Response to comments from Consultees and Commentators

The Clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Assessment Report.

The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Addendum.

Comment	Response
ARMA	
Thank you for the opportunity to comment on the assessment report and the addendum for the above appraisal. We have seen the response made by the National Osteoporosis Society, and fully endorse it	No response from assessment group.
British Menopause Society	
Having reviewed your report, on behalf of the British Menopause Society, we regard Strontium Ranelate as clinically effective in the prevention of osteoporotic fractures. Its use is cost effective and is an alternative to situations where Bisphosphonates may be inappropriate or contra-indicated	No response from assessment group.
British Society for Rheumatology	
Thank you for the opportunity to comment on the assessment report and the addendum for the above appraisal. The BSR has seen and strongly supports the response made by the National Osteoporosis Society	No response from assessment group
Eli Lilly	

We note that this has an Addendum "The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in post menopausal women," for which we are a consultee. The aforementioned Assessment Report also contains the methodology for the Addendum and some work on screening In order to avoid confusion, and hopefully to ensure that our input is appropriately directed, we have therefore separated our response under headings relevant to the various sections of this report as follows:- 1) Comments on the Assessment Report for Strontium Ranelate (Primary and Secondary Prevention) 2) Comments on the Primary prevention Addendum (including comments on screening strategy) 3) Comments on the Primary prevention Addendum relating to Secondary Prevention.	No response from assessment group.
Unfortunately combining these documents in this manner has resulted in some lack of clarity – for example it is not clear how the work on primary prevention screening (section 4.2) of the strontium ranelate TAR relates to treatment with medications other than strontium and alendronate	The overall strategy for identifying and treating women without a prior fracture has been assessed assuming treatment with alendronate. The impact of using alternative treatments is to change the overall net benefit of the strategy, for example, the use of treatments with a lower net benefit than alendronate will lower the overall net benefit.
Finally we welcome the use of the WHO algorithm, but its submission as "Academic in confidence" has not enabled us to comment on its content, as all data has been blacked out.	No response from assessment group.
<u>General Comments</u>	

The clinical effectiveness of strontium ranelate has not been compared with other technologies previously assessed by NICE (other than alendronate). This results in difficulty for the Appraisal Committee in positioning the use of strontium ranelate in the clinical setting We suggest that, based on pharmacological, chemical and economic grounds strontium is an antiresorptive which should be used second line to bisphosphonates (in patients unable to tolerate bisphosphonates) in patients without severe osteoporosis. (The second line position in more severe patients being teriparatide)	No response from assessment group.
a) Primary Prevention	
In support of our general comments above, we note that on page 106 of the Assessment report it states "Thus to maximise the net benefit it appears that strontium ranelate should be reserved for women unable or unwilling to take more cost-effective interventions." In addition on page 110 of the report it states:- "The efficacy of strontium ranelate at the hip is uncertain, and for all women with osteoporosis, is non significant. Analysis has however, been carried out assuming a beneficial effect at the hip assuming the mean relative risk from the trials. Sub-group analyses has been undertaken by the manufacturer of the intervention to show a significant, and more efficacious effect in older women (aged 74 years and upwards). On the advice of the GDG, all interventions for the prevention of osteoporotic fractures are assumed to have the same efficacy regardless of the T-Score, prior fracture history, or age of the woman. If strontium ranelate does have a differential effect based on the characteristics (and absolute fracture risk) of a woman this needs to be proven."	No response from assessment group.
b) Secondary Prevention	
Strontium ranelate has not been compared clinically with other available therapies (eg. raloxifene, teriparatide). The TAR points to a place in therapy similar to that of bisphosphonates but with reduced cost effectiveness	No response from assessment group.

The guidance on strontium ranelate needs to be consistent with existing Guidance number 87. New medicines being reviewed after Guidance is published on comparators should not gain any undue advantage. Based on available clinical and economic evidence, it appears that the appropriate use of strontium ranelate is as an alternative antiresorptive treatment for women unable to tolerate a bisphosphonate However the Guidance in number 87 should stand, and teriparatide should remain the only option in women with an inadequate response to bisphosphonates who meet the defined severity criteria	No response from assessment group.
<u>General Comments</u>	
The methodology for this addendum and information on the WHO algorithm were unfortunately contained in the Assessment Report for strontium ranelate (TAR). We do not believe that this approach was helpful	No response from assessment group.
<u>Screening</u>	
The cost of screening women (on which we previously commented in our letter of 4th April 2005) was also part of the strontium ranelate TAR. It is not clear from this document how the cost effectiveness of screening and treatment applies to raloxifene or other osteoporosis medications other than strontium ranelate or alendronate	The overall strategy for identifying and treating women without a prior fracture has been assessed assuming treatment with alendronate. The impact of using alternative treatments is to change the overall net benefit of the strategy, for example, the use of treatments with a lower net benefit than alendronate will lower the overall net benefit.
<u>Primary Prevention</u>	
The important contribution of this addendum is that it confirms previous work indicating that raloxifene is the only cost effective medication in younger women with less severe osteoporosis when the breast cancer benefit is taken into consideration We would therefore once again urge NICE to reconsider its attitude to the breast cancer benefit of raloxifene as discounting it will deny many women a cost effective treatment for their osteoporosis	Results have been presented both with and without the breast cancer benefit of raloxifene for the consideration of the Committee.
3 - Comments from Eli Lilly and Company on the Primary prevention Addendum (relating to Secondary Prevention)	
Rather than update the Guidance number 87, we would encourage NICE to take into account the findings in the addendum in relation to secondary prevention within the context of the forthcoming Guideline on the management of osteoporosis	No response from assessment group.
For teriparatide, we note that this section is consistent with the previous NICE Guidance	No response from assessment group.

on secondary prevention No. 87. However, in addition (and as previously presented by Eli Lilly at Appeal) we note that teriparatide is cost effective in both younger women with higher level of risk factors (tables 13-15, p22-23) and in older women with lower risk factors (table 19, p25). Now that the proper analysis of cost effectiveness thresholds has been completed, we hope that the Guideline will reflect this in defining more clinically relevant patient groups suitable for teriparatide	
Raloxifene is again shown, in conjunction with the breast cancer benefit to still be the most cost-effective option in secondary prevention in younger women with lower risk factors. In drafting the Guideline, we would once again urge NICE to reconsider its attitude to the breast cancer benefit of raloxifene as discounting it will deny many women a cost effective treatment for their osteoporosis	Results have been presented both with and without the breast cancer benefit of raloxifene for the consideration of the Committee.
Royal Pharmaceutical Society	
This is to advise that the Royal Pharmaceutical Society will not be responding to the above	No response from assessment group.
CPHVA	
On this occasion, the CPHVA are unable to submit any comments on this report	No response from assessment group.
Merck Sharp & Dohme	
Thank you for the opportunity to comment on the Assessment Report for the above appraisal and the Economic Addendum for the appraisal of the clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in post menopausal women Please find below comments from Merck Sharp & Dohme Ltd (MSD). As requested, we have read these documents alongside each other and have separated our comments into those related to primary prevention and those related to secondary prevention We would urge the Appraisal Committee at NICE to take the following points into consideration when preparing Appraisal Consultation Documents (ACDs) for primary and secondary prevention for all referred technologies:	No response from assessment group.

