NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

Response to consultee, commentator and public comments on the March 2008 Appraisal Consultation Documents (ACDs)

Consultee or Commentator	Comment		Institute Response
Manufacturer			
The Alliance for Better Bone Health (on behalf of sanofi-aventis and Procter & Gamble)		**Appraisal Consultation Documents: primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women** Thank you for the above ACDs. The comments from the Alliance for Better Bone Health on behalf of sanofi-aventis and Procter & Gamble (The Alliance) are below. The committee has delivered a set of recommendations for alendronate and risedronate that suggest distinctions between these products which are not supported by the clinical evidence. The Alliance proposes that the Committee should recommend the use of oral bisphosphonates as the first line treatment option with the decision on which bisphosphonate to prescribe taking account of both cost of acquisition and suitability for the patient. A recommendation made in this way is consistent with previous recommendations for product classes, and will ultimately result in a similar outcome that NICE seeks to achieve. Furthermore, the advantage of this approach is that it does not require overly complex recommendations that will be difficult to implement and it avoids potentially discriminatory rules that deny women who cannot take alendronate, the opportunity to take an equivalent alternative treatment.	Comment noted.
		□ For example, some women who cannot tolerate alendronate will not be able to receive risedronate until their T-score worsens under the more restrictive recommendation of Paragraphs 1.2 in both ACDs. These patients will be denied an equally effective treatment on the basis of cost, despite having been initiated on alendronate. □ For those patients not able to comply with the administration instructions, or who are contraindicated to alendronate, the guidance further fails them since the committee already recognised in section 4.3.23 (primary prevention) and 4.3.22 (secondary prevention) that it would	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the

Consultee or Commentator	Comment		Institute Response
		unfairly disadvantage patients if first-line treatment were denied until reaching a higher age or lower T-score, but then fails to fully rectify this imbalance by only providing access in line with the more restrictive T-scores for those unable to tolerate alendronate.	alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention).
		In addition to the potentially discriminatory rule-set outlined above, the guidance regarding women aged 75 and over should be clarified with respect to the need for DXA scanning before treatment. It is recommended in Section 1.1 that women aged over 75 can be initiated on alendronate without the need for a DXA if clinically appropriate. However if any of these women are intolerant to alendronate they need to wait for a scan before initiating risedronate. This is incorrect as in section 4.2.25 risedronate is demonstrated as being cost effective at all osteoporotic BMD levels. The Alliance recommends that the committee remove the need for DXA for risedronate if a patient has not received a DXA before initiation with alendronate. We recommend that no further BMD measurement is required in the over 75 years population.	The Committee agreed that in women aged 75 years or older, where the T-score needed to make treatment cost effective, was -2.5 SD or below, a DXA scan may not be required if the clinician considered it to be clinically inappropriate or unfeasible. (See FAD 4.3.25 (primary prevention) and 4.3.24 (secondary prevention)).
		Paragraph 4.3.33 (primary) and 4.3.34 (secondary) makes reference to the Committee's consideration of a concern raised by Servier Laboratories on the concomitant use of bisphosphonates with acid-suppressing medications. Elsewhere in these ACD documents (paragraph 4.1.35 Primary prevention) and in the Evaluation report the data used to assess this question is described as tentative, being of generally poor quality, open to confounding or not able to distinguish cause and effect and with several observations indicating usage is associated with both increased and decreased risk of fracture depending on the fracture site. In addition we would like to bring to the Committees attention that there is evidence for risedronate that PPI usage does not affect fracture risk. In light of the evaluation of this evidence, we believe that the part of Paragraph 4.3.33 (primary) and 4.3.34 (secondary) in which the Committee recommends caution before co-prescription of acid-suppressing medications and bisphosphophonates requires deletion, or at least, revision as it gives greater weight to this evidence than it currently warrants. The Alliance trusts that the Committee will appreciate the concerns expressed in this response. We hope that the Committee will be minded to make the necessary revisions in order to provide clear, pragmatic and implementable guidance for the NHS.	The Committee acknowledged the issues and concerns around co-administration of acid-suppressive medication and bisphosphonates. The Committee was not persuaded by the evidence and noted that the data are observational and not published in full, and different for different fracture sites and for different acid suppressors. It was also aware of analyses showing that acid-suppressive medication given in addition to risedronate did not increase fracture risk. The Committee did however agree that caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates. Please see FAD 4.3.34 (primary) and

Consultee or Commentator	Comment		Institute Response
			4.3.35 (secondary). The Committee also considered the effect of acid-suppressive medication on the cost effectiveness conclusions. It concluded that even if these effects were included it would not alter the recommendations. Please see FAD 4.2.18, 4.2.27 and 4.3.37-38(primary) 4.2.19, 4.2.29 and 4.3.38-39 (secondary).
Eli Lilly		Re: Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women and Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Thank you once again for the opportunity to respond to the osteoporosis appraisal consultation documents.	Comment noted.
		<u>Teriparatide</u> *Secondary Prevention* For secondary prevention we believe that all the relevant evidence was supplied and available to the Appraisal Committee. We note your comments regarding the exclusion of women on long term corticosteroid therapy (section 4.3.7) and hope that the data on teriparatide by Saag et al (N Engl J Med 2007;357:2028-39) will be considered during the development of the NICE clinical guideline. The clinical and cost effectiveness summaries are reasonable interpretations of the evidence.	Comment noted.
		In October 2004 one of the main grounds of Lilly's Appeal against the Secondary Prevention FAD (which became NICE Guidance 87) was that there was a group of patients who were younger than 65 years but who had a clinical need for teriparatide. Although this was rebutted by NICE at the time, we are pleased that this has now been recognised in the current ACD.	Comment noted.

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		With reference to whether the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS, we would like to understand why the recommendation for the use of teriparatide in patients who have had 'an unsatisfactory response' to bisphosphonates in TA87 has been removed; especially when section 4.3.32 of the current ACD states that 'the committee concluded that a change from the current recommendations for teriparatide (TA87) is not warranted'. We are concerned that there is no recommendation for the use of teriparatide in patients who do not respond to or who are treatment failures on bisphosphonates – this is where the product is used in real life. Patients eligible for teriparatide treatment have had multiple fractures and the vast majority have been initially treated with bisphosphonates. We would therefore like the recommendation for the use of teriparatide in patients who have had 'an unsatisfactory response' to bisphosphonates (in TA87) to be reinstated. Subject to such reinstatement, we believe that the recommendations would be a sound and suitable basis for the preparation of guidance to the NHS.	FAD section 1.4 (secondary prevention) amended accordingly.
		<u>Raloxifene</u> *Primary Prevention* For Primary prevention we consider that relevant evidence was supplied and available to the Appraisal Committee. The clinical and cost effectiveness summaries are reasonable interpretations of the evidence except once again for the omission of inclusion of the breast cancer benefit for raloxifene. We continue to maintain that the breast cancer benefit of raloxifene is of relevance in any assessment of its cost effectiveness. Raloxifene with the full economic consequences of avoided cases of breast cancer was cost effective compared to proprietary alendronate in younger women, and may remain cost effective against non-proprietary alendronate. We do not consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	The Committee considered it inappropriate to fully take into account the effect on breast cancer. Please see FAD 4.3.30 to 4.3.32 (Primary).

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		Secondary Prevention For secondary prevention we believe that all the relevant evidence was supplied and available to the Appraisal Committee The clinical and cost effectiveness summaries are reasonable interpretations of the evidence. We are satisfied that raloxifene is at least given equal status with strontium in the guidance. We consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	Comments noted.
		For your information, Eli Lilly and Company Limited has recently signed an agreement to transfer the marketing and distribution rights for raloxifene to Daiichi-Sankyo throughout Europe. However, the transfer of Marketing Authorisation is still pending. We will let you know when the licence has been fully transferred from Eli Lilly and Company Limited to Daiichi-Sankyo.	Comments noted.
Novartis		Re: Health Technology Appraisals for Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women And Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women Thank you for your letter dated 27th March 2008 inviting comments on the Appraisal Consultation Documents (ACDs) for the above appraisals. Novartis' comments fall under two main headings.	Comments noted.
		1. Complexity of Recommendations and Sequencing of Treatment Given the scope of the appraisals, a recommendation for generic alendronate as the initial treatment option for primary and secondary prevention appears to be reasonable. However, we have several concerns about the draft guidance on subsequent treatment post-alendronate. Firstly, the use of treatment threshold tables based on T-score, age and number of independent clinical risk factors introduces a significant level of complexity that will inhibit widespread implementation of the guidance by clinicians and local NHS organisations. Secondly, it is likely that many patients who require an alternative treatment following alendronate (i.e. those who are unable to comply or who are contraindicated/intolerant) will be ineligible for subsequent treatment until their underlying condition worsens to a point where they meet a T-score threshold for use of a second-line therapy. The ethical basis for providing a first line-treatment then withholding a subsequent treatment until a patient's condition worsens is highly questionable. Thirdly, the sequencing of treatments as it stands in the current ACDs appears to be incomplete. For patients who are either unable to comply with etidronate or who are contraindicated/intolerant, there	The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations. The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the

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		appears to be no subsequent recommended treatment. Sections 1.3 and 1.4 only refer to treatment options available after alendronate and risedronate.	alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention) Sections 1.3 of the FADs have been amended to take into account treatment options for people who cannot take alendronate and risedronate or etidronate.
		2. Need for a Comprehensive Osteoporosis Clinical Guideline Due to the considerable length of time that has elapsed since these appraisals began, the final guidance resulting from the ACDs will not cover all relevant treatment options. Since the scope of the appraisals was finalised, four new treatments have become available in the UK (zoledronic acid 5 mg [marketed by Novartis], ibandronic acid p.o., ibandronic acid i.v. and parathyroid hormone). These newer treatments offer the possibility of monthly, quarterly or annual administration, which represents an advance over the daily and weekly administration of the products covered by the ACDs. Whilst we appreciate that new drugs can occasionally become available during the course of an appraisal, this draft guidance now covers only a small proportion of the currently available treatment options, making it of limited value to clinicians and patients. Given this recent proliferation of treatment options and the complexity of the disease area, a clinical guideline that includes all of the currently available treatment options for all patient segments at risk of osteoporotic fracture (not only post-menopausal women) would be of greater value to clinicians than narrowly focussed technology appraisals. The NICE clinical guideline on osteoporosis is now “suspended” pending completion of the technology appraisals. However, we urge NICE to redouble their efforts to finalise and publish this guideline even in the absence of final technology appraisal guidance. NICE have focussed on clinical guidelines for a number of other complex, largely primary care managed conditions where multiple, relatively low-cost treatment options are available (e.g. hypertension, diabetes and COPD). We believe that clinical guidelines are also the most appropriate medium for dissemination of advice on the management	These drugs have not been referred by the Department of Health for appraisal to NICE. Newer interventions may be captured in the clinical guideline. Comments noted.

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		of osteoporosis. In the absence of a timely and comprehensive national guideline on the risk assessment, diagnosis and management of patients at risk of osteoporotic fractures, there is potential for patients to receive suboptimal care.	
		I hope that these comments are of value. If you require any further clarification, please do not hesitate to contact me.	Comments noted.
Roche		MULTIPLE TECHNOLOGY APPRAISAL – Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women Thank you for sending us the Appraisal Consultation Documents (ACDs) for the above technology appraisals. Our feedback is provided below as per the requested ACD response structure.	Comments noted.
		1 Whether you consider that all of the relevant evidence has been taken into account It is suggested in the ACD that there is a different willingness to pay for a QALY between primary and secondary prevention. The rational being that "in primary prevention where an asymptomatic group of adult patients with a high number needed to treat to avoid a fracture is under consideration" one would expect a lower willingness to pay than in secondary prevention where there is a smaller number under consideration. Rather than suggesting a different value of a QALY between the two analyses, we consider that the uncertainty around whether an individual is going to be suitable for treatment should be accounted for in the costs and benefits assumed in the model.	The consideration of uncertainty would still require the Committee to consider a suitable range of acceptable cost per QALY values. Please see FAD 4.3.15 (primary prevention) and 4.3.16 (secondary prevention).
		2 Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate There appears to be a discrepancy between the Evaluation Report and the ACD for primary prevention in the following subgroup: Age >75; 2 risk factors; T-Score -2.5 to -3.0; ICER: £13,380 The use of 2nd line bisphosphonates in the above subgroup appears cost effective with an ICER	Section 1.2 of the FAD recommends the use of risedronate for this group of women with osteoporosis aged 75 or older who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate.

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		below the £20,000 threshold and yet this is not recommended in the ACD. This appears to be inconsistent with the remainder of the recommendations, which are inline with the Evaluation Report results. Cost effectiveness estimates for etidronate were not provided in the Evaluation Report, however risedronate appears cost effective in subgroups of patients that are not recommended for treatment with "second-line bisphosphonates", risedronate and etidronate, in the ACD. This is due to the exclusion of guidance (in the ACD) on patients with more than 2 risk factors or osteopenia. One might interpret the recommendation tables (p. 5 of secondary prevention ACD and p. 4 primary prevention ACD) to mean that "second-line bisphosphonates" are not cost effective for the following subgroups, where according to the Evaluation Report they are: Secondary Prevention Age 50-69; 3 risk factors; T-Score -2.5 to -3.0; ICER: £24,852 to £18,141 Age 70-75; 2 risk factors; T-Score -1.5 to -2.5; ICER: £30,100 to £18,383 Age 70-75; 3 risk factors; T-Score -1.0 to -2.5; ICER: £28,875 to £9,236 Age >75; 2 risk factors; T-Score -1.0 to -2.5; ICER: £28,666 to £11,861 Age >75; 3 risk factors; T-Score -1.0 to -2.5; ICER: £14,943 to £2,390 Primary Prevention Age 65-69; 3 risk factors; T-Score -3.0 to -3.5; ICER: £12,348 Age 70-75; 3 risk factors; T-Score -2.5 to -3.0; ICER: £10,509 Age >75; 3 risk factors; T-Score -1.5 to -2.5; ICER: £19,171 to £9,220	In line with the WHO definition, the Committee considered women with osteoporosis to have a T score of -2.5 or below. Therefore scores higher than this figure were not included within the guidance. Section 1.2 (primary prevention FAD) recommends risedronate for women in the following groups who are unable to use alendronate: women aged 65-69 with 2 independent clinical risk factors for fracture and a T-score of -3.0 SD or lower; women aged 70-74 years with 2 independent clinical risk factors for fracture and a T-score of -2.5 SD or lower; women 75 years or older with 2 clinical risk factors and a T-score of -2.5 SD or lower. Therefore, except for the limitation of the appraisal only making recommendations on osteoporosis (T-scores -2.5 SD or lower), the current recommendations would cover women with 3 clinical risk factors at the same T-score threshold. The recommendations in section 1.2 of the secondary prevention FAD, would cover women with 3 clinical risk factors at the same T-score threshold (again, the appraisal only makes recommendations on osteoporosis (T-scores -2.5 SD or lower).

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			It should be also noted that risedronate, has a marketing authorisation for the treatment of osteoporosis, and not osteopenia.
		3 Whether you consider that the provisional recommendations of the appraisal committee are sound and constitute a suitable basis for the preparation of guidance to the nhs Aside from the points raised above the provisional recommendation appears a suitable basis for the preparation of guidance to the NHS We hope that our feedback is helpful to the Appraisal Committee in its subsequent deliberations.	Comments noted.
Servier		Thank you for the opportunity to comment on the appraisal consultation documents ("ACDs") for the technology appraisals ***Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women*** and ***Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women*** issued on 25 March 2008. On behalf of Servier Laboratories UK Ltd I have a number of comments on these documents. The comments are summarised in the box below:-	Comments noted.
		Certain patients who would ordinarily have access to alendronate are unfairly denied access to an alternative treatment if they cannot take alendronate Etidronate should not be recommended given its weak evidence base Risedronate efficacy evidence should not be pooled with that for alendronate The analysis of data submitted by Servier Laboratories on increased rate of fracture risk with PPIs should be applied to all bisphosphonates Bisphosphonates should not be recommended where the concomitant prescription of a PPI is required Alternative bisphosphonates should not be recommended as alternatives to alendronate where a patient is unable to take alendronate as the reasons for not being able to take alendronate apply across the class Hip-fracture data for strontium ranelate which was accepted by the EMEA and SMC should be accepted, particularly in the light of further supporting evidence of the treatment effect The ICER values and the compliance period for strontium ranelate should be amended to reflect the correct figures Clarification of the disutility values used for strontium ranelate should be provided Strontium ranelate should be preferred to raloxifene on the basis of the analysis conducted by the Institute	Please see specific response below.

Consultee or Commentator	Comment		Institute Response
		All risk factors should be treated equally rather than assigning an arbitrary value to some of them Permission to provide copies of the disclosable part of the economic model should be sought so that stakeholders should have access to the model The ACDs should be amended to avoid unjustified discrimination which breaches patients' human rights Strontium ranelate's innovative status should be recognised in the ACDs These comments are described in more detail below. Comments relate to Primary and Secondary Prevention ACDs.	
		1. Patients Not Able to Take or Intolerant of Alendronate The guidance in both ACDs discriminates on the basis of a patient's medical condition. It is clear from section 1 of both ACDs that patients who are contraindicated or cannot take alendronate must satisfy a lower T-score threshold than patients who are not contraindicated to and/or can take alendronate before they qualify for treatment. Similarly, patients who cannot take or do not tolerate other bisphosphonates must satisfy an even lower T-score threshold in order to access strontium ranelate. For example, a 66-year old patient with a T-Score of -2.5 (and who is therefore defined as having osteoporosis) and one clinical risk factor would be entitled to alendronate, but if contraindicated or intolerant of alendronate, would get no treatment at all until she reached 75 years of age and only then if she obtained a further clinical risk factor. Even then, she would only have access to risedronate and/or etidronate, which are unlikely to be suitable for patients who are contraindicated or intolerant of alendronate. This is an unjustifiable discrimination among patients. It is manifestly unfair to restrict access to medicines solely on the basis of whether a patient's physical and medical condition allows them to take the cheapest treatment on offer, when other effective and safe medicines are available. Clearly, many patients unable to take these drugs due to contraindication or lack of tolerance will be left without access to therapy. The Appraisal Committee should reconsider the guidance for patients unable to take alendronate for reasons of contraindication or lack of tolerance and make alternative agents, including strontium ranelate, available to these patients without having to comply with more restrictive criteria. A failure to do so unfairly disadvantages those patients unable to take one or more medicines solely on the basis of their medical profile. We note that a concern not to unfairly disadvantage patients on this basis is described in paragraphs 4.3.23 and 4.3.22 of the primary and secondary ACDs respectively, which the Appraisal Committee did take into account in that case.	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention).
		2. Etidronate Recommendation Section 1 of the ACDs (paragraph 1.2 of both ACDs) recommends the use of etidronate as a first-line treatment option for patients contraindicated to alendronate and as a second line option in patients unable to take alendronate.	The Committee considered that there was sufficient evidence to recommend etidronate. See FAD 4.3.26 (primary prevention) and 4.3.26 (secondary

