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

Response to comments received from consultees and commentators on the Appraisal Consultation Document (ACD) issued in Sept 2006

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Alliance for Better Bone Health	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. **Executive summary** 1. The provisional recommendations are overly-complex and suggest distinctions between products which are not supported by the clinical evidence or the Committee's considerations and the Institute's approach in other therapy areas. 2. The Alliance proposes that the guidance recommends the use of oral bisphosphonates for specific patient populations as first line treatment options for the prevention of osteoporotic fractures and that, when the decision has been made to prescribe a bisphosphonate, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost. 3. Furthermore, provision should be made in the guidance to allow patients who are currently receiving treatment with any of the considered technologies to continue with their therapy. 4. We believe that these simple revisions would produce more pragmatic guidance which would be consistent with the evidence, the Committee's considerations and the Institute's approach in other therapy areas. 5. Finally, The Alliance asks the Institute to note that the ability of consultees and commentators to critically appraise the consultation documents has been impaired during the recent course of these appraisals. This is due to a lack of transparency in the way that the information has been written up and the results interpreted.	Comment noted. The 2007 ACD has revised recommendations which are based on clinical and cost effectiveness evidence. Alendronate has been recommended as the first line treatment for the initiation of the primary prevention and is to be purchased at lowest acquisition cost. NICE produces prospective guidance and this issue is clarified in the 2007 ACD section 1.5. Comment noted. Comment noted. See below for a full response to this comment .

Consultee or Commentator	Comment	Institute Response
	1. <u>Provisional recommendations</u> *The provisional recommendations are overly-complex and suggest distinctions between products which are not supported by the clinical evidence, the Committee's considerations and the Institute's approach in other therapy areas.* It is clear from the overview and ACDs that the Appraisal Committee accepts that the bisphosphonates are the most clinically effective and cost effective treatment options for the primary and secondary prevention of osteoporosis fragility fractures in postmenopausal women. <u>Overly-complex recommendations</u> The Alliance believes that healthcare professionals and patients will have difficulty interpreting the provisional recommendations in practice. Section 1 of each document is bewildering, with an array of up to 9 sub-sections, many with multiple drug-specific qualification statements, in addition to the 4 paragraphs of text that precedes the guidance in both documents. For example: • For each patient to receive treatment, a combination of age, T-score, risk factors, tolerability and contra-indications must be considered. • Further, the clinician's choice of treatment is governed for each product by different thresholds of the above qualifications, and may need further investigations before treatments can be changed. • Finally, these qualifications for each product vary between their use in primary or secondary prevention. The Alliance notes that neither ACD includes a 'detail on criteria for audit' appendix and believes that audit criteria for the current provisional recommendations would be significantly more complex than for previous ACDs. As such, the Alliance questions whether audit of these provisional recommendations would be possible. <u>Artificial distinctions between products</u> The Alliance believes that the wording of Section 1 of both ACDs implies distinctions between products which are not supported by the evidence, the Committee's considerations and the Institute's approach in other therapy areas. We understand that the guidance distinguishes between the treatment sequences of the bisphosphonates based on the following considerations: • The guidance for alendronate is based on cost-effective treatment strategies using the assumption of an annual price of generic once per week alendronate and the pooled efficacy of alendronate and risedronate. • The guidance for risedronate is based on cost-effective treatment strategies using the mean annual cost of branded alendronate and risedronate and the pooled efficacy of alendronate and risedronate, despite branded alendronate being more expensive than risedronate for both the once per day and once per week formulations. • The difference between alendronate recommendations and risedronate recommendations (paragraphs 1.1 and 1.3, respectively) is driven by the assumption that alendronate is less expensive than risedronate and therefore more cost-effective in women with lower T-scores.	Comment noted. The Committee has considered these comments in its review of primary prevention recommendations. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and these have been based on clinical and cost effectiveness. Comment noted. The Committee has reviewed the clinical and cost effectiveness evidence and has based its recommendations (and resulting distinction between products) on this.

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However, these distinctions do not reflect the following points:
• Only one form of generic alendronate (once per week) is cost-effective in the population defined in section 1.1.
• All other formulations of alendronate (branded and generic once per day) are equivalent in price or more expensive than risedronate and thus would be equal to or less cost-effective than risedronate.
<table>
<tr><td colspan="3">NHS Drug Tariff Price September 2006</td></tr>
<tr><td colspan="2">Once per day £/Month</td><td>Once per week £/Month</td></tr>
<tr><td>Alendronate</td><td>40.36 (10mg dose)</td><td>13.27</td></tr>
<tr><td>Fosamax</td><td>40.36 (10mg dose)</td><td>20.30</td></tr>
<tr><td>Actonel</td><td>19.10</td><td>20.30</td></tr>
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• That the Committee’s considerations made no distinction between the bisphosphonates on a clinical basis.

We recognise the Committee’s interest in the potential costs associated with identification of women at risk. However, including an assessment of the cost effectiveness of these strategies has also led to artificial distinctions between some of the products assessed. Furthermore, the Alliance believes that an assessment of the cost-effectiveness of screening in these appraisals is inconsistent with other appraisals undertaken by the Institute (e.g. treatments for myocardial infarction and other acute coronary syndromes including: TA080 clopidogrel, TA047 glycoprotein IIb/IIIa inhibitors and TA052 thrombolysis.

The provisional recommendations have therefore made inconsistent and artificial distinctions between alendronate and risedronate.

2. Recommended revision

The Alliance proposes that the guidance recommends the use of oral bisphosphonates for specific patient populations as first line treatment options for the prevention of osteoporotic fractures and that, when the decision has been made to prescribe a bisphosphonate, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost.
To address the difficulties presented by the current provisional recommendations, outlined above, the Alliance proposes that they are revised as follows:
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As stated in the 2007 ACD section 1.1, when the decision has been made to initiate treatment with alendronate, it should be prescribed on the basis of the lowest acquisition cost.