Primary Prevention	
Alendronate should be differentiated from other bisphosphonates for the primary prevention of osteoporotic fragility fractures based on superior clinical and cost effectiveness ▪ MSD has consistently demonstrated alendronate's superior clinical and cost effectiveness for the primary prevention of osteoporotic fragility fractures in post menopausal women.[1] ▪ In the economic addendum, Figures 1-7 and Tables 2-8, demonstrate alendronate is the most cost-effective treatment for primary prevention of osteoporotic fractures. Further, this superiority has been recognised by the team at ScHARR in relation to strontium ranelate: *"Alendronate has been chosen as the drug to be used in evaluating identification strategies since it has better mid-point efficacies than strontium ranelate and is also cheaper"* [2] and as presented in Tables 48-54. Comparing results of cost-effectiveness analysis of strontium ranelate (Tables 41-47) and alendronate (Tables 48-54), the report concluded that strontium ranelate is not as cost-effective as alendronate MSD urges the Appraisal Committee to recognise alendronate's superiority and differentiate between the bisphosphonates in the primary prevention ACD	No response from assessment group.

[1] MSD response to Assessment Report produced by ScHARR for the Clinical and Cost Effectiveness of technologies for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women, 31.3.05

[2] The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in post menopausal women – Assessment Report July 2005, pg 97

Secondary Prevention	
Alendronate should be differentiated from other bisphosphonates for the secondary prevention of osteoporotic fragility fractures based on superior clinical and cost effectiveness ▪ MSD has consistently demonstrated alendronate's superior clinical and cost effectiveness for the secondary prevention of osteoporotic fragility fractures in post menopausal women.[3] • The Economic Addendum further showed that alendronate is the most cost-effective therapy for secondary prevention of osteoporotic fractures (Figures 1-7), particularly when the appraisal is focused on its original objective of assessing technologies for prevention of secondary osteoporotic fractures - This superiority has been recognised by the team at ScHARR in relation to strontium ranelate, in particular, the fact that alendronate was chosen as the bisphosphonate comparator in the economic appraisal (pg 52) and then subsequently demonstrated clinical and cost effectiveneness in several sections of the Assessment Report: *"The results of the probabilistic sensitivity analysis using efficacy data from randomised controlled trials suggest that [strontium ranelate] is not as cost effective as alendronate"* (pg 10) - *"..the same graph is shown for alendronate, which is seen to be more cost-effective at given risks than strontium ranelate".* (pg 67) - *"It is seen that based on our results, alendronate appears more cost effective than strontium ranelate".* (pg 68) - *"As expected, since alendronate has better mid point efficacy at all sites, and has a lower acquisition price, it is optimal on substantially more occasions than strontium ranelate".* (pg 76)	No response from assessment group.
In addition to the points above, MSD would like to add the following more general comments that we believe should be taken into consideration when determining the contents of the new ACD's for primary and secondary prevention:	No response from assessment group.

[3] MSD response to Final Appraisal Determination (FAD) for the secondary prevention of osteoporotic fractures in postmenopausal women, 9.8.04, MSD response to Appraisal Consultation Document (ACD) for the secondary prevention of osteoporotic fractures in postmenopausal women, 20.5.04

Vitamin D adequacy:	
• Guidance 87 (Osteoporosis: Secondary Prevention) covered the treatment of postmenopausal women who have normal calcium levels and/or vitamin D levels, and recommended that *"Unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete, calcium and/or vitamin D supplementation should be provided"*. ▪ MSD urges the Appraisal Committee to ensure this recommendation is transferred to the new ACD because: - Vitamin D inadequacy is widespread in postmenopausal women[4] - The rate of use of vitamin D supplementation remains very low in osteoporotic population[5]	No response from assessment group.
APPENDIX	

[4] See Appendix point 1 for supporting evidence
[5] See Appendix point 2 for supporting evidence

1. Vitamin D inadequacy is widespread in postmenopausal women ▪ Serum levels of the metabolite 25-hydroxyvitamin D, 25(OH)D, are used to measure vitamin D adequacy status. In the medical literature at present there is no internationally agreed consensus on what should constitute a diagnostic serum level for vitamin D insufficiency. A common approach is to consider the level of 25(OH)D at which parathyroid hormone (PTH) is maximally suppressed, as PTH is known to increase resorption of bone and thus reduce bone density. PTH levels have been shown to rise as vitamin D levels fall below a certain level. Estimates of 25(OH)D levels required for PTH suppression have varied from 30 to 99 nmol/L, although there has been a clustering of estimates around the 75-80 nmol/L range.[1-7] • Work presented in 2005 used a cut-off for vitamin D inadequacy of <30ng/ml (equivalent to approximately <75nmol/L), and showed that in Europe, 51.9% of postmenopausal women with osteoporosis had inadequate vitamin D levels.[8] ▪ Separate work in Glasgow has revealed in a retrospective audit that 97.8% of patients aged 50 or over who had sustained a hip fracture had 25(OH)D levels less than 70 nmol/L.[9] Prospective work by the same team showed that 82.0% of patients over 50 presenting with a clinical non-vertebral fracture had levels below 70 nmol/L.[9] ▪ Higher vitamin D levels also allow increased absorption of calcium from the diet. For example, calcium absorption has been shown to be 65% greater at serum 25(OH)D levels averaging 86.5 nmol/L than at levels averaging 50 nmol/L.[10]	No response from assessment group.

2. The rate of use of vitamin D supplementation remains very low in osteoporotic population • A database analysis using combined data from the 2002 and 2003 National Health and Wellness Surveys (NHWS) in France, Germany and the UK indicated that fewer than one in five women with osteoporosis are taking a vitamin D supplement. Even among high risk patients with a fracture history, only 1 out of 5 patients used vitamin D supplementation[11] ▪ A follow-up survey among the 100,697 patients from the National Osteoporosis Risk Assessment (NORA) study evaluated the utilization of vitamin D supplements and factors related to its use in women with osteoporosis, recent fracture or on osteoporosis treatment[12]	No response from assessment group.
3. Teriparatide lacks evidence of reduction of hip fracture risk • As indicated on table 1, page 3 of the Addendum, the confidence interval for relative risk for hip fracture for Teriparatide is very wide and includes 1 (0.09, 2.73) which indicates that there is no defined effect. Considering this it seems appropriate that no hip fracture risk reduction be included in the cost-effectiveness analysis of teriparatide	The results for teriparatide have been presented both assuming midpoint efficacy at the hip and assuming no effect at the hip for the consideration of the Committee.
4. Raloxifene is not indicated for treatment of breast cancer which is also not the focus of the original scope of this appraisal • Figures 2-7 of the Addendum indicate raloxifene's cost-effectiveness is extremely dependent on breast cancer benefits. In fact, raloxifene's cost-effectiveness deteriorates with increase in risk of fracture. This is explained in the report by possible existence of inverse relationship between BMD and breast cancer risk. This may indicate that raloxifene's cost-effectiveness is very much driven by breast cancer benefits • Considering raloxifene is not indicated for breast cancer therapy and the focus of this appraisal is prevention of osteoporotic fractures, it is inappropriate to include breast cancer benefits of raloxifene into the cost-effectiveness analysis for osteoporosis	Results have been presented both with and without the breast cancer benefit of raloxifene for the consideration of the Committee.