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		This recommendation contradicts the statement on the weak evidence base supporting etidronate in paragraph 4.3.25 in both ACDs. Etidronate has no randomised controlled trial evidence, nor does it have a licence for the prevention of hip fracture. The Appraisal Committee's concern regarding the weak evidence base for etidronate is further demonstrated by the fact that it did not request an evaluation report on the cost-effectiveness of etidronate. It is internally inconsistent and unfair for only some of the recommended medicines to have been appraised with scrutiny. The Appraisal Committee should remove the recommendation that etidronate should be considered as an alternative first line or second line agent. Even if NICE is minded to recommend etidronate despite the weak evidence base, it should not do so until a full analysis for etidronate has been performed.	prevention).
		3. Risedronate Recommendation 3.1 Efficacy of Risedronate The Appraisal Committee has meta-analysed the evidence base for alendronate and risedronate and produced a post-hoc analysis as the basis for estimating the efficacy of risedronate. No justification has been provided as to why it could be considered reasonable to pool efficacy data from two different medicines. When questioned at the Appeal Hearing the Appraisal Committee Chairman was unable to provide an adequate explanation. [The statements recorded at paragraphs 23 and 24 of the Appeal Panel Decision on the primary FAD are not adequate justification for this pooling of products with potentially very different effect sizes]. Risedronate has been studied in clinical trials involving over 7000 patients. There is adequate evidence available on its effect on fracture risk. There is no justification for considering the evidence for these two medicines together. The Appraisal Committee clearly does not believe that risedronate can be pooled with alendronate when it comes to potential adverse effects as risedronate is recommended as an alternative to alendronate where alendronate is contraindicated, poorly tolerated or ineffective. This is inconsistent with the Committee's approach on pooling of data for the purpose of calculating a figure for relative risk. The base case for the cost effectiveness of risedronate should utilise the relative risk for risedronate on which the license for in the prevention of fractures in patients with osteoporosis was granted.	The Committee was also presented evidence from the individual interventions. The decision to use the pooled estimate in the modelling was based on advice from the Guideline Development Group as it was considered that the second generation bisphosphonates had an overlapping efficacy range and could be considered a clinical class.
		4. Bisphosphonate Use in Patients at Risk of Concomitant PPI Use <u>4.1 PPI use and altered fracture risk</u> As we have highlighted in past consultation phases, there is evidence of increased risk of fracture associated with PPI use with three independent studies, each with different designs that demonstrate statistically significant increases in the risk of fracture in patients taking this class of medication1,2,3.	The Committee acknowledged the issues and concerns around co-administration of acid-suppressive medication and bisphosphonates. The Committee was not persuaded by the evidence and noted that the data are observational and not published in

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		In addition to these findings a retrospective cohort study using the GPRD has been conducted to examine fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication (ASM)4. This research presents evidence that acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment. We are pleased to see that the Appraisal Committee have considered these data in the latest ACDs and now acknowledge that the various studies outlined above show a trend between acid-suppressive medication and fracture risk and conclude that "*caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates*". However, we do not understand why the Appraisal Committee has not also incorporated this conclusion into the overall recommendations in the ACDs. In support of the Appraisal Committee's decision not to incorporate the trend between acid-suppressive medication and fracture risk into the overall recommendations the Committee refer to an additional analysis that "*included the increase in fracture risk for the proportion of women for whom acid-suppressive medication may be co-prescribed*" (4.3.33 in the primary prevention ACD and 4.3.34 in the secondary prevention ACD). The Appraisal Committee then states, "*this analysis did not decrease the T-scores for alendronate to the T-scores established for strategies including strontium ranelate or raloxifene*". We are unclear as to what analysis is here referred to and we request that the Appraisal Committee provide details on this analysis. As set out above, we also request that the Appraisal Committee apply this analysis to risedronate and etidronate when considered as alternatives to alendronate, as this has been demonstrated to be a class effect across all bisphosphonates. In addition, we are disappointed by the unbalanced summary covering the data on acid-suppressive medication and fracture risk (4.1.35 in the primary prevention ACD and 4.1.41 in the secondary prevention ACD). We are particularly concerned by comments on the retrospective cohort study using the GPRD conducted to examine fracture risk in patients receiving concomitant bisphosphonate and ASM. In response to these comments we have enclosed the full study report (see Appendix A – this report remains academic in confidence and should be treated as confidential). In particular, the Appraisal Committee states that the design of this study is prone to confounding when in fact this study took into account an extensive list of potential confounders (see Table 4 of study report). As highlighted by the Appraisal Committee this study is not yet fully published but the key results from this study are now in the public domain as they have been published in a peer-reviewed abstract5. This was presented as an oral communication at the National Osteoporosis Society Conference on Osteoporosis on the 28th November 2007. We are working towards an anticipated publication of the full study by the end of June 2008, and we will notify you as and when this is published. Therefore, the current recommendations included in the latest ACDs do not go far enough. As we have stated previously, the Appraisal Committee could address this issue by providing guidance	full, and different for different fracture sites and for different acid suppressors. It was also aware of analyses showing that acid-suppressive medication given in addition to risedronate did not increase fracture risk. The Committee did however agree that caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates. Please see FAD 4.3.34 (primary) and 4.3.35 (secondary). The Committee also considered the effect of acid-suppressive medication on the cost effectiveness conclusions. It concluded that even if these effects were included it would not alter the recommendations. Please see FAD 4.2.18, 4.2.27 and 4.3.37-38 (primary) 4.2.19, 4.2.29 and 4.3.38-39 (secondary) Issuing safety considerations to treatments is outside the remit of NICE. The MHRA/EMEA is responsible for safety of drugs. Sections 4.1.35 and 4.1.36 (primary prevention FAD) and sections 4.1.41 and 4.1.42 (secondary prevention FAD) have been amended.

Consultee or Commentator	Comment		Institute Response
		that: Patients being considered for anti-fracture treatment and at risk of gastrointestinal side effects and use of acid-suppressive medication should be prescribed strontium ranelate. Patients who are currently taking a bisphosphonate and are co-prescribed an acid-suppressive medication to control the gastro-intestinal side effects of their bisphosphonate should be switched to strontium ranelate and titrated off the acid-suppressing medication.	
		4.2 Economic Analysis of PPI risk Furthermore, it is uncertain from Section 4.3.34 whether or not the new analysis referred to (but not supplied) was undertaken for newly diagnosed patients with and without a risk for developing GI disease and being prescribed a PPI or if patients were prescribed a PPI with certainty. For patients who have been on bisphosphonate treatment and have suffered a GI side effect and are being considered for a PPI in addition to the bisphosphonate, the elevation of risk as a result of prescription of a PPI cannot be described as 'small'. In this scenario, the treatment effect of the bisphosphonate is virtually negated by the addition of the PPI. If a patient has not been able to take alendronate without the addition of a PPI the cost-effectiveness of alendronate plus a PPI compared to placebo should be determined. Indeed the same analysis should be conducted for risedronate and etidronate to examine their place in therapy for patients of this type. A comparison with a non-bisphosphonate treatment compared to placebo would then be appropriate. Once again, we request that the Appraisal Committee make available for consultation the analysis referred to in Section 4.3.34. In addition, we request that the increased risk of being prescribed a PPI, especially in patients already at elevated risk of fracture, should be a matter noted in evidence, and should be applied to all bisphosphonates. In doing the cost effectiveness analyses, it would be appropriate to apply the elevated fracture risk to the cost and effectiveness of risedronate and alendronate in separate analyses.	The analysis referred to was included in the Decision Support Unit reports, which were sent out for consultation with the ACD, from page 19 onwards. Please also refer to the detailed comments above.
		5. Strontium Ranelate 5.1 Effect in Hip Fracture Section 4.3.26 states that strontium ranelate has 'non-significant' evidence of prevention of hip fractures. In fact, strontium ranelate has statically significant and robust evidence that it reduces the risk of a hip fracture by 36% in an appropriate patient population. This evidence was acknowledged by the EMEA and justified a license for the prevention of hip fracture and is further endorsed in the recently published guidelines for the treatment of osteoporosis in Europe6European guidance for the diagnosis and management of osteoporosis in postmenopausal women. The estimate of relative risk of hip fracture used by the Appraisal Committee in the economic modelling was produced in a study that was not powered to detect efficacy in hip fracture. The	Sections 4.3.27 of the FADs explain the Committee's consideration of the strontium ranelate data. The Committee did not accept the estimate of efficacy for strontium ranelate in preventing hip fracture from the post-hoc subgroup analysis, but accepted the statistically non-significant RR of 0.85 for hip fracture to acknowledge an effect on this important type of fracture. The post hoc subgroup did not fulfil the criteria

Consultee or Commentator	Comment		Institute Response
		sub-group analysis produced in co-operation with the EMEA did have the power to adequately assess a treatment effect on hip fracture and this is the appropriate relative risk to use in the economic analysis for this appraisal. In addition new data have been published that further validates the efficacy in the prevention of hip fracture by strontium ranelate. These data, collected from the TROPOS study, show that patients treated with strontium ranelate were protected from hip fracture five years (which has not been demonstrated for any other treatment) after the commencement of treatment, further reinforcing the data initially presented to the Appraisal Committee. Published peer reviewed abstract are attached in an appendix for your consideration7. Therefore, we request that the assumptions on the treatment effect of strontium ranelate in the prevention of hip fracture are amended accordingly.	specified in the guide to the methods of technology appraisals 5.9.5.
		5.2 ICERs The ScHARR report from February 2008 appears to contain some errors in reporting the ICER values. The table on page 17 of the report contains the same extremely high figure (£391,217) for strontium ranelate for all T scores and clinical risk factors. The same anomalous figure also appears in the table on page 13 for strontium ranelate for patients with a T-score of -3.5 to -4.0 and 2 clinical risk factors. We request that the correct figures are provided.	The Institute responds only to comments on the ACD and not the assessment report which is an externally commissioned document.
		5.3 Compliance Paragraphs 4.1.39 and 4.1.34 of the secondary ACD should acknowledge that the compliance rates reported were after 3 years of treatment with strontium ranelate rather than at 1 and 2 years reported for other drugs. Please amend this section with this information.	The FADs have been amended.
		5.4 Strontium ranelate recommended for patients who are intolerant of alendronate and risedronate It is inappropriate to recommend strontium ranelate only for patients who are unable to tolerate both alendronate **and** risedronate. PEM studies8 have established that the tolerability profiles of both alendronate and risedronate are similar. Therefore, it is likely that a patient who cannot tolerate alendronate is unlikely to tolerate risedronate. The Appraisal Committee should recommend strontium ranelate as the alternative medicine for patients unable to tolerate alendronate. Indeed, the effectiveness of strontium ranelate has been demonstrated in patients who have received prior bisphosphonate treatment9.	The Committee concluded that it was appropriate to recommend strontium ranelate for women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate. Please see FADs for more details.
		5.5 Disutility value We previously raised concerns regarding the disutility values applied to the various medicines under review in a letter of 3 March 2008 (a copy of which is enclosed with this letter). This letter was not forwarded to the Appraisal Committee meeting. It is still unclear whether the disutility of side effects for strontium ranelate was the same as that for bisphosphonates, which was set to 10-times the value of that based on the patient event monitoring study identified by ScHARR. The ScHARR report from February 2008 suggests, at page 9, that the disutility for strontium	The increased disutility was applied only to first line treatment with a bisphosphonate. See FAD 4.3.14 and 4.3.23 (primary prevention) and 4.3.14 (secondary prevention).

Consultee or Commentator	Comment		Institute Response
		ranelate has also been set to this level, despite the fact that strontium ranelate is not associated with the same serious side-effects observed for the bisphosphonates, and it is inappropriate to use the same disutility value for strontium ranelate as has been used for the bisphosphonates. The ACDs do not clarify whether the same ten-times multiplier used for the bisphosphonates has or has not been used for strontium ranelate. Servier Laboratories requests that the ACDs are amended to make clear that a disutility for bisphosphonates has not been applied to strontium ranelate and, if not, that the analysis of the relevant medicines is repeated to take into account the correct disutility figures (with appropriate explanations).	
		6. Positioning of Raloxifene in the secondary prevention ACD Raloxifene has no evidence for the prevention of hip fracture. Therefore, raloxifene clearly offers less potential utility as a treatment for patients with postmenopausal osteoporosis. Strontium ranelate has a license for the prevention of vertebral and hip fractures in patients with postmenopausal osteoporosis. Furthermore, although cost-effectiveness analysis was produced for raloxifene, indicating that it should not be prescribed except in those patients with extremely low T-scores (even lower than those for which strontium ranelate can be prescribed), the secondary prevention ACD recommends raloxifene simply as an alternative to strontium ranelate in all patients who could be recommended strontium ranelate. It is entirely inconsistent to produce a hierarchy of alternative treatments to alendronate based upon the ICER values for those treatments and then allowing one treatment to, in effect, take the benefit of the cost-effectiveness of another. If this is the case, strontium ranelate should be considered as an equal alternative to etidronate and risedronate, or even alendronate, without all the additional T-score, age and clinical risk factor requirements for treatment of a patient with strontium ranelate. In the light of these facts, strontium ranelate should be preferred to raloxifene in any treatment algorithm in the secondary prevention ACD.	The Committee agreed that the possible benefits of raloxifene in addition to fracture prevention meant that, in cases where alendronate and either risedronate or etidronate cannot be used, raloxifene could be recommended for the same groups of women for whom treatment with strontium ranelate is recommended. The FAD states that, in deciding between strontium ranelate and raloxifene, clinicians and patients need to balance the overall proven effectiveness profile of these drugs against their tolerability and other effects in individual patients.
		7. Assumption of 50% Effect on Other Risk Factors The assumption of reducing the treatment effect on fracture risk for clinical risk factors other than age, fracture status and BMD status by 50% is totally without evidence base. There is no reason to believe that medications do not lower fracture risk independently associated with risk factors other than age, BMD and fracture status. In the clinical trials of these licensed medicines randomised patients were enrolled with many risk factors apart from low BMD, older age and previous fracture. For example, the clinical trials of strontium ranelate included patients in both arms of the study with *familial history of a hip fracture, smoking* and patients with a distribution of body mass indices. *Propensity to fall* was not measured and so, through randomisation, would have been distributed between study treatment arms. A recent examination of the strontium ranelate studies demonstrated that the anti-fracture efficacy of strontium ranelate is independent of baseline risk factors10, a copy of which is enclosed. If medicines are less effective or not effective in reducing fracture risks cited by the Appraisal	The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant risk factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention).

Consultee or Commentator	Comment		Institute Response
		Committee then they should, consequentially, be more effective than demonstrated in the clinical studies in reducing risk associated with BMD, previous fracture and age. These medicines have demonstrated relative risks in trials where they have been burdened with being tested in populations with fracture risks that they could not, in fact, affect. Since we only have information on the effect of treatments in populations with all the fracture risk factors identified, it is logical to include all the fracture risk factors that patients are exposed to in the tested and licensed population and to assume that fracture risk reductions are consistent with those demonstrated in the clinical studies. To do otherwise significantly reduces the cost effectiveness of medical treatment unfairly and perversely restricts access to patients who could otherwise benefit from treatment.	
		8. Access to the Economic Model Thus far, the Appraisal Committee has not granted access to the economic model. We note that the Appeal Panel directed the Institute to request permission of the World Health Organisation ("WHO") to release the Institute from its undertakings in respect of the economic model. Please let us know whether this has been done, and supply a copy of the WHO's response and a copy of what is disclosable from the model. It remains our position that the stakeholder should be supplied with the economic model, in read only form if necessary, such that consultees can view and critique the assumptions made. You will, no doubt, be aware of the economic analysis published recently by Kanis et al which detailed the differences between the ICERs demonstrated by the model endorsed by the Appraisal Committee and one using a different set of assumptions11. The results of this analysis demonstrate that medicines for osteoporosis, including strontium ranelate, are more cost effective than characterised by the Assessment Group model. It is obvious that differences in assumptions are a key driver of the cost effectiveness analyses results. It is incumbent upon the developers of the economic model produced by the Assessment Group to address and justify differences in the results of these two analyses. To have one model not visible to stakeholders makes this discussion impossible To continue to deny access to the economic model adds to the lack of transparency of this appraisal and removes confidence that the decisions taken are fair to all parties.	The owner of the data has not given the Institute permission to release the academic in confidence information data within the model. The model therefore cannot be released.
		9. Human rights By refusing access for some patients to publicly-funded medicines, the ACDs breach those patients' human rights. Therefore, the Institute has failed to comply with its duties as a public authority and its own Equality Scheme (the NICE Equality Scheme and Action Plan 2007-2010). In the Equality Scheme, the Institute commits to ensuring that it complies fully with duties contained in the equalities and anti-discrimination legislation. It is a breach of a patient's right to life for the State (through NICE) to refuse to fund medicines for that patient where other patients with the same condition do receive funded medicine, in the absence of strong justification. In addition, selecting patients who qualify for access to treatment on the basis of age, the	The social value judgements document currently out for consultation recommends that NICE guidance should refer to age only when one or more of the following apply. • There is evidence that age is a good indicator for some aspect of patients' health status and/or the likelihood of adverse effects of the treatment.

Consultee or Commentator	Comment		Institute Response
		Appraisal Committee has produced ACDs that discriminate against patients on the sole basis of their age. Furthermore, the amended ACDs now also discriminate between patients based solely on whether they are contraindicated, or intolerant of, alendronate, i.e. based on their medical condition. Certain patients are thus discriminated against based on their age and/or their medical condition. The Institute has recognised that it has a responsibility for ensuring the elimination of discrimination on age *and other grounds* (page 12 of NICE's Equality Scheme). In the absence of a legal justification for this discrimination, the Appraisal Committee should remove restrictions to patients disqualified because of their age and/or their ability to take alendronate.	• There is no practical way of identifying patients other than by their age (for example, there is no test available to measure their state of health in another way). • There is good evidence, or good grounds for believing that, it is likely that, because of their age, patients will respond differently to the treatment in question. In this case age is closely related to fracture risk.
		10. Innovation It is incumbent upon NICE to account for innovation in decisions about access to medicines. Strontium ranelate is a totally different class of medicines to standard therapy in this condition and is an innovation especially for patients unable to take currently available medicines. Strontium ranelate is the only treatment that has been demonstrated to have a dual role in not only preventing bone resorption, but also promoting bone growth. The benefit of this innovative action has been demonstrated by the further analysis of evidence from the TROPOS study, indicating a protective effect five years later, as outlined above. The Appraisal Committee should acknowledge this innovation and grant access to strontium ranelate to patients denied it as a result of this guidance.	The Committee considered the cost effectiveness of the intervention and then considered the additional factors. In this case they were not sufficient to reconsider the recommendation.
		11. Conclusion We request that the Appraisal Committee take the points raised above into consideration and amend the ACDs accordingly. We remain available to discuss any questions you have or clarifications that you may need. [References] 1 Yu E.W. C. Shinoff, T. Blackwell, K. Ensrud, T. Hillier, D.C. Bauer. Use of Acid-Suppressive Medications and Risk of Bone Loss and Fracture in Postmenopausal Women. 2 Vestergaard, P., L. Rejnmark, L. Mosekilde. 2006 Proton Pump Inhibitors, Histamine H2 Receptor Antagonists, and Other Antacid Medications and the Risk of Fracture Calcified Tissue International Vol 79:76-83. 3 Yang Y-X, J.D. Lewis, S. Epstein, D.C. Metz. 2006, Long term proton pump inhibitor therapy and risk of hip fracture, JAMA, 296:2947-2953. 4 De Vries F, Cooper AL, Logan RF, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication or bisphosphonates alone. Osteoporosis Int. 2007; 18(Suppl 3):S261.	Comments noted.