The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and these have been based on clinical and cost effectiveness..

The Committee agreed that all costs should be included in the assessment of the cost effectiveness or primary prevention strategies; this includes this cost of opportunistic identification of women who can benefit from primary prevention therapy.

Comment noted.
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	Primary prevention: • Oral bisphosphonates are recommended as first line treatment for the primary prevention of osteoporotic fragility fractures in women aged 75 years or older, who are identified as having one or more clinical risk factors and confirmed as having a T-score of -2.5 SD or below. • When the decision has been made to prescribe a bisphosphonate, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account the required frequency, dose and product price per dose). • If the woman is unable to tolerate, cannot comply with special instructions for administration or does not make progress with the initial bisphosphonate, treatment with other suitable bisphophonates should be considered before initiating treatment with another class of drugs.	The recommendations for primary prevention have been revised following the Committee meetings in November 2006 and February 2007 . The revised recommendations have taken into account consultees and commentator comments and the clinical and cost effectiveness evidence.
	We have no specific requests for changes to the wording of Sections 1.4-1.7 of the primary prevention guidance and 1.4-1.9 of the secondary prevention guidance, although these sections would also benefit from simplification.	Comment noted.
	3. Patients currently receiving treatment *Furthermore, provision should be made in the guidance to allow patients who are currently receiving treatment with any of the considered technologies to continue with their therapy.* In line with the Institute's approach to previous appraisals, the guidance documents should specify that 'people who are currently receiving the technologies considered in these appraisals, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they and/or their specialist consider it appropriate to stop' [wording adapted from the Institute's Final Appraisal Determination on the use of technologies for the treatment of Alzheimer's disease].	NICE produces prospective guidance and this issue is clarified in the 2007 ACD section 1.5.
	4. Benefits of recommended revision *We believe that these simple revisions would produce more pragmatic guidance which would be consistent with the evidence, the Committee's considerations and the Institute's approach in other therapy areas.* The complexity of the modelling supporting the appraisals has resulted in complex provisional recommendations. The Alliance questions whether the apparent precision in the recommendations is justifiable given the inherent limitations of modelling, the often conservative nature of the assumptions and thus the potential uncertainty of the results. If the real uncertainty of the results in this model were acknowledged, it is likely that the recommendations would not distinguish between branded and generic products on the basis of patient status. Instead, guidance would simply recognise the benefits to the NHS of first line bisphosphonate treatment based on lowest acquisition cost.	The Committee has considered these comments in its review of recommendations for primary prevention. The Committee has also taken into account the differences in clinical effectiveness evidence, dosing regimes (with effect on persistence) and the effect of differences in prices on the cost effectiveness modelling. Comment noted.
	The Alliance's recommended revision to these ACDs is also in line with the Institute's previous approach to appraisals of a class of products with a wide range of acquisition costs (e.g. price variations in the appraisal	

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	of statins for the prevention of cardiovascular events ranged from £1.48 for generic simvastatin 20mg/28 tablets, £29.69 branded simvastatin 20mg/28 tablets and £24.64 for atorvasatin 20mg/28 tablets). In this same appraisal, as with a number of others, the Appraisal Committee has issued pragmatic recommendations with a single intervention threshold, endorsing the class as a whole with the caveat that "therapy should usually be initiated with a drug with a low acquisition cost". If the current ACDs were revised as we propose, the guidance would remain flexible to future changes in acquisition costs or product value offerings. Furthermore, the Alliance believes that healthcare professionals and patients would be able to interpret and fully implement the recommendations in practice. **5. Consultation** *The Alliance asks the Institute to note that the ability of consultees and commentators to critically appraise the consultation documents has been impaired during the recent course of these appraisals. This is due to a lack of transparency in the way that the information has been written up and the results interpreted.* The Alliance has previously highlighted difficulties in its ability to assess the evidence used by the Committee. As we stated in our response to the DSU report in August, not enough data are presented to allow the reader to understand how the results were reached or how they should be interpreted. This remains the case and is also true of additional documentation provided as part of the evaluation report. In addition, the economic models prepared by the Decision Support Unit are not available to consultees and commentators. Although Excel spreadsheets stripped of commercial and academic in confidence material results have were provided, these provide only some of the model outputs upon which the provisional recommendations have been based. As a result, the model is not open to external scrutiny and we are unable to establish the extent to which each component of the modelling process has influenced the model results and, ultimately, the Committee's decision-making process. **Summary** The Alliance trusts that the Committee will appreciate the concerns expressed in this response. We hope that the Committee will be minded to affect the revisions we have recommended in order to provide clear, pragmatic and implementable guidance for the NHS.	Comment noted. As stated in the 'Guide to Technology Appraisal Process', to ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Committee's decision should be publicly available. Ideally all the evidence seen by the Committee should be available to all consultees and commentators. However, under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. The WHO risk algorithm within the DSU models has been provided under an Academic in Confidence agreement and as such only model outputs without the academic in confidence information removed can be provided to consultees and commentators. Comment noted.

