DEPARTMENT OF
CLINICAL BIOCHEMISTRY
C.P.A. Accredited

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King's College Hospital NHS
NHS Trust

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Cathryn Fuller,
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Dear Ms Fuller

Re: Health Technology Appraisal ~ The Clinical effectiveness and cost effectiveness of technologies for the primary prevention of Osteoporotic fractures in postmenopausal women

Thank you for giving me the opportunity to respond formally, as a 'clinical expert' on the Appraisal Consultation Document (ADC). Having attended some of the NICE meetings I have been impressed by the rigour by which the evidence for the diagnosis and management of osteoporosis has been accumulated from peer reviewed studies. I have also been impressed with the robustness of the arguments on the clinical effectiveness of the treatments and the cost effectiveness iterations.

What concerns me in the HTA report is the discordance from the evidence towards cost containment rather than effectiveness. In particular, the decision based in **Section 4.3.9** set at £20K for primary prevention and differently at £30K, for secondary. The end-point for which the HTA is about is prevention of fractures and setting the QALY threshold differently in primary prevention from secondary does not make any sense. The explanation for this decision taken by the committee in this section needs clarification otherwise it will appear that NICE bases its decisions on cost alone.

As a result of this threshold, inconsistencies appear through the rest of the document, in particular the age restrictions so that nothing offered for primary prevention for women between the ages of 60-70 which probably results from the calculations of this lower threshold. The absolute fracture risks in a 60-70 age group is high when risk factors are incorporated with DXA in an assessment, and the burden to healthcare costs remains high and similar for fractures due to primary or secondary causes, if untreated. This concern I raised at the meeting on the 6th September. If one looks at the cost effectiveness of treatment at £20K per QALY it appears to be cost-effective to treat at all ages at a BMD threshold of - 4, but by the criteria of this HTA it will not apply if the patient is under 70.

The Clinical risk selection in **Section 1.3** is peculiarly limited and does not include risk factors incorporated in many of the trials and widely practiced in the routine clinical setting. Risk factors have different weighting at different ages so that parental history of hip fracture

has more significance for the early postmenopausal woman, but not at aged 70. There is no evidence of a genetic link that would make this observation pertinent across all ages, and

since the HTA limits its guidance to the over 70s, this is not a valid risk factor to put into the assessment, as a robust risk factor.

A low body mass index less than 19 kg/m2 is a useful trigger for the elderly because of falls, but in the younger woman because of association with amenorrhoea in the pre-menopausal years. How does one apply this risk factor in women over 70 is unclear. Importantly it may not apply across the ethnic groups with low BMIs but normal BMDs. It would be helpful to revise risk factors, which include excess smoking and alcohol, already in place by the RCP guidelines or the WHO approach, which includes six major factors.

The treatment options, whilst reviewed extensively by the committee in terms of cost and effectiveness, become disconnected in the assessment report. Etidronate for example has the same weighting as Risedronate and Alendronate although it is widely known to be significantly less potent, difficult to comply with and very weak in evidence for prevention of non-spine fractures. In contrast, Strontium Ranelate is offered as a second line drug although there is better evidence in terms of fracture prevention at all sites. Importantly Raloxifene has been given no place in primary prevention and yet the Committee has considered the weight of evidence showing this to be a very cost-effective drug, if breast cancer is taken into account. Breast cancer prevention is of concern to patients and if a side effect is beneficial to the patient, then it ought to have positive weighting in a holistic approach to patient welfare. There are very strong and compelling reasons to use Raloxifene as an alternate to the Bisphosphonate, particularly if there is intolerance to these agents.

In **section 1.6** the definition of intolerance is very restrictive and quite prescriptive implying that the patient will require endoscopy to identify the lesion causing intolerance showing specific changes such as the oesophageal irritation, erosions or strictures. Clinicians will know when patients discontinue because of clinical side-effects, a reason for them to consider alternative treatments.

In **section 4.3.14** it was reported by the experts that there was a rationale for a case based approach using risk factors to identify those women requiring DXA scan. If risk factors are not included in this decision algorithm, it would result in a screening programme for osteoporosis. An assessment of absolute risk would be preferable but the unpublished WHO data referred to in this section needs to be made available for scrutiny and discussed by the medical community before replacing it with current practice.

What has not appeared in the current text is guidance that was in the HTA guidance 87 "*This guidance does not however override the individual's responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient/guardian/carer*". This very important clause should be included, as despite the guidance, treatment and prevention, osteoporotic fractures depends on a decision made jointly between the clinician and the patient.

Kind regards
Yours sincerely

Osteoporosis Clinic