Consultee or Commentator	Comment		Institute Response
		5 De Vries F, Cooper AL, Logan RF, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication or bisphosphonates alone. Osteoporosis Int. 2007; 18(Suppl 3):S261. 6 Kanis J.A., N. Burlet, C. Cooper , P. D. Delmas J.-Y. Reginster, F. Borgstrom, R. Rizzoli European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008 7 Reginster JY, K Brixen, C Cormier J Cannata. Strontium ranelate demonstrates vertebral and non-vertebral ANI fracture efficacy including hip fractures over 5 years in post menopausal osteoporotic women. Osteoporosis Int. 2007; 18(Suppl):S5-S27 8 Barrera BA, Wilton LV, Harris S, Shakir SAW. 2005. Prescription event monitoring study on 13,164 patients prescribed risedronate in primary care in England. Osteoporos Int., 16, 1989 1998; Biswas PN, Wilton LV, Shakir SAW. 2003. Pharmacovigilance study of alendronate in England. Osteoporos Int., 14, 507-514 9 Busse B et al. J Bone Miner Res. 2007; 22 (Suppl 1):S484-S485 10 Roux *et al* 2006Vertebral Fracture Risk Reduction With Strontium Ranelate in Women With Postmenopausal Osteoporosis Is Independent of Baseline Risk Factors. Journal Of Bone And Mineral Research. Volume 21, Number 4 11 Kanis, J.A., Adams, J., Borgström, F., Cooper, C., Jönsson, B., Preedy, D., Selby, P., Compston, J., The cost-effectiveness of alendronate in the management of osteoporosis Bone 2008 42 4–15	
		Appendices to consultation response also provided, including GPRD tables; GPRG Fracture study report; European PMO guidelines; Roux, 2006; Reginster, 2007	

Professional and Patient Groups			
British Society for Rheumatology	Letter 1	**Technology Appraisal Consultation Documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women** The British Society for Rheumatology (BSR) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. This letter has been prepared with the help of Dr Jon Tobias, Consultant and Reader in Rheumatology.	Comments noted.
	Letter 1	We wish to endorse the comments which have been forwarded by the National Osteoporosis Society (NOS). In particular we would like to add our support to the recommendation for the use of the WHO Fracture Risk Assessment Tool (FRAX). Given that the FRAX is evidence-based,	The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines

		and is designed for use across the spectrum including patients with and without fractures, we would have liked to see it form the basis of the present guidance. We were also disappointed at the inclusion of the stepped-intervention approach, by which patients considered suitable for alendronate may not be offered a readily available alternative if they develop side effects.	fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary) and FAD 4.3.37 (secondary). The stepped approach is required to ensure the effective allocation of NHS resources.
	Letter 1	The NICE guidance process has been an extremely positive influence on clinical developments in rheumatology, such as the use of anti-TNF-drugs. In contrast, the present guidance is seemingly out of touch with clinical reality, and there is a real fear that as it stands, it will be side-lined by other more practical approaches, and have little impact on the management of osteoporosis in the UK.	Comment noted.
	Letter 2	Technology Appraisal Consultation Documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women The British Society for Rheumatology (BSR) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. This letter has been prepared with the help of Dr Jon Tobias, Consultant and Reader in Rheumatology. We wish to endorse the comments which have been forwarded by the National Osteoporosis Society (NOS). In particular we would like to add our support to the recommendation for the use of the WHO Fracture Risk Assessment Tool (FRAX). Given that the FRAX is evidence-based, and is designed for use across the spectrum including patients with and without fractures, we would have liked to see it form the basis of the present guidance. We were also disappointed at the inclusion of the stepped-intervention approach, by which patients considered suitable for alendronate may not be offered a readily available alternative if they develop side effects. The NICE guidance process has been an extremely positive influence on clinical developments in rheumatology, such as the use of anti-TNF-drugs. In contrast, the present guidance is seemingly out of touch with clinical reality, and there is a real fear that as it stands, it will be side-lined by other more practical approaches, and have little impact on the management of osteoporosis in the UK.	 The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary) and FAD 4.3.37 (secondary). The stepped approach is required to ensure the effective allocation of NHS resources. Comments noted.
National Osteoporosis Society		**Appraisal consultation documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women** The National Osteoporosis Society thanks you for the opportunity to comment on Appraisal Consultation Documents (ACDs) further to the appeals on the final appraisal determinations for the primary and secondary prevention of osteoporosis.	Comments noted.
		The Society is extremely disappointed that despite the concerns that we have articulated in previous consultation responses, particularly on the 2006 ACDs for these appraisals, the	Comments noted.

		recommendations remain too complex and are unworkable. The tables of thresholds for selecting each treatment are too complicated to use in practice, the use of two classes of risk factors is not an evidenced approach and the challenge of stopping treatment if a patient becomes intolerant of alendronate is unworkable. Furthermore we are very concerned that NICE has failed to consider the recent publication of the World Health Organization (WHO) fracture risk assessment tool (FRAX) in its further consideration of these appraisals, even though undisclosed data "prepared under the auspices of the WHO" have been used in the context of the assessment group's economic modelling. This tool has been developed with support and input from world renowned experts, is endorsed by all of the major osteoporosis groups worldwide and is fully supported by the WHO. FRAX clearly represents the most accurate method currently available for the proper assessment of risk of fractures in osteoporotic patients. We simply do not understand why the appraisal is based on an incomplete measure of fracture risks in circumstances where FRAX now provides the standard approach for assessment. We believe that the approach currently followed in the ACDs, which disregards the significant development represented by FRAX is not in the best interest of patients or clinicians.	The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations. The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary) and FAD 4.3.37 (secondary). The stepped approach is required to ensure the effective allocation of NHS resources.
		As many of our comments overlap between your suggested headings, as previously we have separated our comments on these ACDs into specific areas which reflect our main points of concern. Where points relate to only one of the ACDs we specify which one accordingly.	Comments noted.
		Response to the appeal panel decision We are pleased that NICE has reconsidered the inclusion of all of the technologies under assessment in these appraisals and that the ACDs now include recommendations for treatment for people for whom alendronate is contraindicated or who are unable to tolerate it. However, we do have a number of concerns about how the recommendations for alternative first line and second line treatments have been incorporated, which we refer to below. Furthermore, there were a number of areas in the Appraisal Committee's assessment of the evidence where the appeal panel requested improved clarity and transparency. However, in important aspects the preliminary guidance in the two ACDs remains unclear and we therefore request further reasoning of the Committee's conclusion and/or disclosure of evidence, particularly in the areas identified below:	Comments noted.
		One of the points advanced at the appeal, was that we were unable to find any proper explanation around the Appraisal Committee's approach to mortality benefits associated with osteoporosis treatments in the context of the assessment of cost effectiveness. The Appraisal Committee was therefore directed to provide clarification (as requested in paragraph 44 of the appeal panel's decision documents for both primary and secondary prevention). However, it remains unclear from the ACDs how the Appraisal Committee has taken benefit in terms of mortality into account in reaching its conclusions.	FAD sections 4.2.8 (primary prevention) and 4.2.9 (secondary prevention) have been amended accordingly.

		We would also like further transparency around the use of the “ten times side effects” approach with reference specifically to raloxifene, strontium ranelate and teriparatide (secondary prevention only). The basis for the way in which such effects have been assessed and incorporated into the analysis is currently unexplained and we therefore request that clarification is provided in the next version of these recommendations.	The increased disutility was applied only to first line treatment with a bisphosphonate. See FAD 4.3.14 and 4.3.23 (primary prevention) and 4.3.14 (secondary prevention).
		In the context of the requirement (set out in paragraphs 6.2.6.10-11 of the “Guide to the Methods of Technology Appraisal”) to take into account various listed factors when considering whether a technology should be recommended in circumstances where the cost per QALY exceeds £20,000, it is clearly impossible for such factors to be adequately considered if the relevant cost per QALY figure has not been calculated. It is significant that the Appraisal Committee’s conclusions with respect to the cost per QALY values for the various treatments, following the modifications to the evaluation report, are not provided in the ACDs. It is unclear whether or not the Appraisal Committee did in fact calculate the relevant cost per QALY values in order to put itself in a position to consider the cost effectiveness of these technologies in the various circumstances, described in the ACDs. Furthermore, it is impossible for the Society or other consultees to consider whether the proposed guidance contained in the ACDs fairly reflects the available evidence if the conclusions of the Appraisal Committee are incompletely expressed. In these circumstances, we would ask to be advised of the Committee’s conclusions with respect to the costs per QALYs gained of the treatments and the circumstances under consideration, and to be given an opportunity to make submissions as to the validity of these findings before a final determination is issued. Although the appeal was not upheld on any of the individual points that we raised regarding the inputs to the economic modelling, we remain concerned about the conservative approach taken in determining the assumptions that have been used. We believe that the sum of these decisions has resulted in NICE making very conservative draft recommendations for the treatment of people with this disease.	For primary prevention, the Committee considered that the appropriate cost per QALY value was £20,000 (See FAD 4.3.15), which was used to calculate the net benefits. For secondary prevention, it was considered appropriate to use £30,000 (see FAD 4.3.16). The net benefit approach adopted by the assessment group is a rearrangement of the cost per QALY formula. Comments noted.

		Classification of risk factors We believe that the decision not to ensure that the recommendations could be used alongside FRAX is short-sighted and does not reflect how clinical practice is changing. The FRAX website is currently receiving around 23,000 hits every day and the publication of European guidelines will push this approach well into the operational arena. In sections 4.3.32 (primary prevention) and 4.3.33 (secondary prevention) the Appraisal Committee have provided reasoning for their decision not to use FRAX, however we do not believe that this it is an adequate explanation. FRAX provides an approach to opportunistic case finding which will ensure that treatment is targeted to those who are most at risk of fracture. Although we acknowledge that there is only limited evidence to show that identifying patients by FRAX and treating them results in fracture risk reduction, McCloskey *et al* (2007) showed positive results when patients selected on the basis of fracture risk as assessed by FRAX were treated with clodronate on the basis of FRAX risk. We do not believe there is any evidence whatsoever for the approach that the Appraisal Committee are recommending. Indeed it encourages poor clinical practice and is now hopelessly out of date.	The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary) and FAD 4.3.37 (secondary).
		The way in which BMD dependent and independent risk factors are used in the ACDs still gives us considerable cause for concern and their use in women under 70 has produced inappropriate and unnecessary barriers to treatment. We do not believe that use of the two categories of risk factors in this manner is an evidence based approach and indeed this divide does not consider the weight of individual factors in determining fracture risk. For women aged 65-69 years who have not yet had a fracture, it is clinically inappropriate to ignore the presence of risk factors that are indicative of low BMD when determining who requires a DXA scan, given the importance of BMD in determining fracture risk. To deny women under 65 years, who have multiple indicators of low BMD, a DXA scan because they do not have an independent risk factor is again inappropriate. The Society urges the Committee to take a more pragmatic approach to the use of risk factors.	Comments noted. NICE has not issued guidance on who should have DXA scan. Details of the suitability of people to DXA scanning will be provided by the clinical guideline.

		Additionally, while the so called “independent risk factors” used for the purposes of the economic modelling were based on WHO data, including but not limited to the factors listed in the ACDs at paragraphs 4.2.11 (primary prevention) and 4.2.12 (secondary prevention), the independent risk factors used by the Appraisal Committee to determine access to treatment (both ACDs) and DXA scanning (primary prevention) is limited to only some of those factors defined by the WHO data and some of those used for the purposes of economic modelling. This inconsistent approach appears arbitrary and the exclusion of certain established risk factors from those listed at paragraphs 1.5 of both ACDs, even though they are accepted by both the Assessment Group and the WHO as being significant, is unexplained. In particular we believe that the list of risk factors at paragraphs 1.5 and 2.12 of both ACDs should include: A wider range of conditions that cause secondary osteoporosis (including type 1 diabetes, thyroid disorders and organ transplantation for example). Use of prescribed medicines which are known to increase the risk of fracture (including aromatase inhibitors and some of the anti-epileptic drugs for example). Smoking; we remain unclear as to why the Appraisal Committee continues to fail to include current smoking as a risk factor, when smoking itself is included as a risk factor in the economic modelling (section 4.2.11 of the primary prevention ACD and 4.2.12 in the secondary prevention ACD). This approach will cause even more confusion now that FRAX has been published which does include smoking in its case finding approach. We urge the committee to ensure that it is clear from the recommendations that any list of risk factors provided is not exhaustive and that clinical judgements should be exercised to ensure that persons with risk factors that have not specifically been identified are not subject to discrimination. For completeness, we believe that the current framework of the ACD, which is very prescriptive in terms of the limited conditions that may be taken into account as risk factors for fracture (when considering treatment) or as a risk factor for low BMD (when considering DXA scanning) discriminates against persons who do not have those particular factors, but an equal risk of fracture because of other aspects of their condition or circumstances not specifically recognised by NICE. We would therefore ask the Appraisal Committee to reconsider its position.	The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention). The Committee chose a 50% efficacy assumption for risk factors other than age and T score on the basis that it was a compromise between two unlikely and unrealistic alternatives (0% and 100%). Please see FAD 4.3.13 (primary prevention) 4.3.14 (secondary prevention).

		Treatment of patients for whom alendronate is contraindicated, who are intolerant of alendronate or who do not respond to it	
		In the recommendations sections of both ACDs we notice that the specific circumstances for using a second line treatment (patients who are unable to comply with the special instructions or who have a contraindication to or are intolerant of) fails to include those patients who fail to respond to treatment. Although we suspect that this would relate to a significant minority of patients, there should be provision within the ACDs for them to go onto a second or third line treatment. We suggest that this should be added into sections 1.2 and 1.3 of the primary prevention ACD and to sections 1.2, 1.3 and 1.4 of the secondary prevention ACD.	Failure of first line treatment would present as a fracture and therefore the secondary prevention guidance would apply. In the secondary prevention FAD, teriparatide is now recommended for people who have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate (see FAD section 1.4). Teriparatide is the only alternative that could be interpreted as being more efficacious than alendronate and therefore a valuable alternative in these cases.
		The Society believes that groups of patients who have a contraindication to alendronate will be discriminated against under the current draft recommendations. As this population will often be frail and elderly, failure to treat them, or the use of differential treatment thresholds, could be perceived as ageism. Furthermore, individuals who are unable to comply with the instructions for taking alendronate due to pre-existing medical conditions (for example Crohn's disease, neurological diseases such as Parkinson's and stroke patients) could be unable to benefit from fracture risk reduction unless they were at a much higher risk than patients without these disabilities. A 64 year old lady, who experienced a premature menopause and whose mother had a hip fracture, and who has a swallowing disturbance following a recent stroke would be ineligible for treatment. Her friend who has not suffered a stroke, but who has the same risk factors would receive a treatment to reduce her risk of fracture. Although this is a very specific example it clearly shows that the rigid application of risk factors to determine access to treatment will produce anachronistic and discriminatory results. In particular proposing different treatment methods for different medicines means that clinicians will be in a difficult position when it comes to treating people with disabilities, who are unable to take alendronate, under these technology appraisals.	The Committee recommended that those who cannot take alendronate because of a contraindication or a disability should have access to alternative drugs in the same way as women who cannot tolerate alendronate (that is second-line treatment where the analysis excluded identification and assessment costs). Please see FAD 4.3.24. The Committee also concluded that all reasonable steps should be taken to provide women with a disability that makes it difficult for them to comply with the instructions for administration of alendronate with such practical support and assistance with administration (for example through district nurse visits or other home support services). See FAD 4.3.35.

		We remain extremely concerned about the stepped intervention thresholds for second line treatments for all women. Imagine if you were told that you are very likely to fracture due to osteoporosis (or perhaps have fractured) and have been prescribed generic alendronate. You have taken the treatment for a month but have had very uncomfortable side effects that have affected many aspects of your life. Imagine then returning to your GP and being told that you are going to have to wait for your bones to deteriorate over the next 2 or 3 years before you are bad enough to receive a freely available alternative therapy. Our members are outraged by this decision and the clinicians that we have consulted with during the preparation of this response believe that such a treatment strategy is unethical and would be poor clinical practice.	The Committee considered the potentially disutility of intolerance to alendronate and therefore accepted a base case-like analysis in second line use (where utility multiplier for side effects was applied to 2.35% of women in the first treatment month and 0.35% of women thereafter, rather than a higher rate of side effect assumptions applied to first line therapy). The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective use of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention).
		A woman who has been prescribed a first line treatment due to her high risk of fracture would be considerably fearful of fracture if denied a second line treatment. In this case a second line treatment is essential and the disutility associated with the fear of fracture and knowledge of the presence of this disease should be incorporated into the economic modelling.	The Committee agreed that when considering second line treatment, the base case assumptions for side effects could be applied (0.91 utility multiplier should be applied to 2.35% of patients in the first treatment month and 0.35% of patients thereafter). In addition the Committee removed the identification costs from the analysis. See FAD 4.3.14,,4.3.15, 4.3.16 and 4.3.23 (primary prevention) and

			4.3.15, 4.3.17 and 4.3.22 (secondary prevention).
		The cost per QALY threshold for primary prevention At paragraph 4.3.15 of the ACD for primary prevention, the Appraisal Committee states that a £20,000 cost per QALY threshold has been adopted in the case of primary prevention, because the population in question is "an asymptomatic group of adult patients". While, by definition, the patients eligible for primary prevention are asymptomatic, they suffer from a chronic disease which may result in osteoporotic fractures which "are associated with substantial disability, pain and reduced quality of life" (paragraph 2.6 of the ACD for primary prevention). The ACDs also recognise the lifetime risk of fractures in women over age 50 years and consider the very substantial morbidity and costs associated with osteoporotic fractures, particularly those of the hip. In view of the statement at paragraph 2.9 of the ACD that, following a hip fracture "a high proportion of women are permanently unable to walk independently or to perform other activities of daily living and consequently many are unable to live independently", we believe that the Appraisal Committee should reconsider the arbitrary imposition of a low £20,000 cost per QALY threshold for treatments that are intended to prevent such events occurring. It is, we suggest, inappropriate simply to categorise women who have not yet experienced an osteoporotic fragility fracture as being "asymptomatic" and the very substantial benefits in terms of preventing long term disability are self evident. Moreover, the imposition of a rigid cost per QALY threshold of £20,000 for patients who are currently asymptomatic from their disease, is inconsistent with the approach followed by the Appraisal Committee in the context of other appraisals. The appraisal that considered use of statin medication (TA94) assessed use of statins in the primary prevention of cardiovascular disease in patients who are asymptomatic. In that appraisal, there was no suggestion that the cost per QALY threshold should be limited to £20,000. In circumstances where the use of the QALY is intended to allow for comparison of different products across different therapeutic areas, we believe that similar criteria should be applied in relation to the primary prevention of osteoporosis as those applied in the statin appraisal. Furthermore, the statement that the population receiving treatment is "an asymptomatic group of adult patients" has less force when considering second line treatment for primary prevention. These patients are women who have already been diagnosed as suffering from osteoporosis and received treatment and accordingly the withdrawal of effective therapy may cause active harm to such patients. In the latter case we would strongly encourage the appraisal committee to, at a minimum, adopt a cost per QALY threshold of £30,000 per annum for second line treatment in the primary prevention ACD, as for secondary prevention.	For primary prevention the Committee considered that there were no additional factors (as described in the guide to the methods of technology appraisals 6.2.6.10) to consider and therefore the appropriate cost per QALY value was £20,000 (See FAD 4.3.15) which was used to calculate the net benefits.
		The positioning of etidronate as an alternative to risedronate The positioning of etidronate as a direct alternative to risedronate as a second line treatment is	The Committee considered that there was sufficient evidence to recommend etidronate. See FAD 4.3.2 and 4.3.26

		misleading. We commented on this in our response to the October 2006 ACDs noting that although we accept that etidronate is low cost we strongly question its prominence as an alternative first line treatment simply on economic grounds. Due to the lack of evidence for non-vertebral and hip fracture risk reduction we believe that the prescription of etidronate to many patients would be inconsistent with proper clinical care. At a minimum we would suggest that the following statement is included in both ACDs: "When choosing which treatment to prescribe the decision should be made on consideration of the treatment's efficacy and in consultation with the patient"	(primary prevention) and 4.3.26 (secondary prevention). Please also see FAD 1.2 "In deciding between risedronate and etidronate clinicians and patients need to balance the drugs overall proven effectiveness profile against tolerability and adverse events in individual patients".
		Release of the Economic Model and the WHO data used for the purposes of the cost effectiveness assessment In their findings, the appeal panel asked the Guidance Executive to request permission from the WHO to release the Institute from its undertakings relating to the academic-in-confidence data used to populate the economic model underpinning these appraisals. Further to the publication of FRAX, we requested a copy of the economic model in correspondence with you on 21st February 2008 and also by email on 11th April 2008 (sent to [redacted]) on behalf of the Society. We eventually received a response by email on Friday 18th April, which noted that: *"We* (NICE) *have sought permission from* [redacted]** for the epidemiological data, which have fed into the economic model, to be released from the academic-in-confidence agreement.* [redacted] *has replied that he does not wish to release NICE or ScHARR from the obligation to keep in confidence the information previously supplied. Although we do not regard this as a satisfactory situation, we are not in a position to override the wishes of the owner of the data"* However, we were under the impression that [redacted] is willing to make the algorithms available to NICE. We would welcome clarity on this matter as soon as possible as this issue continues to prevent us from fully considering the evidence behind these appraisals and has again limited our ability to comment on the economic modelling.	The owner of the data has not given the Institute permission to release the academic in confidence information data within the model. The model therefore cannot be released.
		Review Date The review date for both documents is July 2010. We believe that these documents will require review much sooner as they have failed to consider the impact of FRAX on clinical practice. Additionally with zoledronic acid, ibandronic acid and recombinant parathyroid hormone all now licensed for the treatment of osteoporosis, there is a need to further update the guidance positioning these treatments accordingly.	This date has been considered in regards to the availability of new data on the interventions. The drugs mentioned have not been referred to the Technology Appraisals Programme. Newer interventions may be captured in the clinical guideline.
		Although we have tried to be constructive in our approach to this consultation, it is becoming increasingly difficult for us to work with our stakeholders when developing our response. Many people feel that the NICE process is not working in the best interest of patients and they are now reluctant to contribute as they do not feel that their views will be seriously considered. In	Comments noted. Please be assured that NICE considers all comments and values input into the appraisal process.