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Eli Lilly	1) Primary Prevention i. For Primary prevention we consider that relevant evidence was supplied and available to the Appraisal Committee. **Raloxifene** We still maintain that the breast cancer benefit is of relevance in the assessment of raloxifene for primary prevention of osteoporosis, and this has once again been rejected in the ACD We appreciate that the breast cancer benefit cannot be the sole reason for any recommendation, but raloxifene (with the breast cancer benefit taken into account) is, in fact, *the only* cost effective option in younger post menopausal women. We are also concerned that the arbitrary application of a £20,000 per QALY threshold will have excluded patients who may benefit from raloxifene treatment at a cost per QALY that may not have been much above this level.	Comment noted. Section 4.2.10 of the 2007 ACD notes the exclusion of breast cancer benefits, VTE and cardiovascular events for raloxifene in the cost effectiveness analysis. This is in line with the considerations in technology appraisal TA 87. The Committee noted that a higher proportion of the overall benefit associated with raloxifene was attributable to its effect on the prevention of breast cancer than to its effect on the prevention of osteoporotic fractures. The Committee agreed that, in principle, the side effects of using a technology should be considered, but there were a number of reasons why the Committee considered that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost effective option for the treatment of osteoporosis. These were as follows:From the evidence presented, raloxifene was not as effective as bisphosphonates for treating osteoporosis; raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities; full assessment of raloxifene's effect on the prevention of breast cancer and its cost effectiveness in this indication would

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	It remains an inconsistency to not allow raloxifene to at least be used as a treatment option in women for primary prevention, if they are unable to take bisphosphonates or strontium ranelate. Finally at minimum, the ACD should state that women already being treated with raloxifene do not need to stop treatment unless clinically indicated. i. 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, and our concern regarding the application of the arbitrary £20,000 per QALY threshold in the economic analysis. On the basis of our comments above we <u>do not</u> consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	require consideration of how it compares with other drugs that potentially could be used for breast cancer prevention. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and these have been based on clinical and cost effectiveness. NICE produces prospective guidance and this issue is clarified in the 2007 ACD section 1.5. The NICE methods guide states that *"Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, the innovative nature of the technology, the particular features of the condition and population receiving the technology, where appropriate, the wider societal costs and benefits, Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong."*
Merck, Sharp & Dohme Ltd.	Merck Sharp & Dohme Ltd. (MSD) would like to thank you for the opportunity to comment on the new Appraisal Consultation Documents (ACDs) which have been prepared by the Appraisal Committee for the above appraisals. Having reviewed the ACDs we have a number of concerns regarding the recommendations that are being issued to the NHS and we would like to share these with you.	Comment noted.

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	<u>The age limit for which treatments for the Primary Prevention of Osteoporotic Fractures are recommended has been raised for reasons that have not been sufficiently justified.</u> Our primary concern is that the lower age limit for which treatment for the primary prevention of osteoporosis is recommended has been raised to 75, and the recommendations for the 70-74 age group which were contained in the previous ACD have been withdrawn. The ACD states that this decision has been taken because treating this age group with bisphosphonates is not cost-effective, but this statement does not appear to be supported by the additional work on this subject that was completed by ScHARR. Indeed, the ScHARR document would appear to support the use of alendronate in the 70-74 years population as a cost effective treatment option (cost per QALY below £16,000 for each scenario considered). Section 4.3.15 of the ACD (page 32) states the Appraisal Committee's preferred sensitivity analysis, but the cost per QALY of different treatment strategies resulting from this analysis is not discussed, nor is either the Assessment Report or the ScHARR document referenced. In short, the basis upon which these conclusions on cost-effectiveness have been reached by the Appraisal Committee is not apparent from the ACD. Additionally, the cost of alendronate has fallen even further since September 2006, making it an even more attractive option, given its proven efficacy in preventing osteoporotic fractures as stated in the ACD. It appears to us therefore that this raising of the age limit whereby women may be prescribed treatment for the primary prevention of osteoporosis is contrary to the evidence which has been made available to the Appraisal Committee. The ScHARR document seems to be at odds with the decision that has been made and we feel that this has not been sufficiently explained in a robust and transparent manner. Further, this appears to be a result of the curious decision to pool the data for alendronate and risedronate together in order to create the profile of a drug that does not exist. As alendronate and risedronate are two different molecules and evidence of both drugs regarding fracture reductions differ, it follows that pooling the data for both is not a scientific approach and we would urge the committee to consider each drug alone on its individual merits. We are highly critical of this approach and it is our opinion that if current guidance stands it will deprive patients of a treatment which is both cost and clinically effective for no justifiable reason. We are aware that the committee is seeking to provide the NHS with the best possible guidance taking all of the available evidence into account. It appears to us however that all the data we have been privy to so far supports the use of alendronate in a younger patient population than is currently recommended, and the reason for raising the age limit has not been clearly stated in such a way that we can follow the decision-making process. Aside from the recommendations themselves this is also a cause for concern. NICE is currently seen to be an international leader in robust and transparent HTA decision-making and we hope that this is an oversight and that the commitment of NICE to a transparent decision-making process will continue. **<u>Current wording of ACD recommendations suggests that alendronate has been differentiated on grounds of acquisition cost, rather than proven clinical and cost effectiveness.</u>**	The recommendations in the 2007 ACD have been revised following further cost effectiveness analysis carried out in November 2006 and are only for the initiation of primary prevention therapy. The analysis on which the 2006 ACD recommendations were based was available to consultees at the time of the 2006 ACD consultation. The 2007 ACD recommendations are based on the price of non-proprietary alendronate in November 2006 and are for the initiation of primary prevention therapy only.. The analysis was carried out for combined (second generation) bisphosphonates on the advice of the Guidelines Development Group as it was considered that the second generation bisphosphonates had an overlapping efficacy range and could be considered a clinical class Comment noted.

