk independently of BMD and should therefore be included in the assessment of fracture risk. Even were the decision taken to omit these variables it would be expected that the coefficients of the other variables within the algorithm would change in order to maximise the adjusted R2 value. This change would require the cost-effectiveness analysis to be re-run using the new algorithm in order to ensure that the results are robust.

3) Compliance

In section 4.3.13 of the ACD it states that one of the reasons for the Committee's view that the cost-effectiveness results were optimistic was that the cost effectiveness is sensitive to compliance. The sensitivity analysis on compliance presented in the Assessment Report shows that the identification strategy would still be cost-effective if compliance was as low as 50%. This analysis assumes that non-compliant patients receive their prescription for 6 months but do not receive any benefit. If these patients return to their GP and switch therapies (accruing the cost of a GP appointment and equal net benefit on the alternative therapy) then the sensitivity analyses conducted showed little impact on cost-effectiveness. The ACD recommends that patients who are intolerant of bisphosphonates, or who can not comply with the special recommendations for the use of bisphosphonates, should receive strontium ranelate. It is therefore likely that patients who have problems with their treatment may switch therapies rather than stop treatment. It should also be noted that compliance rates are

likely to be higher for once weekly or once monthly preparations than for once daily preparations.

4) Adverse events

The identification strategies were evaluated using alendronate to represent the bisphosphonate class. Bisphosphonates are associated with gastrointestinal side effects, although the RCT evidence shows this to be non-significant compared with placebo. These have not been explicitly included in the model as it was assumed that patients who experienced side effects, which were significant enough to impact on their quality of life, would either switch to an alternative therapy or become non-compliant. The sensitivity analysis on the number of patients switching therapies showed that this did not have a large impact on the overall cost effectiveness of the identification strategy.

5) Accuracy of DXA scanning

We are not aware of any systematic bias in DXA scanning, nor would we expect that the standard deviations would be large enough to change the identification strategy, as women falsely positioned above or below the cost-effectiveness risk, would be those closest to the threshold and the loss in net benefit would be unlikely to be severe.

ACD on secondary prevention

1) Efficient Use of DXA

In the methodology described in the Assessment Report it was assumed that patients presenting with a prior fragility fracture would incur no identification costs. However, the preliminary recommendations for bisphosphonates require a T-Score to be established before treatment is initiated in women under the age of 75 years. In particular for women under the age of 65 years, treatment with bisphosphonates is recommended if they have very low BMD (T-Score of –3SD or below).

A very small percentage of women under the age of 65 years would meet the ACD treatment criteria, given that the average T-Score at age 60-64 is –1.17SD, (page 17 of Strontium Ranelate Assessment Report). The vast majority of women receiving a DXA scan at this age would not be treated. The DXA costs would outweigh the net benefit of those successfully treated, implying that the use of DXA in women with a prior fracture aged 65 years and under is not cost-effective, using the ACD treatment criteria.

The Assessment Group had already considered the problem of developing a simplified strategy for women with a prior fracture and had done so based on the modelling methodology and cost effectiveness estimates presented in the Assessment Report. This strategy was included in the Evaluation Report under the section, “Corrections and further analysis on Strontium Ranelate AR by Assessment Group, 12th August 2005”. This showed that when using T-Score thresholds based on the cost-effectiveness results presented in the Assessment Report, it is cost-effective to identify women above the age of 60. This work was subsequently updated to allow for

the lower average BMD seen in women with a prior fracture. (average BMD assumed lower by 0.2SD). This was provided to the NICE technical lead, but too late to inform the Committee. This analysis showed that, when accounting for the lower average BMD of women with a prior fracture, cost-effective identification strategies could be identified for women over the age of 55.

I hope that these comments will be taken into account by the Committee.

Yours sincerely,

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