		particular, the clinical community feel that the draft guidance is totally unworkable and that it encourages poor clinical practice which would be unethical. We urge NICE to ensure that they include osteoporosis specialists in the discussions at the next Appraisal Committee meeting to ensure that they can work with the Committee to improve clinical workability. We hope that these comments will be helpful in your further consideration of these ACDs and of course if we can be of any additional help, please do not hesitate to contact me.	
Royal College of Nursing		**Health Technology Appraisal** **Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women** **&** **Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women** **Royal College of Nursing** With a membership of over 400,000 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. RCN members work in a variety of hospital and community settings in the NHS and the independent sector. The RCN promotes patient and nursing interests on a wide range of issues by working closely with the Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations. **Response to Appraisal Consultation Documents** The Royal College of Nursing welcomes the Appraisal Consultation Documents for primary and secondary prevention of osteoporosis.	Comments noted.
		Primary prevention – We consider that the relevant evidence has been considered and the document is a reasonable interpretation of the evidence. However, there are some specific questions regarding the evidence base that are unclear: Whether sufficient analysis has been taken into account in the broader more complex clinic issues in relation to managing patients who have more risk factors (in effect those at very high risk of primary osteoporosis) yet do not adequately reflect in T score values? Additional issues related to providing for men Will there be a specific guidance for the management of patients requiring regular steroid therapies?	The guidance covers women only. The Committee did not consider it appropriate to make recommendations for the treatment of women on long-term corticosteroid treatment because this patient group is at greatly increased risk of fracture and therefore requires special consideration. Please see FAD 4.3.5 (primary prevention) and 4.3.7 (secondary prevention).

		Is there sufficient evidence to suggest identifying patients with 2 or more risk factors or other such tools that measure proposed in scoping such as fracture probability measures that might be more useful than DEXA? Is there any evidence that suggests which risk factors DEXA are not required as a decision to treat but should be used as a measure of efficacy and concordance?	The Committee's preferred approach was based on the available evidence and based its recommendations on age and risk factors to help direct DXA scanning. The Committee only considered women with osteoporosis for which DXA is required.
		Secondary prevention – In our view the relevant evidence has been considered and the Appraisal Consultation Document is a reasonable interpretation of the evidence. However, as above, there are some specific questions regarding the evidence base which are unclear: How should patients with more than one clinical risk factor be treated (e.g. different age bands +Rheumatoid Arthritis and corticosteroids for more than 3 months) +/- T score values? Was there sufficient analysis/evidence available that has been taken into account in the broader more complex clinic issues in relation to managing patients who have more risk factors (in effect those at very high risk of secondary osteoporosis) yet do not adequately reflect in T score values?	The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention). The recommendations attempt to take into account those at high risk in terms of age and BMD.
		The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted.
Royal College of Physicians		**Appraisal Consultation Documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women** Thank you for giving me the opportunity to comment on these ACDs in my capacity as a clinical specialist nominated by the Royal College of Physicians. As a result of the successful appeal against the FADs released in June 2007, I note that the scope has been increased to include risedronate, raloxifene, strontium ranelate and (for secondary prevention only) teriparatide. However, in other respects it appears that other recommendations made by the Appeal Panel have been largely ignored. The same is true of feedback that has been produced by stakeholders, patients and healthcare professionals over the past two to three years.	Comment noted.
		The economic model As discussed in earlier responses, despite a greater than 75% fall in the price of alendronate since the original guidance for secondary prevention in 2005 and the draft guidance for primary and secondary prevention in September 2006, the recommendations for the use of this drug have remained substantially unchanged. This has been achieved by alteration of some of the	Comments noted. The increased disutility was applied only to first line treatment with a bisphosphonate. See FAD 4.3.14 and 4.3.23 (primary prevention) and

		model assumptions, in the absence of new evidence, so that the cost-effectiveness of alendronate has apparently remained unchanged despite the fall in its price. Furthermore, these changes to the model have had a negative impact on the cost-effectiveness of the other treatments under consideration. The changes in the model have been detailed in previous feedback and include a progressive lowering of the relative risk reduction at the hip for alendronate, reduction of the disutility associated with vertebral fracture, and the introduction of a disutility for side-effects and its arbitrary ten-fold multiplication. In addition, the cost-per-QALY threshold for primary prevention has been lowered from £30,000 to £20,000.	4.3.14 (secondary prevention). For primary prevention the Committee considered that there were no additional factors (as described in the guide to the methods of technology appraisals 6.2.6.10) to consider and therefore the appropriate cost per QALY value was £20,000 (See FAD 4.3.15).
		Two of these changes are particularly relevant to the outcome of the appeal hearing. In their concluding remarks, the Appeal Panel stated that "the two circumstances of primary and secondary prevention of osteoporotic fractures were so similar that it would be advisable if the Final Appraisal Document for secondary prevention explained more clearly why a higher incremental cost per QALY had been accepted for secondary prevention as compared to that for primary prevention". The explanation provided in paragraph 4.3.15 does not meet these requirements. The description of the primary prevention population as "an asymptomatic group of adult patients" is an oversimplification. Many such women will be aware of their risk and be anxious about the possibility of suffering a fracture. Furthermore, if they are found to meet the criteria for treatment they will know that they have a diagnosis of osteoporosis and have a high risk of fracture.	The Committee was satisfied that the FAD sections 4.3.16 (primary prevention) and 4.3.15 (secondary prevention) explained its reasoning. Please see FAD 4.3.15. The Committee was not provided with a quantification (i.e. utility values) associated with the anxiety about the possibility of experiencing a fracture.
		The Appeal Panel also requested improved clarity and transparency in certain areas. One issue that was specifically raised during the appeal was the use of the 10x multiplication of the disutility for side-effects, not only for bisphosphonates but also for raloxifene or strontium ranelate. In the current ACDs this lack of clarity remains in the case of etidronate, raloxifene, strontium ranelate and teriparatide.	The Committee agreed that, when considering second-line or subsequent treatment, the base-case assumptions for side effects could be applied; that is, a 0.91 utility multiplier should be applied to 2.35% of patients in the first treatment month and 0.35% of patients thereafter. Please see FAD 4.3.14 and 4.3.23 (primary prevention) and 4.3.22 and 4.3.15 (secondary prevention).
		Differential treatment thresholds for different treatments In spite of the almost universal negative feedback from patients and stakeholders in response to the ACDs produced in September 2006, the Appraisal Committee has reverted to the concept of differential treatment thresholds for different interventions. The practical outcome of these is that some women who start treatment on alendronate but are unable to tolerate it have to wait for their disease to progress before they can receive another treatment. Furthermore, some women in whom alendronate is contraindicated will not be given alternative treatment despite being at high risk of fracture. Since the main second-line options, strontium ranelate and risedronate, are both effective and relatively cheap, this results in a situation that is distressing for patients and clinically unacceptable for doctors. Most seriously, it will discriminate against the disabled and	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of risedronate and strontium

		the frail elderly populations in whom alendronate is most likely to be contraindicated as a result of cognitive dysfunction (and therefore inability to comply with the dosing instructions) or physical frailty. For those women who have already sustained a fracture, the fear of a further fracture is substantial and disabling and denial of treatment to such women on the grounds of a cost of around £250-300/year cannot be justified. Notwithstanding these ethical considerations, the complexity of the recommendations for alternative interventions makes them clinically unworkable.	ranelate based on their usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention). The Committee recommended that those who cannot take alendronate because of a contraindication or a disability should have access to alternative drugs in the same way as women who cannot tolerate alendronate (that is second-line treatment where the analysis excluded identification and assessment costs). Please see FAD 4.3.24. The Committee also concluded that all reasonable steps should be taken to provide women with a disability that makes it difficult for them to comply with the instructions for administration of alendronate with such practical support and assistance with administration (for example through district nurse visits or other home support services). See FAD 4.3.35. The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations.
		Inclusion of etidronate as a second-line drug The ACD acknowledges the “weaker clinical evidence base” for etidronate and uses this as a reason for not updating the cost-effectiveness analysis for this drug. The recommendation that etidronate should be used as a second-line treatment alongside risedronate is contrary to the principle of basing recommendations on both clinical effectiveness and cost-effectiveness. There	The Committee considered that there was sufficient evidence to recommend etidronate. See FAD 4.3.2 and 4.3.26 (primary prevention) and 4.3.26 (secondary prevention). Please also

		are no prospective data showing reduction in either non-vertebral or hip fractures in postmenopausal women treated with etidronate, whereas such data do exist for risedronate and strontium ranelate. In their concluding statements, the Appeal Panel reiterate the need to provide guidance on the basis of both clinical and cost-effectiveness.	see FAD 1.2 "In deciding between risedronate and etidronate clinicians and patients need to balance the drugs overall proven effectiveness profile against tolerability and adverse events in individual patients".
		Use of FRAX™ to estimate fracture probability In recent feedback to the Appraisal Committee both the GDG and the National Osteoporosis Society recommended that consideration be given to basing recommendations about treatment on 10-year fracture probability, as in the FRAX™ algorithm, rather than T-scores, age and number of risk factors. FRAX™ is now widely available and increasingly used in clinical practice, both in the UK and in many other parts of the world. It is unfortunate that the Committee has chosen not to respond to this recommendation, since the intervention thresholds on which the recommendations in the ACDs are based cannot be translated into the 10-year fracture probability outputs generated by FRAX™ and will lead to confusion in clinical practice. According to the NICE website, an approach was made in January 2008 to obtain from the WHO access to the algorithms used in the construction of FRAX™, but it is stated in the ACDs that the Committee did not have access to these algorithms. Clarification around this point is required, particularly in view of the recommendation of the Appeal Panel that permission should be sought from the WHO to provide the Institute with this information.	The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary prevention) and FAD 4.3.37 (secondary prevention).
	Email	Please take this e-mail as confirmation that the Royal College of Physicians wishes to endorse the response of the British Society for Rheumatology and the submission of [redacted] to these ACDs.	Comment noted.
Society for Endocrinology		**Re: Health Technology Appraisals: Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women** The Society welcomes the opportunity to comment on these ACDs and hopes that the Institute will find our comments useful in developing your final guidance. We offer our general comments first followed by specific observations on each of the ACD	Comment noted.
		General comments 1. The Society remains concerned that the Institute seems to adopt the most conservative stance available whenever a choice of parameters in the cost effectiveness model has to be made. The result of this is the multiplication of errors all of which tend to be in one direction so that the final effect of the model is far too conservative and at variance with what is seen by any of us in clinical practice. By adopting this stance the Institute appears to be judging osteoporosis against a different set of criteria from those which would be used for the assessment of other disease states. 2. We were concerned to see the summary dismissal of the FRAX fracture risk estimator. This has been something that has been developed over a long period of time by the WHO and is likely	1) The Choice of parameters was based on the Committee's conclusions on the evidence presented. 2) Please see FAD 4.3.36 (primary prevention) and 4.3.37 (secondary prevention). 3) The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective

		to represent the international gold standard for the assessment of osteoporosis risk. Whilst we accept that the way that the risk generated by the FRAX calculator has not yet clearly been translated into a treatment decision we do believe that by such summary dismissal of something that is likely to assume major significance within the field in the very near future the Institute are likely to be producing guidance which may not be relevant to the clinical climate into which it is being released. 3. All our clinical members with whom we have consulted have expressed grave concerns about the way in which a patient who fails to tolerate generic alendronate needs to satisfy substantially more stringent criteria to become eligible for alternative therapies in either ACD. Whilst we understand the argument relating to cost effectiveness regarding this we do not believe that in reaching this decision the committee have taken sufficient cognizance of the adverse effect this is likely to have on the doctor patient relationship and the deleterious effect on an individual's quality of life when she knows that she is suffering from a condition which would justify treatment but has been told that as she cannot tolerate one treatment the NHS cannot "afford" the alternative unless her condition were to worsen. 4. We can see no reason in science or clinical practice why the committee have arrived at their list of risk factors. It is incomplete and if taken as an exclusive list is likely to mean that many patients who could benefit cost effectively from therapy will be denied that treatment. 5. We are concerned that etidronate is afforded equal status to that of risedronate despite the lack of convincing evidence for clinical effectiveness of the former against limb fractures. 6. The review date (2010) is likely to mean that new agents in the categories under consideration (ibandronic acid, zoledronic acid and PTH1-84) are not going to be subject to scrutiny by the Institute for a considerable length of time and may therefore not be used in a cost-effective manner in the NHS.	allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention) 4) Please see FAD 4.3.8 and 4.3.18 (primary prevention) and after consideration of the available evidence the Committee concluded that these were the significant risk factors. 5) The Committee considered that there was sufficient evidence to recommend etidronate. See FAD 4.3.2 and 4.3.26 (primary prevention) and 4.3.26 (secondary prevention). 6) These drugs have not been referred to the Technology Appraisals Programme. Newer interventions may be captured in the clinical guideline.
		Primary prevention 7. The guidance offered here is far too complicated to be of any utility in the day-to-day management of patients unless the Institute is also able to offer some form of computer program or other decision support aid which would assist clinicians through the morass of guidance. 8. The categorisation of risk factors into those that are associated with low bone density and those which are associated with increased fracture risk independent of bone density is not something which is recognised by the clinical community. Furthermore it is actually doubtful whether any of the risk factors so identified by the appraisal committee actually neatly fall into the boxes assigned to them. Those factors which are said to be risk factors for fracture independent of bone density are reasonably good at predicting low bone mass and the fracture risk associated with risk factors said to only predict fracture by virtue of bone density is not	7) The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations. 8) The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant factors. Please see FAD

		completely abolished by correction for bone density. It can therefore be seen that the committee have taken a simplistic and not scientifically justified view in their arbitrary categorisation of risk factors. Of course were the committee to abolish this unjustified distinction and merely base the guidance on the number of risk factors this would, at a stroke, substantially simplify the guidance and therefore make it much more likely to be adopted in clinical practice. 9. One of our members has examined the prevalence of the various risk factors identified by the committee in the Glasgow Fracture Liaison service. His observations would suggest that the actual prevalence of these risk factors in a large unselected fracture population is very low. Although we do not have as much similar data for an unselected population this does raise the possibility that the predictive value of these risk factors may not be particularly strong by virtue of their low prevalence within the British population. If that is indeed the case then one must wonder whether to seek out these risk factors will be cost effective any way.	4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention). 9) The evidence presented to Committee suggested that this guidance would capture the majority of patients.
		Secondary prevention 10. We are not aware of any change in the clinical evidence available to the appraisal committee from the time when they developed TA87. However there are many clinical scenarios where TA87 would have permitted the use of risedronate in which that agent is now explicitly precluded. Clearly it is appropriate that, given the huge fall in the cost of alendronic acid, the cheaper agent should be used in preference to risedronate. The committee however find no explanation of why something that was cost effective three years ago is no longer considered cost effective despite there being no change in the evidence available to them and a small fall in the price of risedronate. In the interests of transparency we would expect the committee to make explicit the reasons for this change of heart.	10) This appraisal has considered a different evidence base to TA87 and an updated cost-effectiveness analysis.
		We hope that the Institute finds these comments helpful and look forward to seeing your revised guidance. If you require any further information do not hesitate to contact us.	Comments noted.
Southwark Primary Care Trust		Southwark PCT's response to the following HTA is as follows; Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women	Comments noted.
		i) whether you consider that all of the relevant evidence has been taken into account Response: Yes	Comments noted.
		ii) whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate Response: Yes	Comments noted.
		iii) whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Response: Yes	Comments noted.

Royal College of Pathologists		Comments on the National Institute for Health and Clinical Excellence Health Technology Appraisal Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women And Alendronate, etidronate, risedronate, raloxifene and strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.	Comments noted.
		The comments that follow are given in accordance with the general headings requested by the Appraisal Committee	Comments noted.
		It is surprising that the documents comment on the fact that the guidance should be read in the context of the clinical guideline which is not available. The exclusions are inappropriate especially since a large amount of literature is available on primary prevention in women who are osteopenic.	The clinical guideline has been delayed until the publication of the technology appraisal. Recommendations for the treatment of women with osteopenia were not made for two reasons. Firstly that it was outside the remit of this appraisal and secondly because not all the drugs were licensed in the UK for the treatment of osteopenia. See FAD 4.3.6 (primary prevention) and 4.3.8 (secondary prevention).
		A number of studies now question the relevance of statements on adequate calcium/vitamin D intake and what constitutes being replete. It is essential that this document addresses what is deemed to be a level of optimal vitamin D and calcium intake with references to published work on the subject or that the statements made incorporate specific guidance rather than waiting for the clinical guideline.	See FAD 4.3.39 (primary prevention) and 4.3.40 (secondary prevention) the Committee suggested that the forthcoming clinical guideline on osteoporosis could specify how such assessments should be made and what supplementation should be prescribed.
		Work from Glasgow (McLellan AR et al Osteop Int 2003) questions the advisability of treating the elderly population without BMD measurements. Several other papers argue against this approach. I would recommend the committee read the work on the lack of age effects and fracture outcomes especially the NORA study which argued against an ageist approach (Siris E et al JBMR 2004).	The choice of DXA scanning is between the clinician and patient, see FAD sections 1.1 and it was required to produce cost effective recommendations.
		It is difficult to agree that the alternative therapy recommended by the committee as alternative treatments to alendronate require patients to be suffering a greater degree of severity of illness. Surely an alternative therapy should be prescribed under the same clinical conditions as the initial recommended treatment.	The second line therapies available have a much higher acquisition cost and are therefore not cost effective at the same level of fracture risk and

			therefore the Committee had to consider either a combined approach (FAD section 4.3.21–24 or different criteria for the second line treatments.
		HRT has been shown to be effective in several publications from the WHI study and yet has been ignored in this analysis	HRT was not part of the scope.
		Alendronate has been made the drug of choice in primary prevention. This commentator would like to see the evidence quoted from the literature that all generic forms of alendronate ("with the lowest acquisition price") have the same efficacy as Fosamax and evaluate the outcome data to support their use before such a recommendation is made. There is some data that suggests this may not be the case (see Epstein S et al Curr Med Res Opin 2003, Hough S. SAfr Med J 2006)	The various forms of alendronate should be bioequivalent and in addition uncertainty around the key parameters was considered see FAD 4.3.17 (primary prevention).
		The data on the effects of proton pump inhibitors on the efficacy of alendronate should be taken into greater account when making current recommendations.	The Committee acknowledged the issues and concerns around co-administration of acid-suppressive medication and bisphosphonates. The Committee was not persuaded by the evidence and noted that the data are observational and not published in full, and different for different fracture sites and for different acid suppressors. It was also aware of analyses showing that acid-suppressive medication given in addition to risedronate did not increase fracture risk. The Committee did however agree that caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates. Please see FAD 4.3.37-38 (primary) and 4.3.38-39 (secondary). The Committee also considered the effect of acid-suppressive medication on the cost effectiveness conclusions. It concluded that even if these effects were included it would not alter the recommendations. Please see FAD 4.2.18, 4.2.27 and 4.3.37-38 (primary prevention) 4.2.19, 4.2.29 and 4.3.38-39 (secondary prevention).