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	Whilst we are glad to see that alendronate has been differentiated from the other bisphosphonates, we are concerned that the ACD implies that this distinction has been made simply on the basis of acquisition cost. We would strongly urge that the requirement to use the cheapest version of alendronate that is available be removed (from both ACDs) as this reinforces the impression that alendronate is being recommended simply because it is cheap. This is not an accurate reflection of the ACDs themselves in which alendronate is shown to have numerical superiority over other therapies in terms of both clinical and cost effectiveness. Thank you once again for allowing us to comment on the ACDs at this time. I trust that we have made our thoughts clear, but should you have any queries or wish to discuss this in more detail please do not hesitate to contact ********** on ********** or **********.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and these have been based on clinical and cost effectiveness. Comment noted.
Servier	Thank you for the opportunity to submit comments on the appraisal consultation documents recently released by NICE for the appraisals of drugs for the primary and secondary prevention of fragility fractures in post-menopausal patients with osteoporosis. In summary, Servier Laboratories' comments on the documents are as follows. • The price of alendronate should be updated to at least the current drug tariff price of £7.31 per 28 days. • There are marked inconsistencies in the approach of the Appraisal Committee to assumptions about the efficacy of therapies in the presence and absence of low BMD. Given the assumption that efficacy can only be assumed in the presence of low BMD, we suggest that the Appraisal Committee should include the evidence for hip fracture prevention by strontium ranelate in at-risk patients if it is to propose that only these at-risk patients can benefit from treatment • There is insufficient evidence for and use of etidronate disodium in post-menopausal osteoporosis. The Appraisal Committee should reconsider the inclusion of this drug in guidance • By not examining the risk of prescribing of PPIs in patients at risk of fracture, the Appraisal Committee is exposing these patients to a safety risk. The Committee should urgently review the clinical trial data. • Patients who fail to respond to bisphosphonates are left unprotected. The guidance needs to be amended to recommend use of strontium ranelate in this group • By setting a higher barrier for alternative treatments to alendronate, many patients who do not tolerate, or are unable to take, this drug will be left unprotected. The guidance needs to be amended to close a treatment gap in this group • There is strong evidence that strontium ranelate protects patients 80 years and over from vertebral and non-vertebral fracture. Guidance should consider recommending strontium ranelate in this patient group <u>Generic Price of Alendronate</u> The price of generic alendronate used in the modelling is now out of date. The NHS drug tariff price is	Comment noted. Amended in the cost effectiveness modelling in November 2006. The cost effectiveness modelling has been revised to the price of £7.31 for

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	currently £7.31 for 4 tablets, implying a yearly cost of £95.03. However, in the near term, the tariff price will fall further and should stabilise at around £3.50 per month, or £45.50 per year. <u>Relative Risk and Clinical Risk Factors</u> The lack of scientific discussion of the decision taken by the Committee that strontium ranelate and the bisphosphonates are ineffective on risk conferred by factors other than age and low BMD makes it very difficult for consultees to comprehend the basis for these decisions. While numerous comments can be made on the Appraisal document, the most obvious relates to assumptions and inconsistencies about treatment efficacy. The analyses of drug efficacy have been derived from the whole study populations for each agent; these populations included patients with BMDs above and below the osteoporosis threshold and with a variety of other risk factors, including prior fracture, but also including, for example, those with low BMI, moderate alcohol intake, smokers and those with a family history of fracture. The relative risk reductions are an average derived from these diverse populations. If the Committee declares that the therapies are unable to reverse the risk due to these other risk factors, then the corollary is that the benefit must be even greater in groups identified by the risk factors that are predominantly responsive i.e. older patients with low BMD. The decision by the Committee to assume that strontium ranelate does not lower the risk of fracture caused by factors other than degraded BMD and age contradicts the basis for the refusal by the Appraisal Committee to recognise the relative risk of 0.64 for hip fracture demonstrated in the at-risk group in the TROPOS study and endorsed by the EMEA as an appropriate measure of the treatment effect in hip fracture (older patients with low BMD). The acceptance of this argument would substantially improve the consistency of decision-making within the ACD. This decision would also be consistent with the fact that a relative risk of 0.85 was demonstrated in the pooled population that included younger patients and patients with a T-score>-2.4, a group the ACDs now suggest cannot benefit from therapy. Strontium ranelate has a totally different mechanism of action to bisphosphonates. Therefore, assumptions about the effect of drugs that suppress bone-turnover do not apply to strontium ranelate. The Appraisal Committee might be interested to note that the relative risk of vertebral fracture in the SOTI and TROPOS studies has been extensively examined and found not to be related to the clinical risk factors excluded from the ACD decision1. This result suggests that there is no evidence to conclude that treatment cannot reduce the risk caused by factors other than those included in the recommendations. In the case of the TROPOS study, it is far more likely that the 0.85 relative risk for hip fracture in the pooled group was a consequence of under-powering due to the inclusion of patients of low absolute risk in the pooled analysis and not a case of relative risk being a function of the source of absolute risk. This conclusion is underlined by the improved confidence in the result in the smaller at-risk subgroup. Servier requests that the Committee reconsiders its position on the applicability of the TROPOS at-risk relative risk of 0.64 for hip fracture and make this estimate a part of the base case scenario of efficacy and that the assumption of zero effect on excluded CRFs be reconsidered.	4 tablets (November 2006). Potential future price reductions have not been included. At the Committee meeting to agree on the content of the 2006 ACD, the Committee concluded that there was insufficient evidence that the drugs under consideration would reduce fracture risk that was not associated with low BMD, age, or prior fracture. The Committee noted that the distribution of additional risk factors was similar across all BMD sub-groups in the large FIT trial. If there was an effect for all clinical risk factors a greater drug effect would have been expected in the higher (less severe) BMD sub-group than was observed. Following consultation on the 2006 ACD, the Committee decided that the assumption of no efficacy on fracture risk associated with risk factors other than low BMD, age, or prior fracture (0% efficacy assumption) was probably too extreme. On balance, 50% efficacy for the fracture risk not associated with low BMD, age, or prior fracture was considered a reasonable, although necessarily approximate position. This position was taken as the Committee was still not persuaded that there was unequivocal evidence that the drugs alone would reduce the overall fracture risk for factors other than low BMD, age, or prior fracture.In addition, the Committee accepted an increased estimate for the RRs

