Central Manchester and Manchester Children's University Hospitals
NHS Trust

Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL

Department of Medicine

21 October 2005

Dr Carole Longson
Director, Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
LONDON
WC1V 6NA

Dear Carole

Appraisal Consultation Documents on the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women

Thank you for asking for my comments on these documents. Although many of my comments and concerns have dealt with by the joint reply which has been prepared by the GDG and which I fully support, I am grateful for the opportunity to comment in my own right as I believe that as a participant in the Appraisal Committee I am able to expand on some of the comments made by the GDG in their corporate response.

Has all the relevant evidence been taken into account?

For the most part I believe that this is the case. However I do believe that in choosing to dismiss smoking and excess alcohol consumption as risk factors for osteoporotic fracture the committee may not have been aware of the strength of evidence in support of their inclusion. I would refer the committee to the recently published meta-analyses on these risk factors (1, 2) both of which demonstrate that these are at least as potent risk factors as the factors that the committee chose to include.

Are the summaries reasonable interpretations of the evidence and are the views on resource impact and implications for the NHS appropriate?

On the whole these are reasonable interpretations of the evidence however there appear to be a few areas where they are not completely faithful to the evidence:

When discussing the side effects of alendronate the summaries suggest that gastrointestinal side effects were found in "at least one third of the participants" (4.1.5.5 for primary and secondary); this is not the case. In the initial dose ranging study for instance the rates (in percentages) of upper gastrointestinal adverse events were(3):

	Placebo	*Alendronate*
Nausea	4.0	3.6
Dyspepsia	3.5	3.6
Abdominal pain	4.8	6.6
Total	12.3	13.8

These rates are typical and suggest that the evidence summary is not appropriate.

The increased VTE risk with strontium ranelate only became apparent when the adverse events from the two large published studies were combined. As far as I am aware it has not been subject to peer review publication and it would therefore be helpful if the summary could state this as it does in other areas of unpublished data within the ACDs.

<u>Are the recommendations sound and do they form a suitable basis for guidance to the NHS?</u>

This is the area where I have most concerns with the documents and will details my comments separately for primary and secondary prevention:

Primary Prevention

The committee make the statement that "As women who have not had a fracture do not present to clinicians, the committee considered it necessary to include the cost involved…". This is a gross oversimplification and if allowed to stand unchallenged will deny potentially beneficial therapy to many women. Whilst that attitude might be correct if the profession were espousing a screening procedure whereby women over a certain age or with a spectrum of risk factors determined from clinical notes were actively sought this is not what the profession proposes. What has standard practice is that a case finding approach be adopted on an opportunistic basis. The costs of identification considered by the committee are therefore much greater than is actually the case in clinical practice where we are frequently faced with a patient in whom we suspect the presence of a high risk of osteoporotic fracture and institute investigations. The advice as currently written would preclude our doing that before the age of 70 and would mean that very many of the women seen in my own practice who are at high risk of fracture would be denied investigation or treatment. Equally it does not answer the question of what one would do with a women of say 60 who has herself identified risk factors for osteoporosis and seeks advice about treatment to prevent fracture. Are the committee really happy for the professions to say "go away and wait until you break something or reach 70"?

I find it incredible that when presented with a well validated set of risk factors by the GDG the Committee has decided arbitrarily to reject two of them. They claim (4.3.7) that their effects on fracture risk are “relatively small”. This is patently not the case; their effects are commensurate with other risk factors identified by the GDG. Equally the comment that “such behavioural risk factors are difficult to confirm reliably” borders on the fatuous; surely this is just the sort of information that all health care workers are using to assess cardiovascular risk where nobody would question the reliability of the information. I am also very concerned that after little more than half a day’s consideration a committee comprised of generalists found itself able to reject on what it purports as scientific grounds a set of risk factors that have been carefully developed over a long period of time by a group of experts also working for the Institute. If they saw fit to reject the recommendations on grounds of public policy or cost that might be plausible but the reasons stated in the ACD do not really stand scrutiny.

In paragraph 4.3.14 the Committee make a set of sweeping assertions many of which do not stand scrutiny and puts the basis for their opinions in the following paragraphs in doubt. The assertion that compliance with antiresorptive therapy is generally low is not well founded. Whilst there is some evidence to support this it is generally from health economies other than the UK whilst the emergent British evidence would point to adherence of up to 80% which is better than many other long term treatments. Likewise the Committee overstate the importance of adverse effects (see above) which are almost invariably transient and do not result in cessation of therapy but movement to a different agent which is usually well tolerated.

There is accordingly little justification for the Committee’s apparently arbitrary decision to reject the risk based model put forward by the GDG which had been demonstrated by the Assessment Group to be more cost-effective than the RCP approach as espoused by the Committee. Furthermore the basis on which they reached their conclusions as to the appropriate intervention threshold is totally opaque and seems to be based more on the development of a pleasing algorithm rather than consideration of the available evidence as the deviations from the model put forward by the GDG seem totally capricious.

The definition of bisphosphonate intolerance (1.6) is inappropriate. What are committee going to advise a prescriber who has a patient who gets such severe dyspepsia on taking a bisphosphonate that she is unwilling to continue taking treatment despite a normal upper GI tract on endoscopy? If it was going to be cost effective to treat her with a bisphosphonate it is very likely that it would be cost effective to use strontium (as the cost effectiveness curves for strontium and risedronate are close) and surely this would be the appropriate course of action. It is certainly what happens in clinical practice at present. Whilst I agree that the committee may which to set a higher threshold for teriparatide for secondary prevention I cannot see the justification for such a high threshold for the move to strontium in primary (or indeed secondary) prevention.

I cannot see the rationale for not including raloxifene as an option when bisphosphonates and strontium are not tolerated as in secondary prevention.

Secondary Prevention

Many of the comments above are pertinent to this ACD.

There is a minor technical point that I am not sure had been considered by the committee. The use of raloxifene requires a woman to have failed treatment with (or be unable to take) bisphosphonates and strontium. The criteria for treatment failure (1.6) could be argued about in relation to bisphosphonates but are undoubtedly inappropriate for strontium. The reason for that is that strontium substitutes for calcium in the bone mineral. As strontium is a heavier atom this leads to an increase in bone density measured by DXA. Thus it is unlikely that patients receiving strontium will ever satisfy this requirement if they are indeed taking their medication. It would be helpful if the committee could reconsider this point.

I realise that in making these comments I open myself up to criticism for not having been so forthright at the Appraisal Committee meeting itself. That may well have been the case and if so I apologise to the Committee. However it would have been difficult to monopolise the discussion at such a large meeting and my thinking on many of these points has clarified following the meeting.

I hope you find these comments helpful and look forward to meeting you at the next meeting of the Appraisal Committee.

Yours sincerely

Consultant Physician

1. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, et al. Smoking and fracture risk: a meta-analysis. Osteoporos Int 2004.
2. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, et al. Alcohol intake as a risk factor for fracture. Osteoporos Int 2004.
3. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. New England Journal of Medicine 1995;333:1437-1443.