5. Strontium ranelate is associated with significant (p<0.05) higher risks of VTE, diarrhoea, loose stools and allergic dermatitis; all have economic implications ▪ The Strontium Ranelate Assessment Report (pg 9, 'Executive Summary' and Table 16) indicates that patients with strontium ranelate had significantly higher risk of venous thromboembolism (RR=-1.42, 95% CI: 1.02 to1.98). ▪ Further, Table 16 indicates patients on Strontium Ranelate also had significantly higher risk of nausea (RR=1.55, p<0.0001), diarrhoea (RR=1.41, p=0.0008), loose stools (RR=5.94, p<0.0001) and allergic dermatitis (RR=1.81, p=0.04). ▪ Evidence based medicine would suggest incorporation of such side-effect in the economic evaluation. Considering the current structure of the model, such events can not be incorporated in the model. Nonetheless, they are associated with substantial economic impact. MSD suggests that future appraisals should consider incorporation of such events into the economic analysis	The assessment group agrees that such adverse event could not be incorporated into the current model.
6. Hip fracture risk reduction with strontium ranelate should only be included the economic analysis if its confidence interval does not include 1 • From Table 26, it seems a point estimate was used for relative risk of hip fracture with strontium ranelate. Since this information is not disclosed, it is difficult to know what effect it had on the economic model. However, incorporation of this point estimate into the economic model is only justified if the confidence interval does not include unity	The crossing of unity is not always a reason to exclude data. Consider two sets of relative risks [0.5 (0.2 –0.999) and 0.5 (0.2 – 1.001)], to assume that the first has an effect whilst the second does not would not be good modelling practice. Based on the data available the assessment group used what they believed was the most appropriate estimate for the hip fracture efficacy of strontium ranelate.
7. Inappropriate use of 10 year time horizon • The assessment team used a 10-year time horizon for Strontium Ranelate, however, the technology does not have data for 10 years. This fact undermines the evidence spanning 10 years that exists for agents like alendronate	The 10 years time horizon reflects the long-term impact of osteoporotic fractures on costs and utilities. The decision to use a five year intervention period followed by a 5 year fall time, during which the relative risk of fracture returns linearly to 1, was taken on the advice of the GDG. It was also assumed that RCT efficacy would also hold across the full 5 year treatment period.

National Osteoporosis Society	
General comment The NOS commends the assessment group for producing a comprehensive and detailed report and accompanying documents. The Society is encouraged to note in the report that collaboration has taken place with the clinical guideline development group and hopes this will continue. The Society believes that in order to reduce confusion and facilitate effective implementation of the guidance by health care professionals, the appraisal guidance for both primary and secondary prevention must be consistent with the recommendations of the clinical guideline. To that note, as a new economic model has now been developed for secondary prevention, the NOS would urge NICE to review published TA no87 in time for inclusion in the clinical guideline	No response from assessment group.
Primary prevention - general The NOS's major concern is about the identification strategy. The Society finds it difficult to accept that women aged less than 70 years will not be offered BMD assessment despite having clinical risk factors. For example, it is counterintuitive to good clinical practice to deny BMD assessment to a 64 year old woman taking 15 mg/day prednisolone who is at significantly increased risk of fracture and in need of anti-fracture treatment. The Society hears from women much younger than 70 years with a variety of different risk factor combinations for whom treatment is deemed to be clinically appropriate	Some women who could be cost-effectively treated on an individual basis, do not receive BMD assessment or treatment in the identification strategy, as the cost of identifying them from the cohort of women at the same age exceeds the net benefit of treating the individual.
Primary prevention - strontium The NOS is pleased to see that cost-effective scenarios for strontium ranelate have been identified for women at relatively high risk of osteoporotic fracture. However, the Society would urge NICE not to impose too stringent criteria around use of the drug for other post-menopausal women who cannot tolerate the bisphosphonates. The NOS often hears from women who are unable to comply with the dosing instructions for the bisphosphonates or experience side effects and therefore need another effective treatment option. Furthermore, as there is a rapidly declining evidence base for using calcium and vitamin D supplementation on its own in older women, there is a real need for an alternative to bisphosphonates in this age group	No response from assessment group.

General comment The NOS is unsure from the report whether NICE is adopting a £20k cost per QALY threshold or a £30K threshold. If adopting different thresholds for primary and secondary prevention the Society is concerned that NICE will be penalising those women who haven't fractured but who are actually at comparable risk to those who have	No response from assessment group.
General comment Finally, the NOS commends NICE for developing an identification strategy based on absolute risk of fracture to direct decisions about treatment but would ask NICE to ensure that in the final recommendations the information is presented in a less confusing manner that has pragmatic use in a clinical setting	No response from assessment group.
NHS QIS	
The first point which I would like to raise is with respect to the confidentiality of this Health Technology Appraisal document. As you have indicated, you already hold a signed confidentiality agreement from me in respect of this appraisal; however the document still has large parts of information missing for reasons of confidentiality. Some of this data relates specifically to hip fracture risk with respect to strontium and without access to this information, the data is less easy to interpret. I would urge QIS to look at this issue carefully from the point of view of future reviews of NICE Health Technology Appraisal documents. The full NICE document should be available to NHS Scotland reviewers	No response from assessment group.
With specific respect to this document; the overall view that strontium ranelate should be restricted to where bisphosphonates are either contraindicated or are not tolerated is appropriate and is compatible with the guidance issued by the Scottish Medicines Consortium (No 178/05). There are no major issues around the implementation of this NICE Technology Appraisal within NHS Scotland however there are two factors which require specific consideration for NHS Scotland	No response from assessment group.
Firstly consideration is needed with respect to the availability of the technology of Dual Energy X-ray Absorptiometry (DXA scanning) in NHS Scotland (at least 4 Health Board areas to my knowledge have no service provision). This NICE Technology Appraisal document acknowledges that in order to implement the guidance appropriately, access to bone densitometry measurement is required. NICE do acknowledge that the provision of this facility may not be adequate in England and Wales and similar issues will apply within NHS Scotland	No response from assessment group.
Secondly the issue relating to starting anti-osteoporosis agents in the absence of bone densitometry measurement needs to be considered again. The field of osteoporosis is	The decision to assume constant relative risks of fracture regardless of absolute

quickly moving towards absolute fracture risk assessment and treatment decisions are being based upon patients reaching certain fracture risk thresholds. Whilst this is entirely appropriate, it does ignore treatment efficacy evidence base. This evidence base indicates that anti-osteoporosis therapies, in particular bisphosphonates, are only effective in reducing fracture risk where an individual patient's bone mineral density lies below a certain T-score threshold. There are no data available to support using anti-osteoporosis agents (including strontium) in situations where bone density sits within the high osteopenic range (even where the presence of multiple clinical fracture risk factors mean that a given patient has a high baseline absolute fracture risk). This has been an issue with the previous NICE Technology Appraisal on osteoporosis (No 87) and sits outwith the recommendations made in SIGN guideline 71	fracture risk was taken on advice from the GDG. The GDG view was that the lack of RCTs in such sub-groups should not be taken to imply that there was a lack of efficacy.
Novartis	
Thank you very much for the invitation to comment on the above Assessment Report. I confirm that Novartis does not wish to make any further comments at this stage	No response from assessment group.
RCGP 1	
Overall, this latest document offers little in the way of surprises. It is most interesting for its reference to the forthcoming risk assessment tool for primary prevention of osteoporotic fractures, for which we have been waiting for some time. I do, however, have a few comments:	No response from assessment group.
1) The WHO term for a T-score below -2.5 SD, with one or more associated fragility fractures, is established osteoporosis, rather than severe osteoporosis, which is the term, used in this assessment paper	The assessment group have chosen to use the term severe osteoporosis and have defined this term in the glossary.
2) On page 23 the document states that 'It is noted that in applying these fractures the incidence of vertebral, wrist and proximal humerus fractures are greater than those we previously used in economic evaluations.23' This incidence will presumably have an effect on the CQG for other medications, including bisphosphanates and SERMs, and might therefore influence the decisions previously arrived at as to the cost effectiveness criteria for both drugs	No response from assessment group.
3) On page 30 the document states that 'The total number of women receiving medication for osteoporosis is approximately 480,000. Assuming that all these prescriptions are for women with osteoporosis, this would equate to 42% of the female osteoporotic population being prescribed medication.' This is probably an overestimate, since at least some of the patients receiving treatment will not yet be osteoporotic, but will have been started on medication because of osteopenia +/- other risks which qualify them under the RCP guidance for medication. This means that at least 60% of patients with existing osteoporosis are not being treated - what steps are being taken to address this shortfall?	No response from assessment group.