		It is very surprising that other efficacious agents have been excluded from use by these documents or given lower ratings based purely on cost. It appears that cost considerations are dominating this appraisal document and pronouncement. Surely the value of second line agents with effectiveness against fracture in post-menopausal women who are unable to tolerate the first line therapy should be recognised by the appraisal group.	The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness (see Guide to the methods of technology appraisals http://www.nice.org.uk/page.aspx?o=201973, section 6.2).
		In making the cost comparisons the etidronate assessment includes the costs of calcium but the alendronate costing does not appear to include this.	The drugs were appraised as indicated in their marketing authorisation. The summary of product characteristics for etidronate states that the drug is administered in 90-day cycles, with each cycle consisting of etidronate (400 mg/day) for 14 days followed by calcium carbonate (1.25 g/day) for the remaining 76 days (see FADs section 3.3).
		It would serve patients better if the NICE panel recognised that all bisphosphonates are best taken on an empty stomach where possible to aid absorption rather than between meals as stated in the document (see etidronate recommendations). Also it is recommended that patients should not take any other treatment along with the bisphosphonate.	The information included in the FADs is taken from the summaries of product characteristics.
		The recent identification of the serious side effect resulting from the use of strontium ranelate, DRESS, should be mentioned in the document (4.1.29).	This effect is reported in the summary of product characteristics, which is referred to in section 3.12 of the FADs.
		The type of screening programme that could be implemented should be re-considered. Costs effective analyses based on peripheral scanning and other approaches should now be assessed in the light of the published literature (Siris E et al Osteop Int 2006, Miller P et al J Clin Densitometry 1998, Miller PD et al Arch Int Med 2004)	NICE is not recommending a screening programme.
		Having identified the very serious nature of this condition within the document the current provisional recommendations are not a sound and suitable basis for the preparation of guidance to the NHS.	Comment noted.
		Additional Comments Related to the Documentation The Committee have disregarded the evidence presented that shows ways of improving persistence and compliance with bisphosphonate therapy for either primary or secondary prevention. For a small amount of investment a significant return can be obtained by using biochemical markers of bone metabolism or nurse/physician led feed back to patients on compliance (Delmas P et al JCEM 2007, Eastell et al JBMR 2003, Clowes et al JCEM 2004).	Comment noted.

		The committee should review the literature that exists in this area of the technology appraisal. The implications of this data should be included in the economic analyses with increased persistence factored into the calculations and assumptions made. Although hip facture is a “crucial goal” in the management of osteoporosis there is significant evidence pointing to the relatively “high cost” of vertebral fracture in terms of morbidity and the importance of reducing vertebral fracture incidence in patients with osteoporosis and this should not be underestimated by the committee (eg Borgstrom et al Osteop Int 2006). Once again the committee have ignored the science base on the effect of strontium on calcium measurement. Despite previous responses on this matter the documentation still incorrectly has a statement that strontium, in the doses currently prescribed, can affect the measurement of calcium in the blood or urine (6.3). At the concentrations of strontium prescribed there is no statistically significant effect on calcium measurement in the blood. There can be an effect at very high doses or immediately after a dose on urinary calcium excretion estimates but even this is minimal. I would like to see a reference quoted that backs up the current incorrect statement on this in the document.	Fractures of various types including vertebral fractures were considered in the economic model. See FAD 4.2.6 and 4.2.7 (primary prevention) and 4.2.7 and 4.2.8 (secondary prevention). Section 6.3 of the ACD has been deleted from the FADs.
Bone Research Society		Appraisal Consultation Documents on Technologies for the Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women Further to our joint appeal with the National Osteoporosis Society, the British Society for Rheumatology and the Society for Endocrinology, I am writing on behalf of our Society in response to these documents, which reached me only this week.	Comment noted.
		I cannot emphasis too strongly how much of a disaster for medical science it would be if you proceeded on the basis of these documents, which are in outright conflict with the now published Technical Report of the WHO “Assessment of Osteoporosis at the Primary health Care Level” (2008). This is even more the case because the methodological basis upon which NICE and WHO each based their evaluations is very similar. While you and I know that mathematical modelling can deliver quite different results according to the initial conditions used in two similarly constructed models, as well as if only slightly varying assumptions concerning causality are adopted, this will not be clear to the intelligent lay person. The impression will be created that NICE is cynically doing the UK Treasury’s dirty work while the WHO is the true guardian of the best interests of the British citizen who can now estimate her own risk with the web-based WHO FRAX model. You cannot allow that feeling to develop.	Comment noted.
		You and I know how much store the UK Department of Health (and the Treasury) place upon	Comment noted.

		their increased investment in medical science. Indeed, in his previous role the Prime Minister made it clear that the new arrangements for funding medical research had his very active support. As a Charity, devoted to research and to education of both the Public and of medical scientists, we acknowledge our interest in ensuring that this Government enlightenment continues. How galling then, for our Society, that we shall now have to conduct a rearguard campaign to deal with the outrage among patients with osteoporosis and their GPs that these documents will create. We shall also have to deal internationally with the fall-out from the growing world view that scientific truth in Britain's government circles takes second place to political or economic expediency.	
		As the documents currently read, you propose to maintain discrimination, despite the ruling of the NICE appeal Chair. Those who can take alendronate without unacceptable side-affects will receive treatment at a very much lower risk threshold (i.e. higher bone density T-score) than those who are precluding from taking it, through no fault of their own. In common speech, this maintains discrimination and contradicts the ordinary citizen's understanding of the meaning of the appeal ruling. What is needed is a common threshold for application to everyone considered, that reflects the average price paid for medication. Thus if 20% cannot take alendronate and require a therapy 5 times more expensive the average price of treatment will be: (1-0.2)*(price of Alendronate)+0.2*5*(price of Alendronate) = 1.8*(price of Alendronate)	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention).
		The new NICE Evaluation Report gives no evidence of having assessed a wealth of new evidence published in the peer-reviewed scientific literature since 2005. In contrast, the WHO Technical Report is much more up to date and employs the best modern meta-analytic techniques with a separate confirmation data-set for its systematic evaluation of world-wide data. Incidentally, the new data (since 2005) used in the WHO report had all been subjected to systematic peer review and had appeared in highly respected scientific journals BEFORE the WHO was satisfied that their report should be published, a sharp contrast with NICE's, in my view, scientifically insecure method of working	This appraisal has made use of the same epidemiological data that underpin the WHO report. The assessment report has been peer reviewed and published. In addition the whole process has been subject to extensive and transparent consultation – while respecting the confidentiality obligations required by the owners of the WHO epidemiological data.

		In my view also, you are unwise to ignore the FDA's considerable concerns about the quality of the evidence concerning etidronate. This has led to its continued exclusion from the USA and as you also know there is not a shred of evidence that etidronate prevents hip fracture.	The Committee considered that there was sufficient evidence to recommend etidronate, but that, in deciding between risedronate and etidronate, clinicians and patients need to balance the overall effectiveness profile of the drugs against their tolerability and adverse effects in individual patients. See FAD 4.3.26 (primary prevention) and 4.3.26 (secondary prevention).
		I could go on at length but I do not want to seem antagonistic. I would like to offer you a way out of this seeming black hole. The Society is willing to assemble a clinical team of experts free of unacceptable Conflicts of Interest to help reconcile the differences between the WHO and NICE documents as they currently read. Such a team has already been put together in shadow form with the active support of the Bone Research Society and its sister Societies. We hope we can proceed with this in collaboration with NICE and I recommend this to you. The scientific honour of England and Wales and the health of our NHS patients demand nothing less.	Comment noted.
Professional and Patient Groups (Experts)			
Clinical specialist Francis, R		As a Clinical Specialist nominated by the British Geriatrics Society (BGS) and National Osteoporosis Society (NOS), I am grateful for the opportunity of commenting on the latest Appraisal Consultation Documents (ACDs). I was extremely disappointed at the proposed guidance, which still appears to be inappropriately restrictive and clinically unworkable. Following the decision of the Appeal Panel in December 2007, I welcome the fact that the Appraisal Committee now recognises the role for other treatments in patients in whom alendronate is either contraindicated or not tolerated. Nevertheless, I am concerned about the increasingly demanding bone mineral density (BMD) T-score thresholds for the use of risedronate (or etidronate), raloxifene, strontium ranelate and teriparatide. This will lead to situations where a patient who is unable to take or tolerate alendronate is denied alternative treatment, because their T-score is not low enough to justify a second line agent. This will be difficult for a clinician to explain and justify to an individual patient. It is also potentially discriminatory in that patients who otherwise fulfil the criteria for the use of alendronate, but have a contraindication such as oesophageal disease, may be denied access to alternative treatment if their T-score is not low enough. In order to address this issue, the Appraisal Committee should consider requesting further refinements to the cost effectiveness modelling, to take into account the increased cost of alternative treatments in the proportion of patients unable to take or tolerate alendronate. This would at least ensure more equitable access to treatment for patients, with or without contraindications to or serious side-effects from	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention)

		alendronate.	The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations.
		Has all the relevant evidence been taken into account? The World Health Organization (WHO) has now published details of their model for predicting the ten year absolute risk of major osteoporotic fractures in general and hip fractures in particular (1). This Fracture Risk Assessment Tool (FRAX™) is now freely available (http://www.shef.ac.uk/FRAX), where it may be accessed by health care professionals, patients, carers and the general public. The risk factors and their appropriate weighting was established from nine large prospective population-based studies from around the world and then validated in a further 11 independent cohorts with a similar geographic distribution (2). Although most previous studies of the efficacy of different osteoporosis treatments in the prevention of fractures recruited patients on the basis of low BMD and/or the presence of fractures, one recently presented study shows that the bisphosphonate clodronate is effective in reducing fracture risk in patients at high risk of fracture identified by FRAX™ (3).	The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary prevention) and FAD 4.3.37 (secondary prevention).
		It is unfortunate that although the NICE ACDs have used some of the risk factors included in the WHO FRAX™ tool, smoking has been omitted from the list of risk factors and the threshold for alcohol consumption has been increased from three or more to four or more units daily. Although FRAX™ may have its limitations in not including falls-related risk factors for fracture, on the basis that these are not necessarily modifiable by osteoporosis treatments, it is more evidence based than the proposed NICE guidance, which has selectively 'cherry picked' and manipulated the WHO risk factors. I therefore suggest that the Appraisal Committee consider fully incorporating FRAX™ in revised guidance, particularly as clinicians in primary and secondary care are already showing considerable interest in this tool.	The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary prevention) and FAD 4.3.37 (secondary prevention). The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention).
		At the Appeal Hearing in October 2007, considerable concern was expressed about the cost-effectiveness modelling underlying the NICE Technology Appraisals, particularly as the model was not made available to the appellants. Although these criticisms were not upheld, considerable doubt remains about the validity of the assumptions made in the cost-effectiveness modelling, including the use of the ten year time horizon, the progressive lowering of the relative	These issues were discussed at the appeal heard in October 2007 and it was considered that the Committee's approach was appropriate. Please see osteoporosis- primary prevention

		risk reduction at the hip for alendronate, the reduction in the disutility associated with vertebral fracture, the different QALY thresholds for primary and secondary prevention and the ten-times multiplier for the side effects of treatment. Concerns about the cost-effectiveness model were also highlighted in a recent Editorial published in Bone, written by the respective Presidents of the International Osteoporosis Foundation and National Osteoporosis Foundation (4). Although the price of generic alendronate is even lower than that used in the previous cost-effectiveness modelling, the resulting guidance remains highly restrictive. It appears that the assumptions used in the model have been uniformly conservative, rather than based on a best estimate. An alternative cost-effectiveness model has now been published, which uses a similar approach to the NICE model, but more realistic assumptions (5). This suggests that osteoporosis treatment is more cost-effective than the NICE model suggests in many situations.	Appeal panel decision letter, 13 December 2007.
		Since work on these Technology Appraisals started in 2002, further treatments have been licensed for osteoporosis, including monthly oral and three monthly intravenous injections of ibandronate, annual intravenous infusions of zoledronate and parathyroid hormone 1-84. Although these agents are outside the scope of the current Technology Appraisals, I would urge that with the long delays in producing final guidance, serious consideration is given to including them at this late stage. This is particularly the case for intravenous zoledronate, which has been shown to be highly effective in reducing the risk of vertebral, hip and other non-vertebral fractures (6). Furthermore, it also decreases the risk of further fractures in patients with hip fractures, where a significant improvement in mortality was also seen (7). Compliance with annual infusion is also likely to be less of a problem than with daily or weekly oral bisphosphonate treatment.	These interventions were not included in the scope. It is possible they may be considered in the forthcoming clinical guideline.
		Are the Summaries of Clinical and Cost Effectiveness Reasonable Interpretations of the Evidence and are the Preliminary Views on the Resource Impact and Implications for the NHS Appropriate? As detailed above, there are a number of concerns about the cost-effectiveness modelling, which were highlighted in the recent Editorial in *Bone* (4) and by the NOS and other appellants at the Appeal Hearing. In particular, the different QALY thresholds for primary and secondary prevention appear illogical, as the opportunity cost in both situations is the same. The Appeal Panel stated that 'the two circumstances of primary and secondary prevention of osteoporotic fractures were so similar that it would be advisable if the Final Appraisal Document for secondary prevention explained more clearly why a higher incremental cost per QALY had been accepted for secondary prevention as compared to that for primary prevention'. Paragraph 4.3.15 of the Primary Prevention ACD does not address this issue adequately, as it describes potential candidates for such intervention as asymptomatic. Patients with osteoporosis but without previous fractures who attend my Bone Clinic are very similar to those who have already fractured, in that many are frail, older women with co-morbid conditions, where a major low trauma fracture would be as devastating if it was the first or a subsequent fracture.	For primary prevention the Committee considered that there were no additional factors (as described in the guide to the methods of technology appraisals 6.2.6.10) to consider and therefore the appropriate cost per QALY value was £20,000 (See FAD 4.3.15).
		Are the Provisional Recommendations of the Appraisal Committee Sound and do they	The Committee considered that there

		Constitute a Suitable Basis for the Preparation of Guidance to the NHS? Given the relative lack of data to support the efficacy of etidronate in decreasing the risk of non-vertebral fractures, I am surprised that it is placed along side risedronate as an alternative second line treatment. Although this bisphosphonate is inexpensive, it is now rarely used in clinical practice, because of the complicated cyclical regimen and the poor data on anti-fracture efficacy. I therefore feel that the limitations of etidronate as a treatment option should be highlighted more clearly.	was sufficient evidence to recommend etidronate. See FAD 4.3.26 (primary prevention) and 4.3.26 (secondary prevention). It also considered that, in deciding between risedronate and etidronate, clinicians and patients need to balance the overall effectiveness profile of the drugs against their tolerability and adverse effects in individual patients.
		Although the ACDs provide guidance on the use of second line treatments in patients unable to take or tolerate alendronate, there are no longer any recommendations on management of patients who fail to respond to treatment. Although this may be difficult to define, this was attempted in TAG 87, where specific guidance on the management of such patients was provided.	Non response of first line treatment would present as a fracture and therefore the secondary prevention guidance would apply. In the secondary prevention FAD, teriparatide is now recommended for people who have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate (see FAD section 1.4). Teriparatide is the only alternative that could be interpreted as being more efficacious than alendronate and therefore a valuable alternative in these cases.
		I am concerned that the ACDs list independent clinical risk factors for fracture and indicators of low BMD separately, as this is potentially confusing to clinicians without a major interest in osteoporosis. Most of these risk factors and indicators of low BMD predict fracture, even after adjustment for BMD. The exception is untreated premature menopause, which may be a risk factor for the development of osteoporosis in younger postmenopausal women, but its effect on BMD and fracture risk later in life is uncertain. Furthermore, the proposed guidance does not weight these factors, but merely uses the total number, age and BMD to guide treatment decisions. The full inclusion of the FRAX^{TM} would allow a simpler, more evidenced based approach to both the primary and secondary prevention of fractures.	The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.36 (primary prevention) and FAD 4.3.37 (secondary prevention).
		Finally, I should like to highlight the lack of data on anti-fracture efficacy of alendronate in women above the age of 80 years, but remind the Appraisal Committee of research indicating that risedronate and strontium ranelate are safe and effective in decreasing fracture risk in this age group (8,9), so should be more readily available to this population. Furthermore, neither the draft NICE guidance nor FRAX^{TM} use falls-related risk factors for fracture, on the basis that these are not necessarily modifiable by osteoporosis treatment. Nevertheless, prospective studies from the US, Australia and Europe show that the combination of low BMD and falls-	Comment noted. The Committee reached the conclusion that there was insufficient evidence for a proven treatment effect on fracture risk related to risk factors

		related risk factors confers a greater risk of fracture than either one alone (10,11,12). As 90% of non-vertebral fractures occur after a fall and the number of falls is related to the risk of hip fracture (13), consideration should be given to the inclusion of falls as a 'permissive' risk factor for low trauma fractures in older women, to avoid disadvantaging this group.	other than low BMD, age and prior fracture.
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		Nguyen T, Sambrook P, Kelly P, et al. Prediction of osteoporotic fractures by postural instability and bone density. Br Med J 1993; 307: 1111-1115. Cumming RG, Klineberg RJ. Fall frequency and characteristics and the risk of hip fractures. J Am Geriatr Soc 1994; 42: 774-778.	
Clinical specialist Selby, P		**Health Technology Appraisals: Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women – Comments on ACDs** Thank you for asking for my comments on this proposed guidance. I will use the headings under which you have sought comments but will comment on both ACDs together unless I state otherwise.	Comment noted.
		Has all the relevant evidence been taken into account? *1.* This guidance has been through so many iterations now that I believe that most of the evidence regarding clinical effectiveness has been taken into account. However there are some areas where there still seems to be insufficient note taken of the available evidence. Most important of these is the area of risk factors. The list of risk factors given by the committee is a small subset of all recognised risk factors. Also the distinction between those that work through BMD and those that are independent of BMD is much less well defined in real life than the committee appear to believe.	The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention).
		2. The committee are wedded to the notion that alendronate is less effective in patients with osteopenia. The evidence they cite is applicable only to the primary prevention setting as the interaction between BMD and treatment effect was seen in women selected on the basis of BMD alone. In those selected on the basis BMD and prior fracture no such interaction was noted. Para 4.1.9 in the secondary prevention ACD is therefore not appropriate.	Recommendations for the treatment of women with osteopenia were not made for two reasons. Firstly that it was outside the remit of this appraisal and secondly because not all the drugs were licensed in the UK for the treatment of osteopenia. See FAD 4.3.6 (primary prevention) and 4.3.8 (secondary prevention).
		3. The committee persist in applying an arbitrary increase in the incidence of side effects to try and capture the “unknown unknowns” they have not been able to model. This seems to be applied to all the technologies under review and it is difficult to see how it is justifiable to take the side effect profile of one drug and apply it across the board to all the other drugs under review. At the appeal we were assured that this was not applied to other agents. Paragraphs 4.3.16 and 4.3.17 respectively appear to suggest that this contrary to that assurance this has been applied across the board.	The increased disutility was only applied to the first line treatment with a bisphosphonate. See FAD 4.3.14 and 4.3.23 (primary prevention) and 4.3.14 (secondary prevention).
		Are the summaries of the evidence and the views on resource impact and implications appropriate? 4. The committee are already aware of my concerns regarding their apparently arbitrary	The Committee was not requested by the Appeal Panel (December 2007) to