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	Etidronate Recommendation In contrast to alendronate, risedronate and strontium ranelate, the use of etidronate to prevent hip fracture remains unproven. To ignore clinical study evidence and assign a relative risk from one observational study is not consistent with an evidence-based assessment. As a result of this selective choice of data, the relative risk of hip fracture assigned to etidronate was lower than was applied to strontium ranelate. The recommendation of etidronate for widespread use discredits this technology appraisal and is very unlikely to be implemented. Servier requests that the Appraisal Committee reconsider the guidance on the use of etidronate with a view to excluding its use on practical and evidence grounds. Safety Signal for Bisphosphonate Use in Patients at Risk of Concomitant PPI Use NICE have undertaken a literature review of bisphosphonate use that demonstrates an increased use of PPIs of up to five fold in clinical practice. Since the previous consultation phase, there has been further evidence demonstrating the increased risk of fracture associated with proton pump inhibitor (PPI) use with three independent data sources that demonstrate statistically significant increases in the risk of fracture2,34. This is a safety signal of concern and current NICE guidance is placing patients on a bisphosphonate who then require a PPI to counteract the adverse effects of the bisphosphonate, at increased risk of fracture. Therefore, it is beholden on NICE, not least from a safety perspective, to request an urgent review of the clinical studies of bisphosphonates to determine if this evidence from clinical practice is also demonstrated in the clinical studies. If this is proven, the guidance must be urgently amended as NICE advice in its current format is putting these patients at unacceptable risk. Patients Who Fail to Respond to a Bisphosphonate In contrast to previous guidance, the ACDs do not recommend that patients who fail while on bisphosphonate treatment should be switched to strontium ranelate. The reason(s) for this change are not presented in the current document. Servier requests that the Committee restores the recommendation that patients who do not respond to bisphosphonates be considered for strontium ranelate. This is especially important since in the proposed guidance these patients would only get teriparatide as an option once they have suffered multiple fractures and have a very much reduced BMD. Servier requests that strontium ranelate again be recommended for patients not responding to bisphosphonate treatment. Patients who are Unable to Tolerate Alendronate The current ACDs open up gaps between first line and second line treatment, where none existed previously. For example, a patient 70 years of age, who has a previous fracture and T-score between –2.5 and -3 and does not tolerate a bisphosphonate could then have no option for treatment. The Appraisal Committee might consider raising the threshold for starting strontium ranelate to close this gap in treatment. Clinical Evidence in Patients over 80 years old	applied to the risk factors age, BMD, prior fracture to allow for this assumption. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. Comment noted. The Committee considered a sensitivity analysis carried out by the DSU in Sept 2006. The 2007 ACD recommendations do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. Recommendations for the treatment of these women will be made within the NICE clinical guideline on osteoporosis See above

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	A statement is made in the ACDs (section 4.1.2) that there is little evidence for treatment effect in patients over 80 years. Strontium ranelate is the only agent to have demonstrated efficacy in both vertebral and non-vertebral fracture in this age-group[5]. It has demonstrated this effect after only one year of treatment, an early onset that is very important for this group of patients. Based on this evidence, strontium ranelate should be recommended first line for patients aged 80 years and over. The current draft recommendation places this age group at risk as current evidence suggests that bisphosphonates do not protect against non-vertebral fracture in the very elderly[6].	Section 4.3.19 notes the committee's reservation on the Strontium ranelate data. The analysis considered all women over the age of 75 years as one group to avoid either over- or under extrapolating the bisphosphonate data to women aged 80 and older.
Nominated patient experts and clinical specialists		
Professor Juliet Compston Clinical Expert	Thank you for sending me the two ACDs. My comments are set out below. **General comments** Since earlier ACDs and TA87 there has been no significant new evidence on the efficacy of interventions, epidemiology and disutility of fractures, or adverse event profile of treatments. However, one major change has been a substantial lowering of the price of generic alendronate that approaches one half of the original price and this has been incorporated into the new economic analyses. At first sight it is therefore surprising that the recommendations for both primary and secondary prevention have become more conservative than previously. On closer inspection, it is clear that this has been achieved by altering other assumptions in the model so as to neutralise the large effect on cost-effectiveness of the price reduction of alendronate. The end result is that osteoporosis is presented as a disease for which treatment is cost-effective in only a minority; this goes against other, peer-reviewed, health economic analyses in Europe and the USA and is clearly motivated by the wish to restrict NHS expenditure on this common and disabling disease. Whilst the need to ration resources is recognised, this should not be done by manipulation of economic models; a more honest approach would be to acknowledge that although treatment of osteoporosis is cost-effective according to current CPQ thresholds, there might be insufficient NHS resources to accommodate these costs. In order to preserve equity of access to treatment across different diseases, therefore, it may be necessary to lower the CPQ for intervention across all disease states. A number of assumptions in the model have been changed since previous analyses. The one with the greatest impact is that of zero efficacy of interventions for the contributions of clinical risk factors other than age, BMD and fracture, to fracture risk. This extreme assumption goes against a body of detailed evidence previously presented to the Appraisal Committee by the Guidelines Development Group and is scientifically	At the Committee meeting to agree on the content of the 2006 ACD, the Committee concluded that there was insufficient evidence that the drugs under consideration would reduce fracture risk that was not associated with low BMD, age, or prior fracture. The Committee noted that the distribution of additional risk factors was similar across all BMD sub-groups in the large FIT trial. If there was an effect for all clinical risk factors a greater drug effect would have been expected in the higher (less severe) BMD sub-group than was observed. Following consultation on the 2006 ACD, the Committee decided that the assumption of no efficacy on fracture risk associated with risk factors other than low BMD, age, or prior fracture (0% efficacy assumption) was probably too extreme. On balance,