RCGP 2	
We certainly need to use the term "established osteoporosis".	The assessment group have chosen to use the term severe osteoporosis and have defined this term in the glossary.
British GP's and their patients are often faced with poor access to DXA scanning and long waiting times. Because Strontium Ranelate has a higher atomic mass than calcium the improvement in T scores is greater than the "true improvement in bone strength" Therefore it seems that if a DXA scan result will influence the decision to prescribe, then Strontium Ranelate should not be prescribed before the DXA scan. It may, however be possible to use DXA scanning to monitor adherence to therapy, using this artifactual finding (ref 1) More research is needed	No response from assessment group.
It is well recognised that poor compliance is an important issue in the clinical setting. Evidence from DIN-LINK suggests that only approximately 20% of patients initiated on a bisphosphonate are persisting with treatment at 12 months. This figure is better, 40% for weekly bisphosphonates	The impact of poor compliance has been explored in a sensitivity analysis in appendix 11 of the assessment report
Furthermore if patients do not comply with the difficult dosing instructions the drug is not as effective and the patient is more likely to experience side effects. In any one year 40% of the population suffer with dyspepsia. However, the symptoms of dyspepsia do not correlate well with the findings at endoscopy (ref 2). It is therefore difficult in Primary Care to decide which patients may have the dyspeptic symptoms that may be cautions or contraindications to prescribing a bisphosphonates Of those patients who consult with their GP with dyspepsia whilst taking a bisphosphonate some will be referred for upper gastrointestinal endoscopy with its associated inconvenience, morbidity and cost. As the side effect profile of Strontium Ranelate does not include dyspepsia, and this is not a contraindication to prescribing it, compliance and persistence to therapy, in the clinical setting may be better with Strontium Ranelate compared to the bisphosphonates We have a study in analysis at present which also shows low levels of persistence with weekly bisphosphonates. I agree with Alun that more research is badly needed to understand why	No response from assessment group.
Ref 1 -Fogelman, I., Blake GM Strontium Ranelate for the treatment of osteoporosis BMJ 18th June 2005 330; 1400-1401 Ref 2 -NICE Dyspepsia-management of dyspepsia in adults in primary care-clinical guideline 17	No response from assessment group.
And finally I think that there's a typo'-p19 line 30."Has the parent ever used corticosteroids" should refer to the patient not the parent.	This is a typo and should read "has the patient ever used corticosteroids"

Royal College of Nursing	
Introduction With a membership of over 370,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. The RCN promotes patient and nursing interests on a wide range of issues by working closely with Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations	No response from assessment group.
Comments on the Assessment Report The RCN welcomes the opportunity to comment on the Assessment Report for Strontium Ranelate (primary and secondary prevention) and the Addendum to the Assessment Report for the use of bisphosphonates and selective oestrogen receptor modulators (SERMs) for primary prevention The comments below refer mainly to secondary prevention of osteoporosis but are also applicable to primary prevention of osteoporosis	No response from assessment group.
- **Comments on the interpretation of the evidence base, particularly with regard to the clinical effectiveness**	
This appears to be a very thorough analysis - although there did not seem to be an analysis looking at QALYs related to the burden of pain and disability related to vertebral fractures	The utility estimate for vertebral fractures (and all other fracture types) was assessed using the EQ-5D which comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). It should therefore be sensitive to the burden of pain and disability related to vertebral fracture.
This is a very comprehensive and thorough analysis which appears to have a good evidence base. Although it is disappointing to note that there is no reference to the burden of disease, regarding how patients suffer in relation to pain, disability relating to vertebral fractures and social status within the QALYs assessment. This group of patients suffer significantly and in our experience the patient can rapidly become disabled and dependent. Its inclusion here would formulate a more holistic approach to the impact of this disease.	See response to previous comment.
Also the inclusion of fractures other than hip, vertebrae and wrist will also direct clinicians in assessing those people who may be at risk. It is interesting to see how parental	No response from assessment group.

fracture has been included with the CRF, and not just maternal	
- **Has any relevant evidence been left out**	
Although costs were analysed to consider the costs of women following fracture to be admitted to a nursing home, there was no consideration of staying at home with carer and community costs related to the disability and costs related to this analysis. Also see comments above, plus the inclusion of nurse specialists (as below on the assumptions underlying the economic model)	The cost of fracture data was derived from a study by Dolan and Torgerson and includes social care costs for patients discharged home after a hip fracture. Non-acute costs relating to GP visits, outpatient appointments and additional referrals are also included.
- **How should the clinical results be interpreted in the context of current clinical practice**	
It appears that patients who have an absolute risk factor of between 8 - 10% or more become cost effective (based upon this analysis) for these therapies	No response from assessment group.
The results in the report will assist in establishing which patients should be treated and when	No response from assessment group.
It is understood that for DXA scanning it is proposed that in the future scans will be reported in terms of fracture risk instead of T and Z scores. It is felt this will be a better way of presenting the information particularly as more patients will be under the care of their GP in the future rather than secondary care	No response from assessment group.
With reference to the information on page 60 regarding levels on non continuance of medication, the most interesting point regarding current clinical practise was the evidence that Teriparatide appears to be more effective when used prior to the use of a Bisphosphonate. Obviously, as Teripartide is a new drug it is currently being given to some patients who have taken Bisphosphonates in the past, but will be a matter for serious consideration for patients in the future who may have a better response to treatment if Teriparatide is given as first line treatment assuming that the individual fulfils the criteria this preparation	No response from assessment group.
- Comments on the assumptions underlying the economic model	
The economics of the assessment appear clear, however within the calculating the cost of selective case finding and patient follow up, in our view, an opportunity has been missed for the inclusion of osteoporosis nurse specialists within the algorithm (pg 100). Clinical Nurse Specialists (CNS) and Allied Health Professionals could utilise this model at a lower cost. The saving that could be made could be offset against the CNS seeing the patient at a later date to check compliance. Overall the cost would not increase, but the patient experience would be improved	The role of clinical nurse specialists in the assessment of fracture risk has not specifically been addressed in the assessment report. However, the sensitivity analyses, discussed in appendix 11, show the impact of changing the costs of identification.
Also see earlier comments regarding other costs related to the individual when disabled by osteoporosis	No response from assessment group.
Expensive drugs such as Teriparatide may be rationed and it is known from current clinical practise that it is problematic to get this treatment funded. There is confusion over	No response from assessment group.

who is responsible for the funding, primary or secondary care	
In the document, at one point, there seemed to be a difference of opinion over the number of patients who need to be cared for in a nursing home after they have had a hip fracture	The number of women entering a nursing home is clearly described on page 29 of the assessment report. In the discussion section of the report, the evidence and assumptions on nursing home entry is compared to the evidence and assumptions used in other published models in order to explain how the analysis carried out by the assessment group differs from other published analyses.
It is felt that there will be economic implications if DXA scanning is offered more routinely to people either because of age or clinical risk factors but that this will always be off set by savings , both financial and in human terms if fractures can be avoided	No response from assessment group.
The Royal College of Pathologists	
Executive Summary	
The report is correct to identify possible side effect issues but the relative risk of all adverse events should be quoted rather than just statements on some being “more common” in patients on strontium ranelate (where the calculation has not been possible this should also be stated).	Table 16 provides the relative risks of adverse events. Where a calculation of relative risk has not been possible this is indicated in the table.
The choice of algorithm for use in making absolute fracture risk is an advance on just using BMD, but the evidence for using some of the criteria such as smoking status is still debatable. Body mass index (BMI) is recognised as important by the majority of authors on this subject but this factor has been omitted (or standardised to 26 for the purposes of analysis).	BMI is omitted from the clinical risk factors for the reasons discussed on page 95-96 of the assessment report. It’s omission is not expected to have a large influence on the results as it is only a significant predictor of fracture risk when BMD is unknown and our analysis assumes a known population distribution of BMD.
Although the report identifies the failings in comparison with bisphosphonates there is no comment in the summary on the role in patients who are unsuitable for or unable to tolerate bisphosphonates. This should be addressed in the next draft of the report	No response from assessment group.
There is no mention of the efficacy dependence on the prevailing concentration of strontium that is measured after the patient is stabilised on treatment. This is rather surprising as this is important data that has either not been supplied to or considered by the committee. For this drug to be used effectively the committee should consider the value/role of measurement of strontium ranelate in plasma	No response from assessment group.
Background	
Table 2 is illegible in my copy. Also page 20, Table A and Table B were only partially	These tables have been deliberately

