Comments from the Society for Endocrinology on the National Institute for Health and Clinical Excellence's proposed technology appraisal guidance on the primary and secondary prevention of osteoporotic fractures.

The Society welcomes the opportunity to comment on the draft guidance has published by the Institute.

Whilst we welcome the availability of guidance for the treatment of osteoporosis believing that it will improve the treatment of this often ignored condition we believe that the guidance as currently proposed has several shortcomings which will limit its utility in the clinical setting.

Secondary Prevention

Although we realise that this is basically a reworking of the previous guidance for secondary prevention of osteoporotic fractures to incorporate the use of strontium ranelate we believe that the Institute has missed an opportunity to improve the previous guidance. In particular we would wish to raise the following points:

1. We are concerned at the continuing way in which the Institute combines all three bisphosphonates as a single therapeutic stratagem. Whilst we accept that the judgement need to be made on the basis of cost effectiveness as well as clinical effectiveness we do not believe that the cost effectiveness data as presented in the assessment report and its addendum support such a stratagem. Figures 9 to 11 in the addendum clearly indicate that it is not until older ages that the cost effectiveness of etidronate comes anywhere close to that of alendronate or risedronate. Moreover even at older ages the cost effectiveness of etidronate is substantially lower than that of alendronate or risedronate at higher fracture risks. We would urge the appraisal committee to consider removing etidronate from the same bracket as alendronate and risedronate and perhaps consider it as an alternative for those people in whom these agents are not tolerated.

2. In figures 9 to 11 of the addendum it is clear that the cost effectiveness of strontium ranelate lies between etidronate any other bisphosphonates. It is unclear to the Society why the appraisal committee have not chosen to grant strontium ranelate the same status as the bisphosphonates.

3. In paragraph 4.3.14 the committee state that their guidance was based on the fact that hip fracture efficacy was less robust for strontium ranelate them for alendronate and risedronate. Whilst we would agree

with this contention it is equally true that the hip fracture efficacy of strontium ranelate is substantially more robust than that for etidronate. We therefore do not understand why strontium ranelate has been given an apparently less favourable status of etidronate when it is apparently both more clinically effective and at least as cost effective.

4. The definition of intolerance of bisphosphonates is far too limited and does not offer itself to easy incorporation into clinical practice. The committee accepted that in order for the treatment to be effective patients must continue to take bisphosphonates. Thus, any upper gastrointestinal discomfort which is sufficient to cause a patient to stop taking bisphosphonate is surely intolerance. As it is written at the moment the guidance would mandate us to seek gastroscopy in the 30% of patients who develop gastrointestinal symptoms on bisphosphonates in order to see whether or not they meet the threshold to use other therapies. This is not the way in which we would normally practice medicine and we suspect that the costs of these investigations have not been built into the committee's cost effectiveness modelling.

5. The definition of failure of response to strontium ranelate is seriously flawed. Strontium gets incorporated into the crystal matrix of the hydroxyapatite within the skeleton. As strontium has a higher atomic number than calcium this leads to an apparent increase in bone density for purely artefactual reasons. If the committee persists in its definition of failure of response to strontium it is unlikely that anyone taking strontium will ever be deemed to have failed. This is clearly a nonsensical situation.

6. The previous high threshold for the use of teriparatide has been retained. Although we realise that this represents the high cost of the drug we do wonder whether this fails to represent its true clinical utility. There must be some patients for whom the risk of fracture is just so high that the use of this agent would still be cost effective particularly at a younger age. Whilst this may not represent a large number of women in the population at large they are much more likely to be seen in specialist hospital clinics since the other treatment options have already been exhausted and specialist help is sought in these cases. Our members therefore would welcome some statement that there may be other circumstances where the fracture risk is so high that the use of this expensive agent is justified.

7. Furthermore, it is difficult to see how the guidance regarding teriparatide can be sustained in the absence of any discussion of the apparent effect of alendronate in abrogating the skeletal benefits of teriparatide treatment.

Primary Prevention of Osteoporotic Fractures

8. The comments made above regarding the placement of etidronate and strontium within the guidance also apply here. Indeed the discrepancy in cost effectiveness between etidronate and the other bisphosphonates would appear to be even greater in this group.

9. Similarly our comments regarding the definition of intolerance made above would also apply here.

10. We are concerned about the way in which the assessment committee have described their approach as being "of the selective case-finding approach currently recommended by the Royal College of Physicians". We do not believe that the approach described in the ACD is sufficiently close to that put forward by the RCP to bear this description. The RCP suggested that anyone with one of many risk factors for osteoporosis or osteoporotic fracture be considered for bone densitometry; on the other hand, the ACD confined to that to a very limited list of conditions in a very limited age group of patients.

11. The reason for this appears to be based on an assumption made by the assessment group that "women without fracture do not usually present to clinicians" (paragraph 4.2.9). As practising clinicians we believe that this is a gross oversimplification and that during the course of consultation for other medical conditions one often becomes aware of the presence of a risk factor for osteoporosis. This does not appear to have been acknowledged by the assessment group and may well have a major impact on the cost effectiveness modelling they performed. Presumably a woman identified as being a risk under these circumstances would be no more costly than a woman who had a pass history of fracture identified during a consultation and would therefore be subject to the secondary prevention guidance.

12. It appears strange to us that the assessment committee chose to use their so-called "RCP" model when the assessment report shows substantial increased net benefit when the WHO model is used in preference to the RCP model.

13. We were surprised to see the committee rejecting the use of smoking and alcohol as risk factors (paragraph 4.3.7). The Meta analyses than had been published of these risk factors suggest that they are just as predictive of fracture as some of the risk factors which had been retained. It would seem to us important that the assessment committee take advice from the guideline development group as to which risk factors should be included in the model in order that the Institute is seen to be giving consistent advice.

14. We were surprised to read the committee's assertion in paragraph 4.3.13 that "compliance with antiresorptive therapy is generally low". Whilst we are aware that there are some reports of low compliance with antiresorptive therapy (but generally no lower than with other long-term therapies such as antihypertensives) there are contrasting reports

with quite remarkable long-term compliance such as 70 to 80%. We therefore do not believe that this assertion can be justified.

15. Whilst we understand the committee's difficulty with knowing exactly where to place raloxifene were surprised to see it excluded from our primary prevention particularly in view of its very favourable cost effectiveness ratio in younger women.

We hope that the Institute find these comments to be helpful and look forward to working with the assessment committee to develop guidance which is of benefit in the management of women with osteoporosis.