		approach to selection of evidence and definition of inputs to the economic model. It is a matter of regret that this approach has been continued here. In particular it would appear that the committee, without any scientific or clinical rationale, has taken the position least favourable to treatment at every opportunity. Coupled with the additional hurdle of an arbitrary increase in side effects (see 3 above) it is unsurprising that the committee has arrived at a position that is unfavourable to intervention. Along with some colleagues I have recently published an economic analysis of osteoporosis treatment using more realistic assumptions which suggests that it could be much more cost effective to treat than the committee suggest (1). As a consequence I believe it is likely that following the advice of the committee will lead to many women being denied treatment that could be offered cost effectively.	re-consider the inputs to the economic model.
		Do the recommendations constitute a suitable basis for guidance to the NHS? In addition to the concerns I have on the validity of the assumptions on which the guidance has been based I also have several concerns about the way in which could be implemented. 5. Especially for primary prevention the guidance is far to complex to be easily used in busy clinical practice. The concept of different types of risk factor is alien to most people's understanding of the disease and the multilayered tables are very user unfriendly. Unless the treatment paradigm can be simplified or offered in more convenient form (eg simple program) then it is unlikely to be used.	The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations.
		6. Like many of the colleagues with whom I have discussed the proposed stepped guidance for women who are intolerant of alendronate I find it hard to see how these proposals can be meaningfully translated into clinical practice. Whilst I accept that the Institute has to give advice based on cost effectiveness it also needs to give guidance that is realistic in a clinical setting. The current proposals fail to do that and will be difficult to implement in practice. I do not see how I can easily explain to a patient who has been made ill with alendronate and is now worried about her osteoporosis and fracture risk that we cannot offer her any further treatment until she deteriorates as the alternatives are too expensive. Of course in TA87 risedronate was judged cost-effective as an alternative to alendronate. Whilst I realise that the fall in price of alendronate means that we should look to that as our first therapeutic choice I can see no explanation in the ACD as to why (in absence of any new evidence) something that was cost effective 3 years ago is no longer so.	This appraisal has considered a different evidence base to TA87 and an updated cost-effectiveness analysis.
		I hope that you find these comments helpful and look forward to working with you to ensure that the Institute eventually is able to produce meaningful and useful guidance.	Comments noted.

Other		

NHS Quality Improvement Scotland	Reviewer 1	**Section 1. Comments on the NICE ACD - PRIMARY** In this section, we are particularly interested in receiving your comments on the ACD under the following general headings: Whether you consider that all the relevant evidence has been taken into account. This ACD is long overdue. Unfortunately as a consequence of this – it hasn't included some of the more recent SMC –approved drugs such as intact PTH & iv zoledronic acid.	Zoledronic acid has not been referred to the Technology Appraisals Programme. Newer interventions may be included in the clinical guideline.

Given that the primary prevention ACD aims to reduce fracture incidence, it is instructive to report the prevalence of the risk factors, cited in this ACD among women who have actually presented with new clinical fractures. It would appear that a strategy that depends exclusively on possession of 1 or more independent risk factors for fracture – even assuming that these patients' fracture risk could be eliminated completely- is likely to fail to impact on fracture incidence, at least in women age 70+ or 75+. In those <65yr – the prevalence of these risk factors suggests that these independent risk factors are more relevant, provided alcohol access doesn't attenuate the efficacy of alendronate and provided the falls & fracture relationship associated with alcohol excess don't over-ride the potential fracture risk benefits of treatment.The extremely low prevalence of IBD (composite of Crohn's disease & ulcerative colitis) in our fracture population suggests that a strategy that uses this as a criterion will not impact on fracture incidence at all. Ankylosing spondylitis is also extremely rare in our population. Our data suggest that the primary prevention strategy proposed by NICE is not clinically relevant to our population.

Independent risk factors for fracture

	Parental (maternal) hip fracture	Alcohol excess	RA	
≥75 (n=2551)	4.5%	0.7%	1.9%	
≥70 (n=3806)	5.2%	1%	1.9%	
<65 (n=3117)	8%	5.8%	1.7%	

Indicators of low BMD

	BMI <22	IBD	Early menopause*	
≥75 (n=2551)	23.8%	0.7%	20.7%	
≥70 (n=3806)	21%	0.7%	22.1%	
<65 (n=3117)	13.8%	0.6%	25.7%	

* reflects hx of menopause<45 irrespective of retention of ovaries during hysterectomy; no data on use of HRT

Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence..

What is proposed by NICE is irrelevant to women who actually experience fractures in Scotland – see above data.

Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

These recommendations will be unlikely to impact on preventing fractures in Scottish women.

The Committee based its recommendations on epidemiological data from WHO and current clinical data for the UK. The Committee also heard evidence that the guidance would capture the majority of eligible women.

	Reviewer 1	**Section 1. Comments on the NICE ACD - Secondary** In this section, we are particularly interested in receiving your comments on the ACD under the following general headings: This ACD is long overdue. Unfortunately as a consequence of this – it hasn't included some of the more recent SMC –approved drugs such as intact PTH & iv zoledronic acid. The ACD is controversial because it recommends different treatment thresholds for different drugs – based on the cost of drug. The consequence of this is a scenario that is highly politically charged. If a patient doesn't tolerate generic alendronate (& I believe firmly that that is and should be first choice given its efficacy and relatively low cost) –then this ACD requires a significantly lower BMD to justify any alternative treatment to reduce fracture risk. It is doubtful if that is ethically justifiable – it is unlikely to be politically acceptable. Whether you consider that all the relevant evidence has been taken into account. This ACD suggests that treatment of women >75yr with fracture doesn't necessitate prior DXA. Among women ≥75yr with fractures (all sites), the percentages with osteoporosis, osteopenia & normal BMD are 50%, 44% & 6% respectively. There is a prerequisite to have confirmed osteoporosis to justify treatment in younger women – and yet there is an assumption that women ≥75yr will necessarily respond to blind treatment with alendronate. Our data suggest that 50% of such women will not have osteoporosis –is the potential for adverse effects justifiable given that it is unlikely that half those being treated empirically may not have prospect of deriving benefit? Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. See above Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Beyond treatment with alendronate – the sub stratification for treatment appears complex – to the extent of being impractical. The complexity is added to because of the further requirement for risk factors termed 'independent risk factors for fracture'. The relevance of this concession is debatable given the low prevalence of each of these. Among 8901 women age ≥50yr with fractures (all sites) presenting to the North Glasgow Fracture Liaison Service, the prevalence of the key risk' independent risk factors for fracture' is: Parental (maternal) hip fracture – 6.4%, RA (all grades of severity) – 1.9%, Alcohol excess – 3.1%. Only 9 patients overall had 2 of the required risk factors. At best this may a cynical veneer to create the illusion of addressing other aspects of osteoporosis risk – but in reality these risk factors are irrelevant to those women from	These drugs have not been referred to the Technology Appraisals Programme. The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness (see Guide to the methods of technology appraisals http://www.nice.org.uk/page.aspx?o=201973, section 6.2). See FAD 1.1 "…a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible." The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate

		the West of Scotland who do present with new fractures to our A&E and acute orthopaedic services. [NAME REMOVED]	based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention). The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations.
	Reviewer 2	**Section 1. Comments on the NICE ACD Primary and Secondary** In this section, we are particularly interested in receiving your comments on the ACD under the following general headings: Whether you consider that all the relevant evidence has been taken into account. In general I am happy that relevant evidence has been considered in this review. I do have some concern though that there is an acceptance that BMD measurement is not necessary in some situations over the age of 75 years. This guidance is restricted to the treatment of women with osteoporosis and specifically excludes women with osteopenia. Excluding women from BMD measurement implies that there is an expectation that these women will have osteoporosis. However it is well recognised that even in the context of women presenting with fracture a large proportion of elderly women do not have osteoporosis. This is illustrated for example by Seeman et al. who demonstrated that in a population of women over the age of 80 years presenting with fracture approximately one third did not have osteoporosis. This limitation is not acknowledged but should be. In general terms anti-osteoporosis therapies are most effectively used where BMD proven osteoporosis is present. This is because the absolute benefit of treatment is greatest in this context. This however is overly simplistic as a large proportion of women with osteopenia may be at equal (or higher) absolute fracture risk depending on what other fracture risk factors are present. These patients therefore will receive equal (or higher) absolute benefit of treatment with intervention. Since most fractures occur in osteopenic (not osteoporotic) women; these patients are disadvantaged by this guideline. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. In general I would accept the summaries of cost-effectiveness as reasonable interpretations of	Comment noted "…a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible." Recommendations for the treatment of women with osteopenia were not made for two reasons. Firstly that it was outside the remit of this appraisal and secondly because not all the drugs were licensed in the UK for the treatment of osteopenia. See FAD 4.3.6 (primary prevention) and 4.3.8 (secondary prevention). The model was based on the same

		the evidence. There is some conflict though between this document and the work carried out by WHO. WHO state alcohol use of 3 units per day – NICE state 4 units per day. NICE do not include current smoking as a risk factor whereas this is included by WHO. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. I am concerned about the differing levels of thresholds for intervention amongst the different treatments. Whilst these are consistent with the modelling used; these will pose difficulties in practical implementation. The implications of these thresholds is that if a patient cannot tolerate generic alendronic acid unless their BMD is sufficiently low they will then have to be told that they are no longer eligible for therapy. I do not think this is appropriate. [NAME REMOVED]	data as the WHO analysis however there were differences in the assumptions. The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention)
	Reviewer 3	**Comments on the NICE ACD - Primary** In this section, we are particularly interested in receiving your comments on the ACD under the following general headings: Whether you consider that all the relevant evidence has been taken into account. *A significant amount of evidence has been taken into account. I may have overlooked it but I did not see the agreement between T scores of less than minus 2.5 SD and drug effectiveness. Paragraph 4.2.6 mentioned a model prepared under the auspices of WHO and academic in confidence – is this where the link is made?* Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. *I can understand the summaries but I am not sure about the details due to my lack of*	The modelling assumed a constant relative risk across age and T score. An algorithm linking risk factors to absolute risk was developed under the auspices of the WHO and is now available (FRAX). The epidemiological data feeding into the WHO algorithm and the model used in the appraisal are from the same source. Comment noted.

		understanding between scores and drug effectiveness, Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. *I would welcome a clinical view point*	Comment noted.
	Reviewer 3	**Comments on the NICE ACD - Secondary** In this section, we are particularly interested in receiving your comments on the ACD under the following general headings: Whether you consider that all the relevant evidence has been taken into account. *A substantial amount of evidence has been taken into account* Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. *I cannot relate the precise and low T Scores to clinical evidence or drug effectiveness – could this be part of the fracture risk algorithm or is it elsewhere?* Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. *Since I am not sure of the clinical relevance of the low T scores, I cannot comment on whether the provisional recommendations are a suitable basis*	Comment noted. An algorithm linking risk factors to absolute risk was developed under the auspices of the WHO and is now available (FRAX). The epidemiological data feeding into the WHO algorithm and the model used in the appraisal are from the same source. Comment noted.
	NOS response via QIS	I attach a revised version of the document I sent yesterday, incorporating some material which arrived after I left the office last night. I also attach a letter for Carole Longson from NOS, which may be a duplication as they are commenting directly on the Appraisals. However, it is probably useful to have it passed on as it was channeled through QIS.	Comments noted.

Other (Guideline Development Group)			
Guideline Development Group		**GDG Response to Osteoporosis ACDs April 2008** The comments in this document are the considered response of the NICE osteoporosis guideline development group (GDG), NICE's other advisory body, that is developing guidance in parallel with these technology appraisals. Much of this response draws on the clinical expertise of key people in the osteoporosis field, all	Individual comments are addressed below.

		of whom are practising clinicians, specialist pharmacists or patient representatives. Under conditions of parallel development, the GDG has a responsibility to share its clinical expertise with the Committee in order that the appraisal recommendations are clinically meaningful and possible to implement, to the benefit of patients and the NHS. The GDG did not welcome the outcome of the appeal hearing in as much that the Committee, rather than the GDG, is now required to make recommendations for second-line treatments. This is an area that requires great clinical understanding and the GDG is concerned that the Committee is inexperienced in work of this nature. Therefore it is vital that the comments in this document are treated seriously. We address three main issues in this response: Firstly, the GDG is concerned about the medical ethics and clinical manageability of the ACD recommendations for second-line treatment; that is, giving a woman alendronate because she is at risk of osteoporotic fracture, and then, if she is intolerant of the drug, being forced to tell her that she can have no other drug until her risk increases. We consider how these neglected clinical and ethical issues can be quantified and translated into more appropriate recommendations for practice Secondly, the GDG doubts whether the clinical community will be able to cope with the complexity of the ACD recommendations, as they stand, and suggests that implementation will only be possible if an electronic tool is used. A prototype is considered. Thirdly, the GDG requests that the recommendations in the ACDs are changed so that it is obvious that they apply solely to the osteoporosis population, in order that these recommendations can be inserted into the guideline, without negating the guideline's recommendations on other populations.	Comments noted. Individual comments are addressed below.
		1. Second-line therapies The GDG does not consider that all of the relevant clinical evidence has been taken into account and does not consider the provisional recommendations contained in the ACDs to be sound. They do not constitute a suitable basis for the preparation of guidance to the NHS. <u>1.1. The problem</u> The GDG believes the recommendations for second-line therapies in both primary and secondary prevention are unethical and clinically unmanageable. The true clinical position has not been fully taken into account in the modelling and its interpretation. The GDG's ethical position is this: for a patient who is suffering from osteoporosis and at risk of a potentially life threatening fragility fracture, it is unethical to refuse to treat them except with a drug that they can not tolerate, when other effective drugs are available, **unless** the risks of the second-line treatment outweigh the advantages.	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the

		In primary prevention, there are also arguments surrounding the ethics of *causing* illness in a well person. For example, the woman who has intolerable gastrointestinal side effects from a drug, along with anxiety regarding her continued risk of fracture when that drug is withdrawn with no replacement treatment. The GDG's clinical position is, firstly, that each patient is different and when faced with drug intolerance, the clinician and patient need to work out what is the best option within certain constraints. There must be the facility for clinicians to apply their clinical knowledge to benefit the patient. Secondly, the GDG notes that it would be extremely difficult for a clinician to deny a patient a second-line drug when the clinician is aware that, not only is the cost step to risedronate or strontium ranelate relatively small, but that the cost of these drugs is relatively low in terms of other treatments given in primary care. This is illustrated as follows: if the only alternative drug to alendronate were teriparatide, most clinicians would think it acceptable to say to the patient, "*I'm sorry that you cannot tolerate our main drug for preventing fractures since you are at risk, but our other osteoporosis drug is extremely expensive and only suitable to be used when people have really bad osteoporosis*". The difficulty for clinicians in this field is that they do not find it credible that they can use this explanation if the second-line step would be to risedronate or strontium for instance. A further point is the question of adherence to therapy: Clinicians are currently stressing the importance of patients taking and continuing to take the medication provided for osteoporosis. Indeed data (Siris) suggest that if compliance falls below 50% then no fracture benefit accrues. GDG clinicians are concerned about the impact on compliance if the message of the appraisals is that they should simply stop therapy without considering the alternatives, which are well known to most patients, in the face of an adverse reaction. Some of these points are further illustrated in Appendix I by two examples relating to primary prevention. In secondary prevention, GDG clinicians believe that these ethical and clinical manageability issues are even more significant because the recommendations involve refusing to treat a woman who has already had an osteoporotic fracture.	costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention). The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations.
		<u>1.2. Proposed solutions</u> When making cost-effective recommendations for the NHS, it is necessary to attempt to model and quantify the clinical factors described above, but, so far, the GDG does not believe that they have been taken into account. The GDG therefore proposes the following:	Comments noted.

		1.2.1 For both primary and secondary prevention At the outset, the GDG reiterates that if more appropriate parameters had been used in the model, particularly by using the side effects parameters derived from the evidence in the ScHARR systematic review rather than inflating it 10-fold, there would still be a 'step' between alendronate and risedronate, but more patients would be cost-effectively treated second-line. With respect to the position taken in the current ACDs (i.e. using 10 x side effects for alendronate), the 10 x side effects assumption is even less tenable for risedronate as a second-line treatment for three reasons: The ACD recommendations group together patients contraindicated to alendronate with those intolerant of it. The SPCs clearly state that the contraindications for alendronate are greater than those for risedronate. In their consideration of the evidence (4.3.16 primary), the Committee attempts to justify further their assumption of the 10-fold factor in the side effects, by incorporating other issues such as: the probability that more GP time would be involved in identifying women with risk factors, and the likelihood that DXA scanning outside a clinical trial environment would not be as effective as in clinical trials. These factors are not appropriate for second-line therapies as they have already been taken into account first line. The only justification for giving risedronate second-line to patients who are intolerant of alendronate, is that these patients may be able to tolerate risedronate instead. Therefore the side effects profile for risedronate in these patients cannot be the same as for alendronate. **Thus, the GDG proposes that for both primary and secondary prevention, the sensitivity analysis used for second-line risedronate should be 1x side effects.**	The increased disutility was applied only to first line treatment with a bisphosphonate. See FAD 4.3.14 and 4.3.23 (primary prevention) and 4.3.14 (secondary prevention).
		1.2.2. For primary prevention only In this section, the GDG has attempted to model the clinical picture as represented in section 1.1 and Appendix I. To do this, we have considered two types of patient (represented by Mrs Jones and Mrs Smith in Appendix I). Both groups of patients have osteoporosis and have intolerable side effects from alendronate. The patients in one group also have pre-existing anxiety or depression - which may worsen on being told they are at risk of fracture but cannot be treated – or they may be at risk of developing anxiety for the same reasons. a) *patients with side effects and osteoporosis, but without depression or anxiety* The MAICER for primary prevention has been set at £20,000, because the situation is '*an asymptomatic group of adult patients with a high number needed to treat to avoid a fracture*' (section 4.3.15). According to the ACD recommendations, only those with osteoporosis may be treated with alendronate. However, for those women who have intolerable gastrointestinal side effects in addition to osteoporosis, the situation is no longer the same: the woman is no longer asymptomatic and her ill health can be considered to have been caused by the treatment. **Therefore, for these patients intolerant of alendronate the MAICER should be raised to £30,000.**	For primary prevention the Committee considered that the appropriate threshold was £20,000 (See section 4.3.15 of primary prevention FAD).