legible. This is a significant improvement on previous methodology but still requires further work. In future it is assumed the final report of the WHO group will used for all such assessments	blacked out due to the inclusion of confidential data.
The report should include the date that was used when the current service provision data was established. Did this include changes that may have happened when generic alendronate prescription was possible?	The prescribing data has been taken from 2002. As such generic alendronate has not been included.
Product Characteristics	
It is surprising that a rather “generic” renal function cut-off of 30 ml/min for creatinine clearance has been quoted as the recommended level below which strontium ranelate should not be prescribed. What data has been produce to support this statement and the recommendations relating to other levels of renal impairment?	The recommendations for the use of strontium ranelate in patients with renal impairment (p32) are taken from the EMEA Annex I, Summary of Product Characteristics, 2004.
Surprisingly there is no mention in this section either of the effect of the prevailing concentration of strontium ranelate nor the effect of strontium ranelate and the interpretation of BMD. How can the appropriateness of therapy be established by BMD when the molecule itself makes a significant contribution to BMD measurement?	No response from assessment group.
Clinical Effectiveness	
Continuance and compliance may be reflected in the prevailing strontium concentration in the blood not just by measurements of the therapeutic response. Since fracture outcome can be related to these measurements these should be taken into account by the committee	No response from assessment group.
The report quotes the data on BMD increase but no mention of the confounding factor of the molecular mass of the strontium molecule in BMD measurement is mentioned. This is rather surprising considering the importance of the document	No response from assessment group.
It should be made clear that the magnitude of effect on “bone stimulation” by strontium ranelate and teriparatide are significantly different. The simple expedient of comparing the changes in bone formation markers demonstrates this long before the changes in BMD	No response from assessment group.
The authors should update the comments on teriparatide and bisphosphonate use using the recent articles published in the New England Journal of Medicine in particular	Unfortunately these articles were published after the cut-off date for the literature review.
Alendronate: The report needs updating to comment on the availability of generic alendronic acid.	Unfortunately this was launched too late to be included in the report. A comment will be added within the discussion in the HTA report.

Economic Analysis: The modelling looks very interesting but not all outcomes have been included as there is surely a difference between residence in the community where the individual is dependent on other carers or independent. The cost will be completely different and so the analysis will be unfavourable to the intervention. GP and hospital costs are also going to be greater in this population. Chronic or repeated pain as a result of fracture(s) will also vary in these patients and is not equivalent between the groups. If the comparison uses the generic priced alendronate then this will presumably show an even greater advantage in this analysis	The cost of fracture data was derived from a study by Dolan and Torgerson and includes social care costs for patients discharged home after a hip fracture. Non-acute costs relating to GP visits, outpatient appointments and additional referrals are also included.
Alternative Identification Approaches:	
It is correct to state that it is appropriate for clinicians to treat women at a high risk of fracture without performing a DXA scan if it is unlikely that the DXA scan would change the decision to treat. It is easy for us to define a severely affected group falling into this category but precise recommendations regarding this approach are not available. Further detailed guidance is required on the patients meeting the criteria for DXA measurement. The RCP approach was defined many years ago when the current level of knowledge was not available	No response from assessment group.
I do not agree with the statements regarding BMI and the lack of references in this section may suggest that the authors felt that the work involved to use BMI in the calculations would be excessive for an assumed modest return. BMI measurement is much cheaper than a BMD and could quite appropriately be included in the GP algorithm. This may also have a significant effect in younger women where the identification cost using BMI would be cheaper	BMI is omitted from the clinical risk factors for the reasons discussed on page 95-96 of the assessment report. It's omission is not expected to have a large influence on the results as it is only a significant predictor of fracture risk when BMD is unknown and our analysis assumes a known population distribution of BMD.
It is interesting that the cost implications are expected to be low for strontium ranelate. However if 30% of patients on alendronate are "unwilling or unable" to take this therapy after 6 months and an even greater number come into this category with the passage of time a substantial number of women would become eligible for strontium ranelate. The costs would then be significant	No response from assessment group.
Alternative methods of DXA scanning are available and a significant literature, especially on peripheral scanning, is now available. This should be considered and costed	The assessment group followed the advice of the GDG with regards to the appropriate role of bone densitometry

Discussion The comments above should be reviewed in the context of the discussion.	No response from assessment group
Although subjects do not enter nursing homes significant costs will accrue for care in other environments as discussed above. These need to be taken into account. The assumption that there are not high costs from patients residing outside nursing homes is incorrect. Research in this area should be recommended	The cost of fracture data was derived from a study by Dolan and Torgerson and includes social care costs for patients discharged home after a hip fracture. Non acute costs relating to GP visits, outpatient appointments and additional referrals are also included.
It is highly unlikely that a comparator study of bisphosphonates and strontium ranelate with fracture outcome as the primary end-point will be performed. The “false” increase in BMD seen with strontium and the differences in action on bone metabolism also make it impossible to perform comparator studies using these end-points as comparators with bisphosphonates. It is surprising that these problems with strontium are not mentioned in detail within the document	No response from assessment group.
The interference with calcium depends on the concentration of strontium circulating in the blood and the methodology used to measure calcium. The mean concentration of strontium circulating in the blood in the vast majority of patients on strontium ranelate does not cause interference in the methods used in most clinical biochemistry laboratories in the UK. The urine Ca concentration may be subject to interference in some methods after collecting an overnight sample containing a large proportion of the excreted dose and sampling immediately following ingestion of the 2g sachet can cause interference. The problem however in comparison to other issues raised is minimal	No response from assessment group.
Review of the comparative data suggests that strontium has significant advantages over raloxifene in the models used and is significantly closer to the bisphosphonates in terms of cost effectiveness. This presumably has significant implications for the current recommendations and raloxifene will be replaced by strontium in the algorithms for secondary prevention or included alongside as an alternative when there are issues with bisphosphonates. Further classification depending on hip fracture prevention will need to be addressed in the recommendations	No response from assessment group.
The Royal College of Physicians	
The Royal College of Physicians is grateful for the opportunity to comment on the assessment report for the above appraisal. The only point we wish to make is a relatively minor one. We notice that in the discussion it is stated that Strontium increases bone formation, whereas we do not think that this has been proven at least in humans. From our reading of the papers Strontium increased alkaline phosphatase activity, but that does not equate to an increase in bone formation. The histomorphometric data show no	No response from assessment group.

evidence of an increase in bone formation (eg mineral apposition rate). However this does not undermine the recommendations for clinical use	
Servier	
Thank you for the opportunity to comment on the Assessment Report for Strontium Ranelate. We believe that the Assessment Report makes assumptions about the evidence base and draws conclusions on this evidence base that results in a serious under-estimation of the efficacy and cost effectiveness of strontium ranelate. For the Appraisal Committee to be effectively informed about the evidence supporting the use of strontium ranelate, NICE should consider requesting that the Assessment Group revise the report and present further analysis where needed The comments provided below are set out according to the page and paragraph number of the report	No response from assessment group.