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	implausible. Moreover, it is irrelevant for the secondary appraisal analysis, since the characteristics of women under consideration are very similar to those of women taking part in the trials from which the original efficacy estimates were derived. Thus the use of the zero efficacy assumption in the secondary prevention appraisal assumes that none of the women taking part in the pivotal trials had clinical risk factors in addition to low BMD and fracture. This is not the case; the prevalence of clinical risk factors at baseline has been documented in a number of trials and is similar to or higher than that encountered in the normal population. Another assumption that has a significant impact on cost-effectiveness is that of the anti-fracture efficacy of alendronate, particularly for hip fracture. Since the first technology appraisal there has been a progressive lowering of the mean relative risk reduction for hip fracture by alendronate from a RR of 0.49 to 0.62 to 0.71, despite the absence of any new evidence to support this move. The value of 0.49 is that established in the FIT study in women with established osteoporosis and thus should be used for the secondary prevention appraisal. The value of 0.62 represents the relative risk obtained from meta-analysis of studies in women with low BMD ± fracture and in those with osteopenia. Since osteopenia is now apparently outside the remit of the HTA there is no justification for using relative risk estimates derived from analyses that include studies in osteopenic women. Finally, the change from 0.62 to 0.71 in the current ACDs has been achieved by pooling efficacy estimates for risedronate and alendronate. This cannot be justified since risedronate and alendronate are treated separately in the appraisal and each drug has its own robust evidence base. Finally, reduction of the disutility of vertebral fracture on the basis that is should be lower than that of hip fracture is a specious judgement and a stronger argument would be that a higher disutility for hip fracture should have been used. **Primary prevention ACD: specific comments** 1. The exclusion of women under the age of 75 years, regardless of risk factors, from either investigation or treatment would set the field back by several decades. Spending money on DXA in older women with clinical risk factors is a misuse of scarce resources that could better be allocated to detecting women in younger age groups at high risk of fracture. 2. Unlike the secondary prevention appraisal, this appears to include women with medical conditions associated with osteoporosis, but excludes those taking oral glucocorticoid therapy. 3. The ethical and management problems associated with imposing more stringent intervention criteria for second line treatments have already been mentioned in the context of secondary prevention. Likewise the inadequate evidence-base supporting the use of etidronate as an alternative first-line option is discussed above.	50% efficacy for the fracture risk not associated with low BMD, age, or prior fracture was considered a reasonable, although necessarily approximate position. This position was taken as the Committee was still not persuaded that there was unequivocal evidence that the drugs alone would reduce the overall fracture risk for factors other than low BMD, age, or prior fracture. In addition, the Committee accepted an increased estimate for the RRs applied to the risk factors age, BMD, prior fracture to allow for this assumption. The analysis was carried out for combined (second generation) bisphosphonates on the advice of the Guidelines Development Group as it was considered that the second generation bisphosphonates had an overlapping efficacy range and could be considered a clinical class The Committee recognises that hip fracture is a major event and often argued to be a key goal for prevention of fractures. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that it was unlikely that this would so greatly outweigh the utility decrement associated with a hip fracture. The Committee therefore considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip

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		fracture. 1. Age at which therapy can be initiated and DXA requirements for older women have been revised following the comments received. 2. Women who are on long term corticosteroid therapy are not covered by the guidance. 3. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy.
Dr Peter Selby Clinical Expert	Many thanks for asking for my comments on these two ACDs. I have tried to answer them in the framework of your letter of 21 September but there are some areas in which I have strayed from the suggested structure. *Whether I consider that all of the relevant evidence has been taken into account* There are several areas in which I feel that the committee has failed to take full account of the evidence base. 1 In discussing the clinical importance of osteoporosis the committee appear to downplay the usually accepted figure of in excess of 2 million women with osteoporosis preferring to rely on a single study, which only measured BMD at a single site, and which may very well not be representative of the United Kingdom as a whole, to arrive at a figure of the roughly half this magnitude. 2 In my mind the most serious perversion of the evidence base has been the arbitrary assumption that bisphosphonates have no effect on fracture risk unless the bone density is within the osteoporotic range. This has had a major effect on the modelling of cost effectiveness such that in the secondary prevention ACD despite a reduction in alendronate acquisition costs of nearly 50% the cost effective intervention thresholds are virtually unchanged. There is no scientific justification for the acceptance of this bizarre notion. In the first place there is a wealth of literature indicating that bisphosphonates are equally effective at preventing vertebral fractures in patients in whom the bone density is not osteoporotic as they are in those with low bone density. Thus, even if the committee were to decide that the evidence base was insufficient to support a similar effect in nonvertebral fractures, there is no justification whatsoever in excluding an	1. The 2007 ACD has been amended accordingly. 2. see response to Juliet Compston's comments.