		b) *patients with side effects and osteoporosis, who also have depression or anxiety (or are at risk of these)* Women who have anxiety or depression, or who are considered at risk of these conditions if osteoporosis drugs are withdrawn, are likely to experience a further reduction in their quality of life if treatment is withdrawn. **The clinical workability solution is that these patients should be offered an alternative second-line treatment if the responsible clinician considers it to be clinically appropriate**. **The GDG recommends that the ACDs should take into account the factors described above for second-line drugs in primary prevention (1 x side effects for risedronate, £30k MAICER and the potential for a reduction in quality of life as a result of depression and anxiety caused or worsened by the withdrawal of treatment).** It is unclear what the combined effect these factors would be, but we note that the thresholds generally change by 0.5 SD for a MAICER of £30k (see current assessment report) and 1x side effects for risedronate has a similar effect (see assessment report January 2007). The effect of both factors needs to be determined, with the additional factor relating to anxiety taken into account as well.	The Committee was not provided with a quantification (i.e. utility values) associated with the anxiety about the possibility of experiencing a fracture. The Committee agreed that for second line treatments, base-case assumptions on side effects should be used.
		1.2.3. For secondary prevention only As mentioned in section 1.1., the ethical and clinical position regarding secondary prevention is more extreme for a number of reasons: the woman already has a fracture, with its associated pain and she has osteoporosis and intolerable gastrointestinal side effects and, arguably, a higher risk of anxiety/depression if drugs are withdrawn, because she has already had a fracture and fears another one. She also knows there is a higher risk of another fracture. In addition, there are some women with multiple fractures who are at even higher risk (both of further fracture and anxiety/depression). As in section 1.2.2, the GDG contends that the model has not taken into account the additional decrement in quality of life because of these factors. In addition, the intervention thresholds for second-line risedronate are likely to be too restrictive because of the assumption of 10x side effects. *Numbers of women* A further important point which is especially pertinent to secondary prevention (because of its higher T-score intervention thresholds), is to consider what proportion of women with osteoporosis treated with alendronate will not be permitted to receive risedronate second-line. This proportion depends on age and, from the ACD recommendations, the following can be determined: the over 75s do not need a DXA scan to get alendronate first-line, but the ACD recommendation implies they should have one to get risedronate or strontium ranelate. In fact, the assessment report shows it is cost effective for all over 75s with osteoporosis to receive risedronate and cost effective for those with 1 or more CRFs to receive strontium ranelate (although risedronate is more cost effective than strontium). The clinical workability solution is that all patients over 75 should be offered risedronate or strontium ranelate as alternatives to alendronate if the	The Committee agreed that in women aged 75 years or older, where the T-score needed to make treatment cost effective was -2.5 SD or below, a DXA scan may not be required if the clinician considered it to be clinically inappropriate or unfeasible (See FAD 4.3.17 and 4.3.25 (primary prevention) and 4.3.18, 4.3.24 and 4.3.28 (secondary prevention). Comments noted.

		responsible clinician considers it to be clinically appropriate. **The GDG requests that the recommendations are modified to take this into account (i.e. all over 75s who cannot tolerate alendronate should receive risedronate or strontium ranelate without the need for a DXA scan).** the 70-74s: the assessment report shows it is cost effective for all 70-74s with osteoporosis to receive risedronate second-line. 65-69s: the assessment report shows the treatment threshold for risedronate to be -3.0 SD for 0, 1 or 2 additional CRFs and -2.5 SD for 3 CRFs and so on. From data [redacted] **the number of women eligible to receive alendronate first-line, who are intolerant to alendronate but not eligible for risedronate second-line, as a proportion of all those with osteoporosis and a fracture and receiving alendronate, to be 4% (Appendix II)**. Contraindication of alendronate is age dependent, which may reduce this proportion further. Repeating the analysis using an assumption of 1 x side effects for risedronate, calculates the proportion not allowed risedronate second-line to be 3%. Taking into account both the reduced quality of life and the small proportion of women who would not be treated second-line, **the GDG recommends that all women with a prior fracture who are intolerant or contraindicated of alendronate should be offered risedronate second-line.** The recommendations on strontium and raloxifene should also be modified accordingly.	The increased disutility was applied only to first line treatment with a bisphosphonate. See FAD 4.3.14 and 4.3.23 (primary prevention) and 4.3.14 (secondary prevention). Recommendations were reconsidered with this alteration.
		2. Complexity of recommendations <u>2.1. The problem</u> The GDG is concerned that the recommendations in the ACDs are too complex to be readily interpreted and implemented by busy clinicians. For example, in primary prevention there are around 12 different recommendations for first-line treatment, depending on age and number of risk factors (of two types), 10 different recommendations on second-line and 10 more for third-line. Furthermore, there are a number of discrepancies or areas needing clarification, for example: i) it is implied that women over 75 years, who don't need a DXA scan for alendronate, should be sent for DXA before they can receive second-line treatment ii) women under 65 years can receive alendronate under certain circumstances, but may not receive second-or third-line treatment at all (or not until they fracture or reach 65 years) iii) it is unclear what happens if a woman has rheumatoid arthritis – does this count as both an independent risk factor and an indicator of low BMD (i.e. 2 risk factors)? Although the GDG agrees that the complexity is the correct interpretation of the evidence, it presents the clinician with an unworkable set of recommendations.	When guidance is published, the Institute also issues implementation advice and tools to support health care professionals in the implementation of the recommendations.

		2.2. Proposed solution The GDG is clear that the only way the ACDs' recommendations can be applied in clinical practice is for a computerised implementation tool to be developed. The NCC has produced a prototype using Microsoft Access and screen dumps of some examples are given in Appendix III. It provides a simple way of implementation (and tracking changes in a patient's treatment). **We would strongly encourage the Committee and NICE to consider this approach, as the alternative (many sets of tables) is too cumbersome to use**.	
		3. Wording of recommendations The GDG is conscious that the appraisals cover only part of the population at high risk of osteoporotic fracture and only some of the licensed interventions, and that the guideline covers the whole spectrum. Therefore, it is important that the wording in the appraisal recommendations does not prevent the application of guideline recommendations to these other populations. For example, primary prevention recommendation 1.1: *Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups: women aged 70 years or older who have an independent risk factor for fracture or an indicator of low BMD* ***and who also have a T-score of -2.5 SD or below.*** This reads that women who have a T-score above -2.5SD (i.e. osteopenia and normal BMD) should not be treated with alendronate. However, the assessment report clearly shows that it is cost effective to treat women aged 70-74 years with alendronate where their T-score ranges from -2.0 SD for no clinical risk factors (CRFs) to -0.5 SD for 3 CRFs. The GDG is aware that the ACDs state at the outset that they relate only to postmenopausal women who have osteoporosis, but experience shows that clinicians focus solely on the recommendations. The wording in the ACDs' recommendations appears to indicate confusion between the threshold for treatment and the inclusion criteria for the ACDs' population. The GDG is required to insert the recommendations, not the appraisals' inclusion criteria, word for word into the guideline, and the current wording would make this procedure difficult. **The GDG therefore requests that this is rectified as follows:** Recommendation 1.1 (primary prevention), by adding an asterisk as follows: *Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups:* *women aged 70 years or older who have an independent risk factor for fracture or an indicator of low BMD and who also have a T-score of -2.5 SD or below*.*	Although the GDG's suggested wording has not been adopted, other revisions have been made to the recommendations in order to improve clarity. Results of the model which relate to T-scores outside of the scope of the appraisal (that is, those -2.5 SD or higher) are presented in the evidence

		*those aged 65-69 years who have an independent clinical risk factor for fracture and a T-score of -2.5 SD or below** *etc* ** applies only to women with osteoporosis (a T-score of -2.5 SD or below).* In recommendation 1.2, the women intolerant of alendronate have already been determined to have osteoporosis, so it would be better to group together the inclusion criteria (primary prevention, women, postmenopausal, osteoporosis) as follows: *Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women with osteoporosis (a T-score of -2.5 SD or below): etc* In secondary prevention, recommendation 1.1 would better read: *Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with osteoporosis (a T-score of -2.5 SD or below)…* (or an asterisk could be used as in the proposed recommendation 1.1 for primary prevention). In recommendation 1.2 (secondary), the GDG believes that the table is somewhat misleading for the over 70s, in that the thresholds for cost effective treatment are not -2.5 SD: these are the inclusion criteria. Therefore, this recommendation should be written as: *Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women with osteoporosis* ***(a T-score of -2.5 SD or below):*** *who are unable to comply…***and** who are aged 70 years or older **or** who have a T-score age and number of clinical risk factors for fracture as indicated in the following table: Then table, but without the row for 70 or older. As noted in section 1.2.3 above, there is also a need to revise the recommendation for the over 75s in second-line treatments for secondary prevention. As mentioned in the GDG's previous correspondence, we envisage that the drug zoledronic acid is likely to be more cost effective as second-line therapy than risedronate, and may be more cost effective than alendronate for some patients as first-line therapy. However, we do not believe that the wording of the appraisal recommendations precludes the addition of guideline recommendations on other cost effective drugs not covered by the appraisals.	section of the FAD in order to be transparent. Where T-scores are above -2.5 SD in the results a table footnote has been inserted to highlight that recommendations can only be made for women with osteoporosis (that is, T-scores of -2.5 SD or lower). Footnotes have been added in, for example, 4.2.24 (primary prevention) and 4.2.25 (secondary prevention). Comment noted.

		Appendix I – sample case histories (hypothetical, but based on experience in general practice) Mrs Smith and Mrs Jones both have the same score in risk factors which entitles them to alendronate but nothing else. Both get gastrointestinal symptoms as a result of taking alendronate. Mrs Smith is a phlegmatic individual and a reluctant tablet taker. Two years previously her husband had a fatal gastrointestinal bleed following gastric symptoms as a result of taking diclofenac for his osteoarthritis. Mrs Jones is an anxious lady with a history of depression, despite this she is helping the GP to try to persuade her feckless daughter to have her three children immunised. She has always been anxious about her health and last year her sister was admitted to hospital after fracturing her neck of femur. She died one month later of MRSA contracted in hospital. Mrs Smith is far more concerned about the adverse side effects of tablets than she is about her fracture risk. It would be quite reasonable to suggest to Mrs Smith that in view of the problems with the medication the best thing to do is to stop it and monitor her osteoporosis. Mrs Jones is understandably petrified of the osteoporosis that she now knows she has. Not to allow Mrs Jones to try an alternative therapy would, in the author's opinion, be a dereliction of care sufficiently serious to justify disciplinary action. You do not need to have spent 20 years in general practice to realise that the harm caused by not prescribing an alternative is vastly different in these two cases.	Comment noted.
		Appendix II: proportion of women not treated second-line in secondary prevention [redacted]	Comment noted.
		Table 1 | Age	50- 55	55-59	60-64	65-69	70-74	75-79	80-84	Total
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		1. number with osteoporosis and a fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2. number with a fracture who can be treated with ALN (from ACD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		3. number with a fracture who can be treated with RSD 2nd line (from ACD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		4. number with a fracture who can be treated with ALN but are intolerant / contraindicated of it and who can **not** have RSD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		5. % of those with osteoporosis and a fracture, who are intolerant of ALN but can **not** have RSD 2nd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		6. Number with a fracture who can be treated with SRN 3rd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8%
		[redacted]									

[redacted]

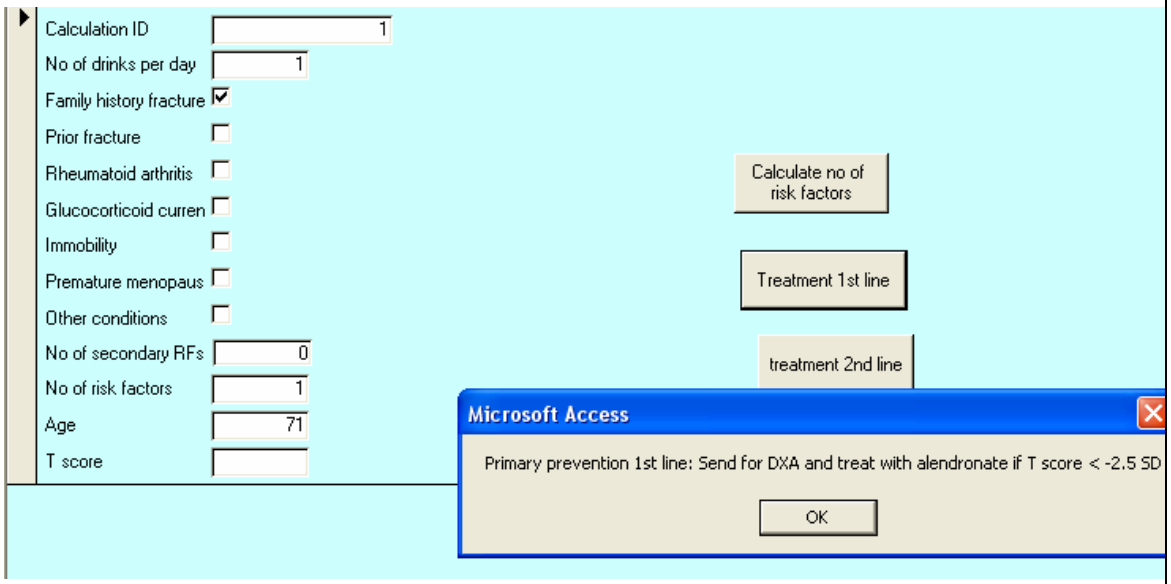
Table 2

Age	50- 55	55-59	60-64	65-69	70-74	75-79	80-84	Total
1. number with osteoporosis and a fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. number with a fracture who can be treated with ALN (from ACD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. number with a fracture who can be treated with RSD 2nd line (assuming 1x side effects)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. number with a fracture who can be treated with ALN but are intolerant / contraindicated of it and who can **not** have RSD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. % of those with osteoporosis and a fracture, who are intolerant of ALN but can **not** have RSD 2nd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

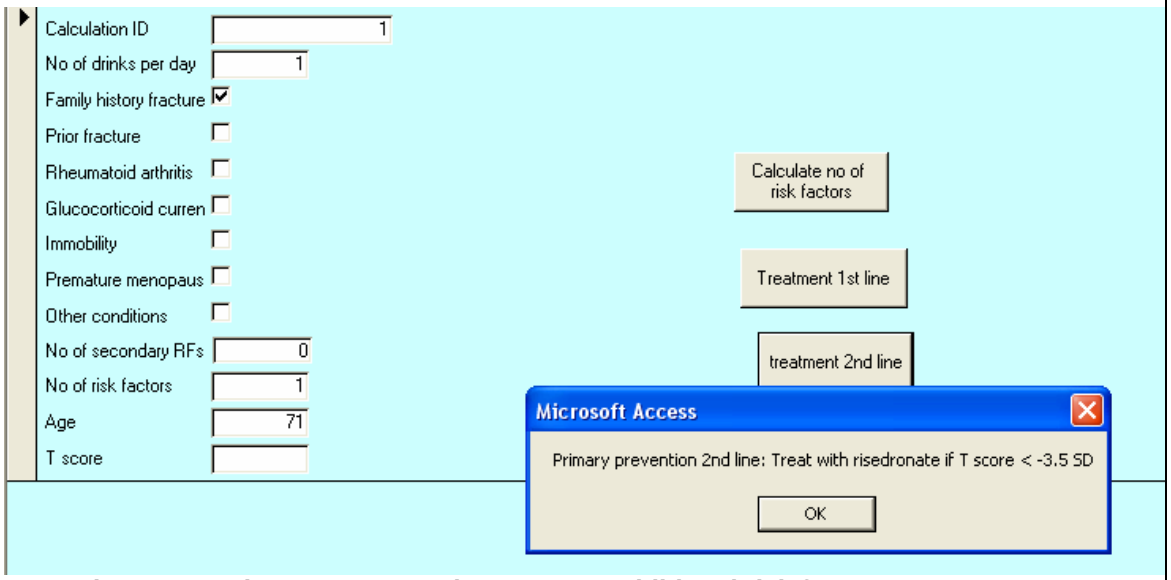
Comment noted.

Appendix III: examples of electronic tool to implement appraisal recommendations
Primary prevention, woman aged 71 years, 1 risk factor
advice for first-line

Comment noted.