Page 10/Para 5 – Efficacy in hip fracture prevention The report states that efficacy in fracture prevention needs to be strengthened, particularly in hip fracture. A large amount of evidence is already available to establish the efficacy of strontium ranelate as efficacious in the prevention of hip fracture. Indeed, this evidence was sufficient to justify a license in the prevention of hip fracture. We request that the Appraisal Committee recognise the weight of the evidence in support of this approved claim and adjust their comment accordingly	The relative risk of hip fracture in the intention to treat population of the TROPOS study did not reach statistical significance (Reginster Y et al, JCEM 2005). Although strontium ranelate has been licensed for the prevention of hip fractures on the basis of the evidence currently available, it is the opinion of the assessment group that the evidence base for hip fracture prevention needs to be strengthened as doing so would provide a more accurate estimation of the cost-effectiveness of strontium ranelate.
Page 18-23 – WHO Risk Algorithm and Economic Model The failure of the Assessment Group and NICE to supply the methods used to estimate cost effectiveness to any consultee makes it impossible for consultees to review the methods of this technology appraisal. This lack of transparency is not consistent with previous NICE appraisals and we therefore request access to this algorithm and to the economic model	No response from assessment group.
Page 42/Para 2 – Additional Data Additional supportive data were provided in-confidence to the Assessment Group. Analysis of these data should inform any decision made by the Appraisal Committee	These data were taken into consideration by the assessment group

Page 43 – Choice of the Relative Risk of Fracture The economic analysis produced by the Assessment Group made use of three basic rates of treatment effect: the risk of vertebral fracture, the risk of peripheral fracture and the risk of hip fracture. The assessment group took advice that relative risk was not related to absolute risk. The same degree of risk reduction was assumed no matter what the baseline risk of fracture. This comment will focus in particular on the choice of relative risk of hip fracture. A relative risk of hip fracture is available for the entire TROPOS patient population. Another estimate of relative risk is available and was presented in the submission and is published as part of the published clinical paper and in the Summary of Product Characteristics. This estimate of relative risk was taken from the analysis of patients over or equal to 74 years of age and with a T-score≤-2.4 according to NHANES normative values. This analysis was undertaken under the instruction of the EMEA as a method for testing the efficacy of strontium ranelate in the prevention of hip fractures. Both results were published in a peer-reviewed clinical journal[6] [Meunier PJ et al, NEJM, 2004, Reginster Y et al, JCEM 2005] The Assessment Group justified this choice on the grounds that because patients were not randomised within the sub-group, the baseline risk of the patients in these groups could not be verified as being the same. Therefore, it was more scientifically correct to use the data from the fully randomised group, even if it did contain a large proportion of patients with low hip fracture risk Another justification that can be implied, although it is not specifically stated, is that all data were considered for the appraisal of bisphosphonates. The analysis proceeds to compare the data from the bisphosphonate data set to the strontium ranelate data and generate a prioritisation of treatments based on the outcome of the economic analysis of all drug efficacies There are a number of flaws in the analysis of the assessment group. These will be set out in turn	No response from assessment group. Each point is discussed individually in our responses.

[6] Meunier, P. J., Roux, C, Seeman, E, Sergio, O, Badurski, JE, Spector, TD, Cannata, J, Balogh, A, Lemmel, E-M, Pors-Nielsen, S, Rizzoli, R, Genant, HK, and Reginster, J-Y The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. New England Journal of Medicine 2004; 350 459-468;

J. Y. Reginster, E. Seeman, M. C. De Vernejoul, S. Adami, J. Compston, C. Phenekos, J. P. Devogelaer, M. Diaz Curiel, A. Sawicki, S. Goemaere, O. H. Sorensen, D. Felsenberg, and P. J. Meunier Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Postmenopausal Women with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study The Journal of Clinical Endocrinology & Metabolism 90(5):2816–2822

Baseline Characteristics of the At-risk Sub Group On a number of occasions in the Assessment Report, the authors refer to sub group data used as the basis for the economic analysis submitted as part of the Servier Laboratories submission. The Assessment Group judged that these data were not usable because patients were not randomised to treatment and placebo groups upon entry into the sub group. In fact, as outlined above, this post hoc analysis was requested by the EMEA after previous discussions on trial design had defined the non-vertebral fracture endpoint as being appropriate to measure efficacy for licensing purposes The approach taken by the Assessment Group was made without reference to the evidence establishing that the baseline risk of patients in the placebo and treatment groups in the sub-groups of concern could be verified as the same. This evidence was published in the TROPOS publication made available to the Assessment Group. It is disappointing that the Assessment Group chose not to correspond on this issue before the Assessment Report was finalised. We respectfully request that the Assessment Group take note that the EMEA endorsed the use of this endpoint and included it in the SPC and that the data were published in an eminent peer-reviewed clinical journal as a guide that the relative risk from the sub-population was indeed a valid estimate of efficacy Data available and published show that patients in these sub-groups were well balanced for baseline characteristics. Please see the table below The table shows that the baseline characteristics of the placebo and the treated groups were entirely consistent. Please be aware that the T-scores shown refer to the Slosman T-score levels for BMD. Using the NHANES III scale significantly increases these levels. In fact, mean BMD T score –3 according to Slosman corresponds to around –2.4 according to NHANES Again, discussions about this matter were at the core of the decision making process conducted by the EMEA which accepted that the sub-group was adequately balanced for baseline risk In summary, the sub group analysis of patients at risk of a fracture is an unbiased and appropriate measure of efficacy in hip fracture prevention. It is incumbent upon the Appraisal Committee to consider requesting an economic analysis inclusive of the use of these data in order for its decision to be fully informed by the facts	Whilst the efficacy within the sub-group is lower than that for the whole population, it still has confidence intervals wide enough to not exclude the pooling of the whole data set. The GDG advised the assessment group that efficacy should be constant regardless of absolute risk of fracture or clinical risk factors. As such the full data were used. It is also noted that some correspondence from Servier arrived after the deadlines published by NICE.

Scientific Validity of the At-risk sub group	
The at-risk sub-group from TROPOS was chosen by the EMEA as the group in which to test the efficacy of strontium ranelate for hip fracture prevention for two major reasons, both of which relate to the risk of fracture Firstly, it is this at-risk group that provides sufficient power to demonstrate a treatment effect. To elaborate, the TROPOS trial was set up in 1996, more than one year before the first CPMP guideline on osteoporosis, but still in line with this guideline and that issued by the FDA in 1994. Non-axial fractures including hip were documented separately, as requested in the CPMP guideline issued in 2001. A placebo-controlled study based on hip fractures as the primary endpoint would have led to exposing a much larger population to the test product: in the target population (with a 1% incidence per year of hip fracture, as observed in the placebo group in TROPOS, and with a 15-20 % theoretical difference between groups at 3 years) 24600 and 13600 patients per group, respectively, would have needed to be followed and analysed in a phase III study to ensure a 90% power to establish superiority (at the type one error rate of 5%). Under these circumstances it is not reasonable for regulatory authorities, or indeed for NICE, to demand such a study. Instead, the EMEA agreed to investigate the efficacy in a sub-group that had sufficient events and therefore the power to identify a stable treatment effect Secondly, and following on from the first point, it was in the at-risk populations that alternative bisphosphonate medications had been assessed. A comparison of these populations is made below The post-hoc analysis was specified by the EMEA external to Servier Laboratories Ltd[7]. In effect, the analysis was independently generated and did not represent a data-mining exercise. Under these circumstances, NICE should consider the relative risk generated as an entirely legitimate estimate of treatment effect and instruct the Assessment Group to use it in the analysis of cost effectiveness	The assessment group accepts that the TROPOS trial was not powered to measure a statistically significance reduction in hip fractures. The assessment group has used what it judges to be the most appropriate estimate of hip fracture efficacy for strontium ranelate given the data available and the population to which this efficacy is applied in the model. Reference is also made to previous answers.

[7] As detailed in the EPAR, page 18

Bias in Summarising of Data	

The Assessment Group decision to use the entire TROPOS data set rather than the data in the at-risk sub-group to inform the estimate, significantly biased results against strontium ranelate because of the breadth of the data set in which the drug has been tested. By comparison, an alternative drug, risedronate, was tested in a population with a significantly higher risk of hip fracture. A comparison of the treatment effect of strontium ranelate and risedronate, where the drugs have been tested in populations of a similar baseline risk, shows that strontium ranelate is indeed more effective in hip fracture prevention Underlying the choice of the Assessment Group to use the low risk group relative risk data from TROPOS is the assumption that relative risk of treatment would not vary with absolute risk at baseline. This assumption was not evidence-based. Rather it was based on the "wide knowledge of the vast published literature of members of the guideline development group". While there is evidence for this conclusion for vertebral fractures, there is evidence from bisphosphonate studies as well as strontium ranelate studies that baseline risk is very important in determining treatment effect for hip fracture. For example, there is substantial evidence within the trials of alendronate and risedronate that the relative risk reductions for vertebral fracture are consistent across study populations but the relative risk for hip fracture is dependent on underlying femoral neck BMD. This is illustrated by the wide discrepancy in the point estimates for the relative risk for hip fracture in the FIT studies and in the two randomised strata of the risedronate hip fracture study. The FIT1 study[8] recruited patients with a mean t-score of –2.4 (NHANES). It achieved a relative risk of hip fracture of 0.49. However, the FIT 2 study[9] recruited a sample with a mean BMD of –2.2 and achieved a relative risk of hip fracture of 0.79. Indeed, the Cummings article makes extended reference to the relationship. In the case of risedronate, there is additional evidence for the importance of baseline risk. The McClung study[10] of this drug was split into two stratums. The stratums differed in baseline risk of hip fracture. Again the results were consistent with the hypothesis that testing hip fracture efficacy should rely on recruiting patients at risk of fracture. These observations are entirely consistent with and supported by the analysis of efficacy for strontium ranelate on hip fracture In the light of these facts, it is useful to consider the difference between the baseline risk of patients included in the meta-analysis of the risedronate data and the patients in the entire population and in the at-risk sub-group from TROPOS that was the basis for the license for hip fracture prevention In the meta-analysis that the Assessment Group used to generate the relative risk for risedronate, almost 80% of patients came from one study, McClung et al (2001). The meta analysis is presented below At entry into McClung (2001) study, patients T-scores were recorded at between –2.9 and –2.7 standard deviations (using NHANES III) below the mean for health adults lower than those observed in TROPOS study. The rest of the patients included in the meta-analysis of the risedronate data were in patients with a previous fracture and thus severely osteoporotic. Both the Reginster[11] (2000) and the Harris[12] (1999) study only included high-risk patients. T-scores were not reported in these publications. In the case of the Harris study, patients had to have at least 2 fractures at baseline or one fracture	Whilst the point estimates for the two FIT trials are correct the width of the confidence intervals are large (0.77 and 1.00). Thus there is not conclusive proof that these are taken from different efficacies. The assessment group have, on GDG advice, assumed that relative risk of fracture is not affected by baseline risk. Therefore, where there is data for an intervention in patients at high and low baseline risk of fracture these data have been combined in a meta-analysis. This is true for all the interventions considered.

To reiterate the point made above, TROPOS was not design to assess hip fracture prevention. If it had been, the study population would have been selected for its risk of such a fracture and would have had similar characteristics to the risedronate studies and to the at-risk sub-group within TROPOS. The method used by the Assessment Group in selecting data for the comparison of drug efficacy and cost effectiveness resulted in very significant disadvantage for strontium ranelate because it was tested in a patient group with a lower average risk than risedronate. All three risedronate trials imposed entry criteria that significantly increased patient risk. It was in part due to this fact that the EMEA decided that a sub-group of patients at a significantly elevated risk of hip fracture would be appropriate to test the efficacy of strontium ranelate. As stated above, the analysis in this group produced results comparable or better than bisphosphonate alternatives. In these circumstances, the Appraisal Committee might consider asking the Assessment Group to provide an analysis of the cost effectiveness of strontium ranelate that includes the estimate of hip fracture reduction that fairly reflects the testing of that efficacy consistent with the testing applied to alternative medications	See earlier responses.
Alternative Estimate Of Relative Risk of Hip Fracture	
An alternative estimate of efficacy in the prevention of non-vertebral fracture is provided in the relative risk of major non-vertebral fractures, published in the TROPOS study. In this study, strontium ranelate treatment was associated with a 19% reduction in the risk of major non-vertebral osteoporotic fractures [RR = 0.81; 95% CI (0.66; 0.98), P = 0.031]. Compared to the estimate of 0.85 for hip fracture, this estimate has a narrower confidence interval and is thus a more stable estimate of non-vertebral fracture efficacy	The assessment group have not accepted that all non-vertebral fracture efficacy are a sufficient proxy for hip fracture efficacy.

[8] Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348(9041):1535-1541.

[9] Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280(24):2077-2082.

[10] McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. New England Journal of Medicine 2001;344:333-40.

[11] Reginster J, Minne HW, Sorensen OH et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporosis International 2000;11(1):83-91.

[12] Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA 1999;282(14):1344-1352.

in the entire TROPOS population. As stated above, the TROPOS study was not powered to demonstrate an effect in rare fractures such as fractures to the hip. This estimate of efficacy is more efficient should efficacy in the entire population be required	
Page 49 Para 4 – Compliance Sensitivity Analysis	
Comment was made in the Assessment Report that insufficient information is available on the method of compliance measurement. In fact, compliance was extensively measured as a part of the studies of efficacy and safety. Two methods were used to assess compliance. The principle method of measuring compliance to strontium ranelate treatment in TROPOS was the monitoring of the levels of strontium in the blood. In addition, compliance was measured by counting sachets returned to the investigator by the patient at each visit. The second measure of compliance is termed Global Compliance and is useful for both the placebo and treated patient groups	No response from assessment group.
Per Protocol Analysis (comments provided commercial in confidence)	

In conclusion, the Assessment Report recently distributed to consultees has a number of shortcomings that significantly hamper its usefulness to the Appraisal Committee in providing the basis for making a decision about the place in therapy of strontium ranelate. Specifically, the Report misrepresents the core estimate of efficacy in hip fracture prevention by assuming the most pessimistic estimate of treatment effect. A treatment effect was demonstrated in a patient population at-risk of this fracture and consistent with the population in which bisphosphonates medications were tested. It was this estimate upon which the EMEA granted a license for the prevention of hip fracture. To better inform the Appraisal Committee of the cost effectiveness of strontium ranelate, an analysis could be supplied using the efficacy detailed. In addition, cost effectiveness could also be assessed using in-confidence data and data on major non-vertebral fracture supplied to the Assessment Group in the previous correspondence. Where compliance to medication can be monitored, specific data are available that could prove useful in estimates of cost effectiveness. To better insure that the process is fair, the Committee should also consider directing the release of the economic model and the WHO algorithm to consultees for review	No response required from assessment group as these issues have been covered above.
We value this opportunity to comment on the process and substance of the NICE appraisal. We trust that this response will prove useful in your consideration of the Assessment Report. I remain at your disposal should you wish to consult me on any matter regarding this or previous correspondence	No response from assessment group.
Society for Endocrinology	
The Society for Endocrinology welcomes the opportunity to comment on the institute's guidance regarding the use of strontium ranelate in postmenopausal osteoporosis We have several comments to make regarding the assessment document:	No response from assessment group.
1. The cost effectiveness of strontium ranelate will be highly dependent upon the actual reduction in fracture which is ascribed to it. It is therefore unfortunate that we are not able to see the values that have been used in the analysis (tables 13, 21 and 26). We presume that this is the result of the use of commercially sensitive information but nonetheless feel that it has substantially inhibited our ability to make meaningful comments upon the whole economic analysis	No response from assessment group.
2. Whilst we welcome the use of clinical risk factors as a means of identifying patients the way in which the data has been presented in the report is very cumbersome and would not be of practical use in a clinical setting. It would therefore be very helpful if some way could be found of grouping the clinical risk factors together and perhaps giving a clinical risk factor score	No response from assessment group.
3. It is confusing to find both fracture risk (given as a %) and T score threshold given	Cost-effectiveness is not solely determined