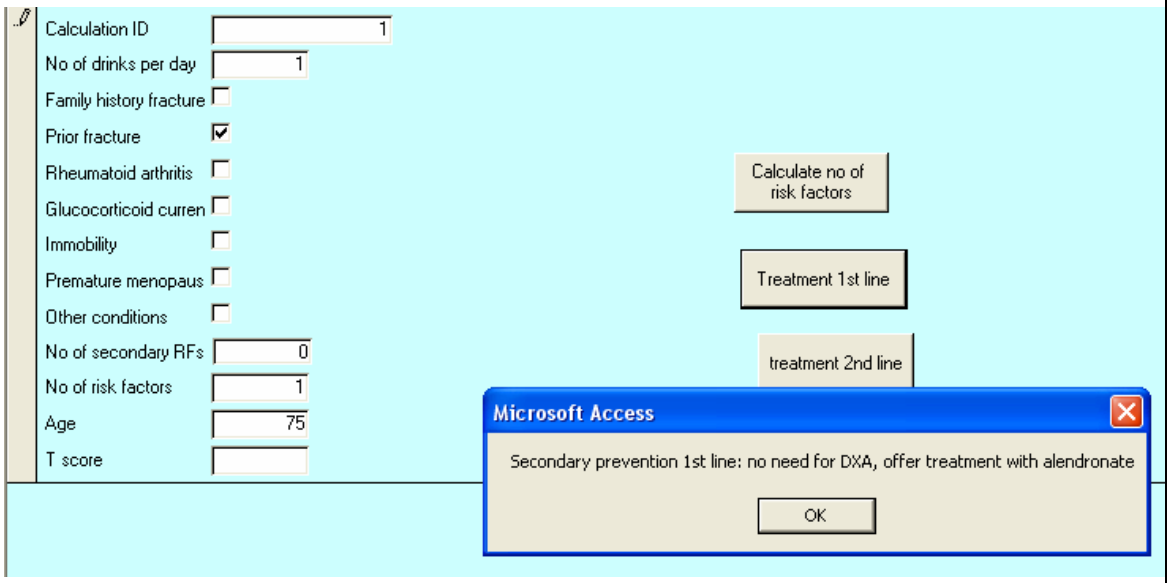


Advice for second-line

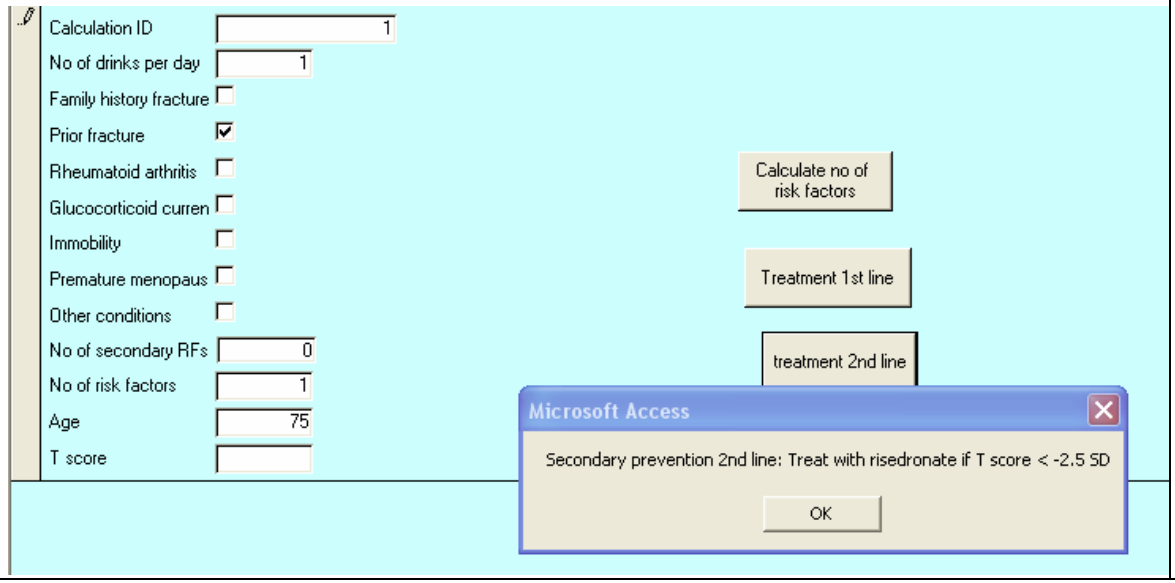


Secondary prevention, woman aged 75 years, 0 additional risk factors

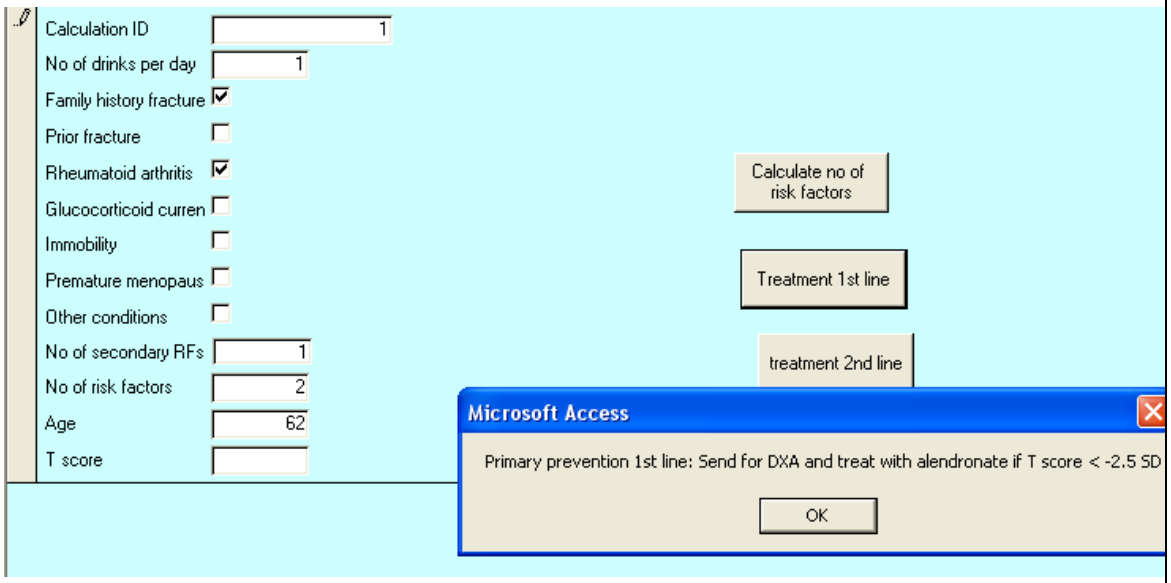
advice for first-line



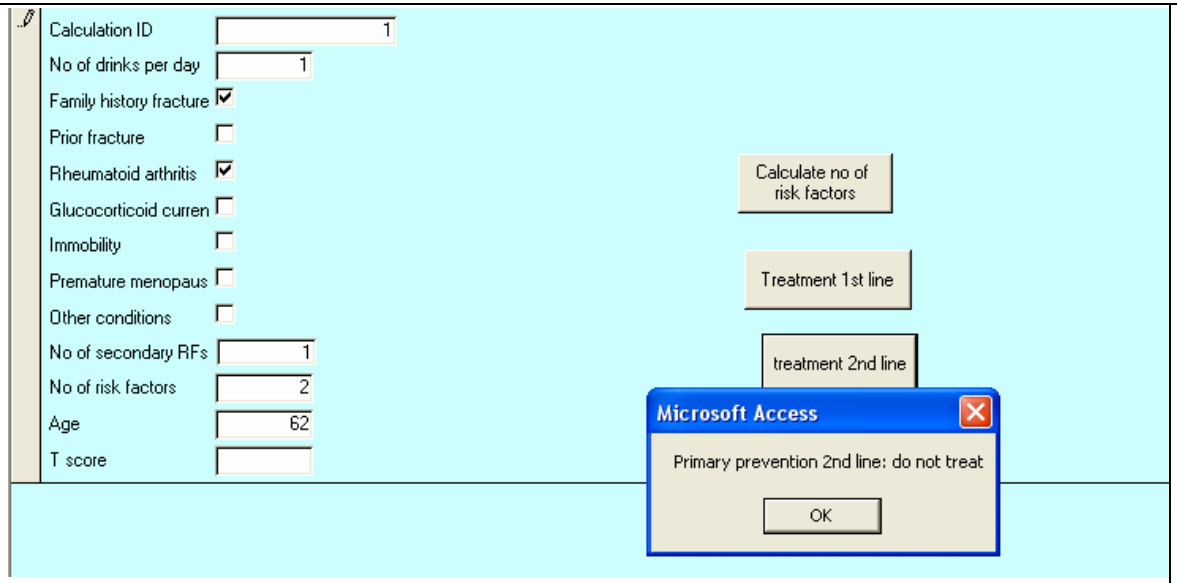
advice for second-line



Primary prevention, woman aged 62 years with premature menopause and rheumatoid arthritis (which appears to be in both categories of risk factor)
primary prevention



secondary prevention

Reply received but no comments:

- Other: Department of Health

Comments received from website consultation - on primary prevention ACD:

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
NHS Professional Representative Falls Prevention and Bone Health Section of the British Geriatrics Society	1	The NICE guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment have an adequate calcium intake and are vitamin D replete, calcium and or vitamin D supplementation should be considered. Further guidance however needs to be given as to the optimal dose in the elderly, but more importantly the target vitamin D levels that should be achieved to ensure optimal bone treatment, particularly in the presence of renal impairment, which is know to affect vitamin D metabolism. We are pleased that second line treatment has now been included in the consultation documentation, however : • we are concerned that the stepped intervention thresholds for treatment are too complex and will be difficult to translate into everyday clinical practice. • although specific guidance is given to whom second line drugs should be prescribed, it is unclear on the recommendations for those who fail to respond to treatment. • given the current evidence base for second line treatment, particularly in the elderly, the positioning of etidronate, risedronate, and strontium ranelate needs to be made more explicit. The classification of risk factors still gives us considerable cause for concern. We accept there are no clinical RCTs of falls interventions that have shown a reduction in fracture outcomes, however 90% of low trauma limb fractures are related to a fall. Previous falls and falls related risk factors should be included in the ACDs risk factors for fracture. Additionally, the list of indicators for low BMD is incomplete and should be broadened to include other diseases related to secondary osteoporosis and prescribed medications know to increase fracture risk (proton pump inhibitors, anti-convulsants).	See FAD 4.3.39 (primary prevention) and 4.3.40 (secondary prevention). The Committee suggested that the forthcoming NICE clinical guideline on osteoporosis could specify how such assessments should be made and what supplementation should be prescribed. The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention). The Committee reached the conclusion that there was insufficient evidence for a proven treatment effect on fracture risk related to risk factors other than low BMD, age and prior fracture.
	4	The cost per QALY threshold of 30K per annum should be used as with patients for secondary prevention.	For primary prevention the Committee considered that there were no additional factors (as described in the

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			guide to the methods of technology appraisals 6.2.6.10) to consider and therefore the appropriate cost per QALY value was £20,000 (See FAD 4.3.15).
NHS Professional Consultant Oncologist, prescribing bisphosphonates for women treated with adjuvant aromatase inhibitors for breast cancer	1	It is not logical to have different criteria to qualify for treatment with risedronate, etidronate and strontium over and above intolerance/ inability to manage alendronate when the primary criterion for the use of these drugs is intolerance of alendronate	The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness (see Guide to the methods of technology appraisals. http://www.nice.org.uk/page.aspx?o=201973, section 6.2).
	2	This is a fair summary	Comment noted.
	4	Whilst there are clearly differences in the cost-effectiveness of the various agents considered by the committee, the primary decision on treatment will be made in relation to the criteria for first line treatment. It will be very difficult for patients (and hence their physicians) who are intolerant of alendronate to be told that their condition must deteriorate before they qualify for treatment with an alternative drug	The Committee agreed that the use of the T-score and risk factor criteria was necessary for the cost effective allocation of NHS resources. See FAD 4.3.22 to 4.3.24 (primary prevention) and 4.3.21 to 4.3.23 (secondary prevention). The Committee considered that the alternative would be to combine the costs of generic alendronate, risedronate and strontium ranelate based on their estimated expected usage. However, this approach would result in more restrictive recommendations and consequently fewer women being offered treatment for their osteoporosis. See FAD 4.3.22 (primary prevention) 4.3.21 (secondary prevention).
	6	These are very sound recommendations	Comment noted.
	8	This seems reasonable as newer bisphosphonates are becoming available	Comment noted.

Consultee or Commentator	Section of ACD (if specified) - Comment	Institute Response

Comments received from website consultation - on secondary prevention ACD:

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
NHS Professional 1 Representing Falls and Bone Health Section of the British Geriatrics Society	1	The changes from the previous Draft ACD, to allow the possibility of pragmatic second line treatment, are welcomed by the Falls and Bone Health Section of the BGS. However, the appraisal document still does not draw an explicit link between falls and fractures. Over 90% of osteoporotic fractures occur following a fall. Falls interventions can reduce falls by around 30%. Bone protection should never be considered in isolation of falls prevention. In Section 1.5, Falls must be considered a BMD-independent risk factor for fracture. Even though not included in the economic modelling, there should be specific reference in the text to falls prevention (directly referencing NICE CG21 at least) to draw clinicians attention to the explicit link between falls prevention and fracture prevention. The other Sections are approved, however there are a couple of typos: In Section 1.2, need to change 1.7 to 1.6 in first bullet point. In Section 1.3, need to change teriparatide to strontium ranelate in the note below table.	The Committee reached the conclusion that there was insufficient evidence for a proven treatment effect on fracture risk related to risk factors other than low BMD, age and prior fracture.
	2	2.11 Should include specific reference to assessment of falls risk. It is good clinical practice to consider falls risk when measuring BMD (see, for example, BOA/BGS Blue Book, NICE CG21).	See response immediately above.
	6	Given the paucity of evidence for non-vertebral fracture prevention with teriparatide, further RCTs are required to demonstrate significant reduction of hip fracture. Although this is now unlikely, given that teriparatide has obtained a license, NICE is in a position to make such a recommendation.	The Committee concluded that the evidence is sufficient to make a recommendation for teriparatide for women at high risk of fracture (FAD section 4.3.33 (secondary prevention)).
	8	In view of the introduction of Ibandronic acid and Zoledronic acid, the Guidance Executive should consider reviewing the technology for secondary prevention of osteoporosis at an earlier date. Both drugs offer alternative modes of delivery that may reduce the likelihood of adverse effects. In addition, Zoledronic acid is the only bisphosphonate with evidence for reduction in mortality, as well as in vertebral and non-vertebral fractures.	These two drugs have not been referred by the Department of Health for appraisal to NICE. Newer interventions may be captured in the clinical guideline.
NHS Professional 2 Consultant	1	These recommendations will be very difficult to put into practice without a dedicated clinician interviewing and assessing every patient. What would the treatment algorithm look like? How will this be	The Institute will develop implementation advice and tools to support health care professionals in the implementation of the recommendations.

Rheumatologist	5	It will prove very difficult to establish compliance with such complicated guidance.	The Institute will issue audit advice as part of the Implementation advice.
	7	It would be a more logical approach to determine the level of	Incomplete comment.
NHS Professional 3 Formulary Pharmacist	1	section 1 - could details of what constitutes adequate Ca & Vit D supplementation be specified? section 1.3 refers to strontium and raloxifene however at the bottom the table it gives explanation of superscript b as: b Treatment with teriparatide or raloxifene is not recommended. Surely this should be: b Treatment with strontium or raloxifene is not recommended? I have a consultant who thinks you are recommending teriparatide in women over 50.	Comment noted, FAD text corrected accordingly.
	3	section 3.3 Didronel ia actually Didronel PMO	Drug information is taken from the British National Formulary and summary of product characteristics.
NHS Professional 4 Consultant Rheumatologist	1	Explain adequate Ca and vit D. Most GPs dont know. All trials give supplements. DEXA:Say if you mean lowest of L1-4 or hip.Or if you mean lowest of individual vertebral bodies or femoral neck? 1.2:Do you mean risedronate or etidronate? 1.3: raloxifene or strontium I think 1.4: teriparatide trails show benefit in younger pts. Where does age 65 come from? Neer et al trail had mean starting T-2.4 so we dont know how much benefit at -3.5 or -4 Why omit other TAG87 risk factors smoking and low BMI etc? Why persist with etidronate when your own data show poor cost-effectiveness and no hip data? You have dropped failure to respond as a reason to switch. Good. The definition in TAG87 was poor and involved fall in BMD when you said in over 75s no DEXA was needed at baseline). But GPs need advice on how long to continue treatment as pts often ask when they start. And what to do if further fractures occur: you and I know that does not mean failure but many GPs stop treatment.	Comments noted. The Committee concluded that calcium and/or vitamin D supplementation should be provided unless clinicians are confident that women who receive treatment for osteoporosis have an adequate calcium intake and are vitamin D replete. The Committee suggested that the forthcoming NICE clinical guideline on osteoporosis could specify how such assessments should be made and what supplementation should be prescribed. See FAD 4.3.39 (primary prevention) and 4.3.40 (secondary prevention). The Committee considered that there was sufficient evidence to recommend etidronate. See FAD 4.3.2 and 4.3.26 (primary prevention) and 4.3.26 (secondary prevention). The Committee did not consider that the fracture risk associated with all risk factors mentioned would be

			amenable to change with treatment and therefore selected the most significant factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention). Please see FAD 1.8 for information on the definition of unsatisfactory response.
	2	2.12 So why not include them as well in guidance? You did in 2005	The Committee did not consider that the fracture risk associated with all risk factors mentioned would be amenable to change with treatment and therefore selected the most significant factors. Please see FAD 4.3.8, 4.3.13 and 4.3.18 (primary prevention) and 4.3.9, 4.3.14 and 4.3.25 (secondary prevention).
	3	Why no oral ibandronate? Now available for almost 24 months. Where does it stand? Some pts prefer monthly dosing and get better compliance. Why not allow that choice? 3.6: all the more reason to move to parenteral versions asap Staying upright just means not going back to bed. for most pts it all means a tablet with water on getting out of bed and by the time they are washed and dressed its 30 mins up and they can have breakfast. Not complex really, except for etidronate which Id omit due to poor cost effectiveness at any age cf the others 3.10 Even more impt that strontium pts get the calcium and vit D. in trials they took supplements for at least 2 wks pre-active drug. Not everyone realises this. DEXA after strontium is useless. We dont know for how long and it depends on dose/time given. Artifactual elevation will make it more difficult to justify teriparatide in these high risk pts. Teriparatide has never been tested in pts whose bones are loaded with strontium so you are not evidence-based in suggesting this order of use.	Ibandronate was not included in the scope of this appraisal as the drug has not been referred to the technology appraisals programme. This intervention may be included in the clinical guideline. Comments noted.
	4	I cant see where the figure of Â£30,000 comes from? Who/what/where set this? Health Select Committee Jan 08 agrees. Why use Â£20,000 elsewhere eg statins? 4.3.8 Look at data from Kanis 2005 T-2.5 as osteoporosis was a WHO epidemiological tool but got hi-jacked by pharmaceutical companies entering pts into trails and thus into guidance. Please remember that even at T-1.5, and certainly at -2.0, 10 year fracture risk at age 50 is almost as high as at -2.5 The graph flattens out	The Committee considered that women with an osteoporotic fracture constitute a different population from the primary prevention population and that there were some factors that justified considering a higher ICER range in line with the 'Guide to the methods of technology appraisal'. For Secondary prevention £30,000 per QALY was considered to be an acceptable use of NHS resources

			(see FAD 4.3.16).
	5	My 2 local PCTs are struggling even 3 yrs from TAG87 to get GP interest and cooperation as osteoporosis is not a QOF target. The 3 month rule needs stricter monitoring please	Comment noted.
	6	6.3: There is a lot of evidence! Who does NICE suggest does this work? I wonder when I see this at end of all NICE TAGs. There's nothing in it for the companies now that they have licences? Is it a prompt for DOH funding? We need data on the efficacy of strontium and of teripratide after bisphosphontes and about teriparatide after both. The difficulty is long bone retention of these drugs. Trials use pts not exposed to other drugs but this does not reflect real life. The sequential use suggested in this TAG is not evidence-based in this regard and it may be worth saying so openly.	Recommendations on research are suggested to highlight evidence gaps and encourage research.
	7	Please involve more clinicians in the process! Just 1 rheumatologist out of 51 Appraisal Committee members for this TAG seems strange, none on guideline team or expert list (appx B section D)	Comment noted. Clinicians are involved throughout the appraisal process, for example, clinical experts are invited to attend Committee meetings and are asked to provide written testimonies of their experience in the area.
	8	Can we wait with no advice on iv bisphosphonates until then? Good data, partic with zoledronate and overcomes the compliance issues you list. Ivs need inclusion next time please.	It was not included in the scope of this appraisal.
Other Associate Lecturer [COI: yes, I have received consultancy fees from several manufacturers of products indicated for the treatment of osteoporosis.]	1	Unfortunately, the current ACD is obsolete and without a change of scope will result in publication of final guidance that will add no additional value to TA87. Publication of the FRAX tool enables absolute fracture risk assessment to be calculated. Limitations aside, FRAX provides a far more holistic assessment for intervention than reliance on stepped BMD criteria. The current TA refers the reader to an unpublished Clinical Guideline for details of how osteopenic fracture patients should be managed. The population burden of fractures has been shown to emanate from women with osteopenia not osteoporosis (Osteoporosis Int 2006 17:1404-1409 Pasco JA et al). Given that a proportion of osteopenic fracture patients will be at comparable, or possibly higher fracture risk than some osteoporotic fracture patients, the scope of the current TA could be viewed as discriminating against such patients as CG guidance is non-mandatory. NICE should explore whether options exist to re-scope the entire osteoporosis TA and CG guidance programme to ensure that the product of this effort is fit for purpose.	Please see FAD 4.3.33 (primary prevention) and 4.3.34 (secondary prevention). The Assessment Group's model is underpinned by the same epidemiological data as FRAX. The Committee did not have access to the algorithms underlying FRAX. In addition, FRAX only determines fracture risk, not cost effectiveness. Please see FAD 4.3.33 (primary prevention) and FAD 4.3.34 (secondary prevention). Recommendations for the treatment of women with osteopenia were not made for two reasons. Firstly that it was outside the remit of this appraisal and secondly because not all the drugs were licensed in the UK for the

			treatment of osteopenia. See FAD 4.3.6 (primary prevention) and 4.3.8 (secondary prevention).
	4	The scope of this ACD does not include new agents that could provide useful alternate management options to patients and clinicians when oral bisphosphonates, particularly alendronate, are not tolerated. IV preps of zoledronate and ibandronate have been available for several months and several years respectively. SMC approved iv ibandronate for patients intolerant of oral BPs in 2006 (http://www.scottishmedicines.org.uk/smc/files/ibandronate_acid_Bonviva_301_06.pdf) whilst zoledronate was similarly approved by SMC in February 2008 (http://www.scottishmedicines.org.uk/smc/files/zoledronic%20acid%205mg%20solution%20for%20infusion%20(Aclasta)%20FINAL%20Feb%202008.doc%20for%20website.pdf). SMC also approved restricted use of a new PTH preparation in Feb 2007 (http://www.scottishmedicines.org/smc/files/parathyroid%20hormone%20100mcg%20powder%20for%20injection%20_Preotact%20(356-07).pdf). Accordingly, in respect of treatments available to the NHS this guidance will be obsolete on publication and will remain so until the review date of July 2010. Publication of such guidance is not in the interest of patients, clinicians or NICE and as such provides another reason to re-scope the TA & CG.	These drugs have not been referred by the Department of Health for appraisal to NICE. Newer interventions may be captured in the clinical guideline.