in the same table. Surely the whole idea of giving a fracture percentage risk was to get away from the slavish application of T score thresholds when any given level of risk could be reached from an infinite combination of different clinical factors and different bone density levels	by absolute fracture risk. It is also dependent on how that fracture risk is made up in terms of the risk at different fracture sites. As clinical risk factors and BMD have different impacts on hip and non-hip fracture risk it is possible that two women with different clinical risk factors and BMDs will reach the same level of total absolute fracture risk but that different proportions of this risk will relate to hip fractures. The cost-effectiveness of treating these two women will differ despite their common absolute fracture risk.
4. We are surprised that the utility loss associated with a clinical vertebral fracture is greater than that associated with a hip fracture (table 23).	No response from assessment group.
5. Whilst we understand that on the current modelling assumptions strontium ranelate does not appear to be as cost-effective as alendronate (although data for other bisphosphonates has not been shown in this document) we are concerned by the statement in the executive summary that "strontium ranelate is not expected to be the first line therapy". Our own clinical experience would lead us to believe that when a treatment has been relegated to second line status then it is increasingly difficult to get approval from formulary committees and PCTs for its use. As strontium ranelate has a totally different mechanism of action from other available therapies and a very different side-effect profile we would be very anxious to see a means whereby it is not denied to patients who would benefit from it if the committee to decide to afford it second line status. To this end we would urge the committee to think carefully about the wording of any such advice to make it clear that this is a reasonable option where bisphosphonates are unsuitable	No response from assessment group.
The alliance for better bone health	
Assessment Report	
Why is there an identification strategy mentioned in section 4.2 of this Assessment Report? This is a deviation from the original scope and indeed from the purpose of an Assessment Report. Surely such a strategy would form part of a Guideline not a Guidance.?	When assessing the cost-effectiveness of strontium ranelate in the primary prevention of osteoporotic fractures, it was necessary to consider the costs associated with identifying women who can be treated cost-effectively, as failure to do so would give an incomplete picture of the cost-effectiveness

	of this intervention.
Addendum to Assessment Report	
Inappropriate inclusion of Raloxifene's breast cancer reducing effect. ISSUE: The inclusion of raloxifene's effect on breast cancer is inappropriate for several reasons: 1. It is contrary to the previous Committee decision during the assessment of "Osteoporosis – secondary prevention", Section 4.3.14, where the Committee noted "that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost effective option for the treatment of osteoporosis. From the evidence presented, raloxifene was not as effective as bisphosphonates for treating osteoporosis. Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities. The long-term risks of raloxifene treatment beyond 8 years are uncertain. Full assessment of raloxifene's effect on the prevention of breast cancer and its cost effectiveness in this indication would require consideration of how it compares with other drugs that potentially could be used for the prevention of breast cancer." 2. To include such an effect would be out of the original scope and unethical considering that in this patient population there is an inverse correlation between the incidence of breast cancer and that of low BMD. 3. In the previous assessment of "Osteoporosis – secondary prevention" the NICE appeal panel rejected Lilly's appeal that raloxifene's effect on breast cancer should be fully considered as part of the products cost effectiveness in the treatment of osteoporosis. PROPOSED RESOLUTION: The effect of raloxifene on breast cancer should not be given further consideration in the assessment of raloxifene's cost effectiveness for osteoporosis.	Results have been presented both with and without the breast cancer benefit of raloxifene for the consideration of the Committee.
Inappropriate optimal ranking within the bisphosphonates class. ISSUE: There are no head to head fracture trials involving bisphosphonates. A thorough analysis of the data from the bisphosphonates studies has shown that the different study designs, heterogeneous populations, different Ca/Vit supplementation, different classifications for fractures, dose switching in alendronate studies and age of the etidronate studies mean that in the absence or robust well designed head to head fracture studies, the existing data is too similar with overlapping confidence intervals to permit any within class optimal ranking. Thus, it would be inappropriate to differentiate between the bisphosphonates in the textual summary or in in-text tables that could be used out of context. In addition it would appear erroneous to rank product when the relative risks for risedronate appear to be incorrect.	The scope of the appraisal did not allow the assessment group to consider bisphosphonates as a class. As there were no head to head trials an indirect comparison was undertaken. Any decision to treat bisphosphonates as a class (or not) will be taken by the appraisal committee.

PROPOSED RESOLUTION: Remove optimal ranking of bisphosphonates in the text and tables and present the data for each product with the caveats that bisphosphonates should be considered as a class.	
Unexplained change in the efficacy estimates for risedronate. ISSUE: Without any scientific justification the efficacy estimates (relative risk) for risedronate have been altered from the value of 0.66 used in the assessment report for the prevention and treatment of osteoporosis (2003, pg 56), to 0.74 for the hip, and 0.68 to 0.76 for the wrist. PROPOSED RESOLUTION: Provide an explanation and clarification for the change in fracture incidences or correct this error, as this negatively affects the cost effectiveness of risedronate.	The efficacies used in the Addendum are drawn from the updated clinical effectiveness review carried out for the primary prevention DSU report / assessment report. On the advice of the GDG it was assumed that the relative risk (RR) of fracture for the interventions considered are constant across all age groups. The meta-analysis of the RR of hip fracture for Risedronate therefore included the whole of the McClung study. This differs from the approach used in the 2003 assessment report on the prevention and treatment of osteoporosis which only included the younger stratum from the McClung study in the meta-analysis of hip fracture efficacy for risedronate. The value of 0.76 is the RR of non-vertebral fractures as opposed to wrist fractures specifically. In the methodology used for the strontium ranelate assessment report and the addendum, fractures of the wrist are grouped together with fractures of the rib, sternum, clavicle and scapula and due to the model structure the same RR had to be applied to all of these fracture types. Therefore the RR on non-vertebral fractures was chosen as the most appropriate RR for this group of fractures.
Exclusion of the effect of etidronate on hip and non–vertebral fractures. ISSUE: Etidronate is not credited with the data it has on hip and non-vertebral fracture risk reduction due to a lack of RCT data. However this ignores the decisions of the Committee in the Guidance on Osteoporosis – secondary prevention Section 4.3.7 ie "The Committee heard from clinical experts that although an effect of etidronate on non-	The GDG advised the assessment group that only RCT evidence be used for estimating efficacy.

vertebral fractures is likely, this effect is less pronounced that with alendronate and risedronate, the evidence base is weaker, and the mode of action is slightly different. However, given the lack of direct head-to-head comparisons, the Committee concluded that all of the bisphosphonates were treatment options for women with established osteoporosis who fulfill the criteria for treatment." PROPOSED RESOLUTION: Due to the age of this product it does not have the comprehensive data package to support it like risedronate and alendronate. However, as with the previous assessment on Osteoporosis – secondary prevention, it is reasonable to assume that since it has comparable vertebral efficacy to the newer bisphosphonates, and has demonstrated hip fracture risk reduction in a large well controlled GPRD study, that etidronate's non-vertebral and hip fracture efficacy estimates should be considered to be broadly similar to the other bisphosphonates.	