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	effect on vertebral fracture from the modelling. However there is now substantial evidence to support the contention that bisphosphonates are efficacious in the reduction of nonvertebral fractures in patients with bone density which is not osteoporotic. I believe that this will be spelt out in considerable detail by the Guideline Development Group but can supply further information and evidence if the committee wish. Furthermore all the clinical trials considered in the assessment report have included patients with a variety of different clinical risk factors and broadly the treatment response was the same in all these groups. This was the argument accepted by the Institute to recommend the use of clinical risk factors for the assessment of cardiovascular risk in the administration of statins (TAG 94). It seems gross discrimination against women with osteoporosis to take a contrary view in the face of similar evidence. 3 There is no basis in evidence for adjustment of the disutility value of vertebral fracture to match that of hip fracture. Perhaps the committee do feel that it is implausible that the disutility associated with vertebral fracture is greater than that of hip fracture, I am not sure that this is indeed the case, even so what is the justification for reducing the disutility of vertebral fracture rather than increasing the disutility of hip fracture? The disutilities derived from clinical evidence are the best estimates we have at present and therefore the committee should respect these values. 4 The committee appears to gloss over the paucity of robust clinical evidence surrounding the efficacy of etidronate. *Whether I consider that the summaries of clinical cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate* Because of the major flaws adopted by the committee in their interpretation of the evidence base outlined above it is impossible for the cost effectiveness estimates in these ACDs to be a reasonable interpretation of the evidence. They appear to represent a major underestimate of the potential benefit of these interventions to women with osteoporosis within the NHS. I suspect that the committee have failed to consider the true resource implications of insisting that elderly, potentially infirm, women must have DXA confirmation of the diagnosis of osteoporosis before they can be offered treatment. This is a group which is likely to be at very high risk of osteoporotic fracture and therefore should be able to benefit from the interventions under consideration. I suspect the reason that this is being insisted on relates to the unwarranted belief (outlined above) that bisphosphonates are ineffective at fracture reduction unless there is demonstrated osteoporosis. *Whether I consider that the provisional recommendations of the Appraisal Committee are sound and*	3. see response to Juliet Compston's comments 4. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. DXA requirements for older women have been revised following the comments received.

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	constitute a suitable basis for the preparation of guidance to the NHS Because of the problems with the committee's interpretation of the clinical evidence as outlined above I have grave doubts as to the soundness of their advice. Furthermore, as a practising clinician in the field of osteoporosis, I have major concerns about the way in which it might be possible to translate this advice into clinical practice within the NHS: 1 The structure given for choice of agents in both primary and secondary prevention is cumbersome and unlikely to fit easily into a busy clinical consultation. In particular, the increasing severity of osteoporosis required to move from alendronate (or etidronate – see below) to other agents is likely to cause difficulties, especially in the primary prevention situation where the hierarchy is even more complicated. In clinical practice I am not sure how I am going to be able to explain to a patient that she was eligible to receive treatment with one agent but as she cannot tolerate this I am not in a position to offer any further therapy; am I supposed to offer the choice of osteoporosis or oesophagitis? In that regard is it actually more cost effective to continue with alendronate plus a PPI or to swap to risedronate? 2 The inclusion of etidronate as a first line option is bizarre and flies in the face of clinical practice the world over. Although it may be a cheap therapy the evidence of its clinical effectiveness is much weaker than that available for any of the other agents under consideration. I would certainly not be happy to see relatives of mine receiving treatment with etidronate as I do not believe that we can have sufficient confidence in its fracture reduction efficacy. 3 The insistence on the use of DXA in elderly patients is impractical. Many patients in this age group are unable easily to attend for a bone density measurements and it seems likely that the insistence on this either to move from alendronate for secondary prevention and for any treatment in primary prevention would merely result in many patients who might benefit from therapy being denied that treatment. I also have specific comments about each of the ACDs in addition: **Primary prevention** 1 Although the ACD explicitly excludes women receiving long-term glucocorticoid therapy it makes no mention of what should be done about women who are suffering from diseases that might have a significant effect on the skeleton. These represent an important high risk group of patients and reference needs to be made to them. As the committee are aware the upcoming clinical guideline will address both these issues and it would be appropriate for the committee's recommendations to point explicitly to that guideline for these circumstances.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. DXA requirements for older women have been revised following the comments received. Medical conditions associated with low BMD are included as risk factors (2007 ACD section 1.3)

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	I am sorry that these comments present such a critical tone but I fear that if the current ACD proposals are adopted unchanged they would produce guidance which is unworkable and bears little or no relationship to the clinical evidence. It is important for the NHS as a whole and the integrity of the processes that the Institute has pioneered that this does not happen. I am ready and willing to work with the committee and the Institute to try and ensure that the many deficiencies in the draft guidance are removed so that guidance that is useful to the NHS and beneficial to women with osteoporosis results.	Comment noted.
Professional and Patient Groups		
Arthritis & Musculosketal Alliance	The Arthritis and Musculoskeletal Alliance (ARMA) is pleased to have the opportunity to comment on the most recent Appraisal Consultation Documents on the primary and secondary prevention of of osteoporotic fragility fractures in postmenopausal women. As the UK umbrella association that brings together support groups, professional bodies and research organisations in the field of musculoskeletal conditions, we have read and endorse the comments made by the National Osteoporosis Society and the British Society for Rheumatology	Comments noted.
Bone Research Society	The working group to review the Appraisal Consultation Documents (ACDs) and their preliminary recommendations included academics and clinicians with specialised interest in osteoporosis, and also covered a wide range of medical sub-specialities. We have grave reservations that the current recommendations will limit the availability of effective treatments to people at risk of osteoporotic fracture. These points are considered in more detail below. We cannot support the inclusion of cyclical etidronate, particularly as a second-line treatment above risedronate, strontium ranelate or raloxifene. The ACDs comment that the data from a meta-analysis suggests a non-significant effect on non-vertebral and hip fracture (4.1.6.2). The committee must justify their inclusion of this drug when the scientific evidence for its efficacy is weak. In clinical practice, many patients find that etidronate is not easy to take when compared to the weekly bisphosphonates (alendronate and risedronate). We cannot support having differing DXA thresholds for interventions, particularly within a therapeutic class such as bishopshonates. This will potentially mean a patient aged 73 years with a history of fracture, will be denied treatment if she has failed to tolerate alendronate and etidtronate, and has a T-score of -2.8. This will place clinicians in a very difficult ethical dilemma where they are being forced to stop treatment on the basis of cost. The differing thresholds for drugs across different ages will also mean that the proposed NICE guidance will	Comment noted. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy

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	be very difficult to implement at a local clinical level. There is a risk that the guidance will be confusing to patients and physicians, and that patients will not be managed effectively even if they fulfilled the clinical criteria for assessment.	
	There is now published data regarding the comparison between raloxifene and tamoxifen in the reduction of breast cancer risk (section 4.3.25). This data from the STAR Study should be included in the modelling analysis. (Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295:2727-41).	Comment noted.
	The failure to offer treat for patients under 75 for primary prevention is unacceptable. The Committee must provide more information for them discounting the WHO model for selective case finding and the identification of high risk individuals. There is the possibility that patients without a history of fracture, aged < 75 yrs with a higher absolute fracture risk will be denied treatment when compared to patients with a history of fracture.	The age at which therapy can be initiated and DXA requirements for older women have been revised.
	The Committee must justify the decision to include costs for screening and provide information on whether this type of cost has been included in HTAs for other chronic disease management.	The Committee agreed that all costs should be included in the assessment of the cost effectiveness or primary prevention strategies; this includes this cost of opportunistic identification of women who can benefit from primary prevention therapy.
	The Committee should provide additional information about the recommendations for treatment if a patient has opted to have a DXA scan undertaken privately. What impact does this have on the modelling analysis?	This has not been considered in the cost effectiveness modelling.
	The committee must justify the dropping of the cost per QUALY from £30,000 to £20,000, particularly for the secondary prevention ACD when this appears to have been changed from HTA 87.	The Committee applied the levels of cost effectiveness as outlined in the Guide to the Methods of Technology appraisal, section 6.2.6.10 and 6.2.6.11(Available from URL http://www.nice.org.uk/page.aspx?o=201974)
	We hope this information and feedback will be of use to the Committee.	
British Geriatrics Society	As the Clinical Lead in one of the leading UK Centres for the management of osteoporosis I am writing on behalf of my colleagues to give some feedback we have in relation to these consultation documents. I apologise for sending a letter but unfortunately it was not possible to incorporate our feedback within the constraints of the website.	
	Whilst we were encouraged to see that the secondary care guidance now recognises the need for anabolic therapy in a wider group of women with very severe osteoporosis we feel that in general, the proposed	Comments noted.

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	guidance is extremely restrictive, and nihilistic in its approach to osteoporosis as a clinical entity. There are serious illogicalities within the consultation documents and we are concerned that implementation of the proposed guidance would have a major adverse impact on osteoporosis management in the UK. We outline some of our specific concerns below: **1. Anti-fracture efficacy** A great deal of confusion has arisen as the appraisal process has progressed. In TA 87, the relative risk reductions were derived from studies of patients with osteoporosis (low BMD and/or a prior fracture). Subsequently, in the first ACD for primary prevention and the revised ACD for secondary prevention, the relative risk reductions were derived from the whole study populations, i.e. included patients with BMD above the osteoporosis threshold with or without a prior fracture. Generally, these led to small but important decreases in the apparent efficacies of most interventions. Importantly, these populations also included patients with a variety of other risk factors, including low BMI, smoking, moderate alcohol intakes and family history of fracture to name but a few. The relative risk reductions are an average derived from these diverse populations. If the Committee declares that the therapies are unable to reverse the risk due to these other risk factors, then the corollary is that the benefit must be even greater in groups who lack these risk factors. This inevitable result has been ignored by the present analysis that uses the average risk reduction from the whole study populations and yet excludes an effect on the risk associated with these risk factors. The focus appears to be on limiting drug use in osteoporosis.	The Committee accepted an increased estimate for the RRs applied to the risk factors age, BMD, prior fracture to allow for this assumption.
	2. Didronel PMO/Etidronate In contrast to alendronate, risedronate and strontium ranelate, the use of etidronate to prevent hip fracture remains unproven. It is unclear from the data presented about the assumptions made for the efficacy of etidronate on hip fracture. If the relative risk is correctly assumed to be 1, then it is difficult to see how etidronate would be more cost effective than risedronate, given the latter's effect to reduce hip fracture incidence. If the relative risk for hip fracture with etidronate is taken as the "single-point RR of fracture calculated from the log-normal efficacy distributions" then clearly this ignores the very wide, non-significant confidence intervals derived from 2 small RCTs. It would appear that the Committee has little regard for the quality of evidence, a stance that would inevitably lead the whole field of clinical research into disarray, with a progressive weakening of the evidence base. The recommendation of etidronate for widespread use totally discredits this technology appraisal and is very unlikely to be implemented in practice by clinicians educated in the principles of evidence-based medicine. If the Committee persists with a low evidence threshold for etidronate, a similar approach should be taken to other therapies but we strongly argue that this would also discredit the whole process.	The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy.
	3. Incremental cost-effectiveness ratios (ICERs) In the setting of secondary osteoporosis, an ICER threshold of £30000 has been chosen for first line therapies but for any subsequent use of another agent (second-line treatment strategy) the threshold is set at £20000. While we recognise that the second-line strategy will not incur identification costs or BMD scanning, there appears to be little or no justification for moving to such a stringent threshold when the second line therapies are equally efficacious to generic alendronate and yet incur a higher cost. The latter would already	The Committee applied the levels of cost effectiveness as outlined in the Guide to the Methods of Technology appraisal, section 6.2.6.10 and 6.2.6.11(Available from URL

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	limit their use to some extent without the artificial and unjustifiable move to a lower ICER.	http://www.nice.org.uk/page.aspx?o=201974)
	4. Generic Price of Alendronate The price of generic alendronate used in the modelling is now out of date. The NHS drug tariff price is currently £7.51 for 4 tablets, implying a yearly cost of £95.03. However, in the near term, the tariff price will fall further and should stabilise at around £3.50 per month, or £45.50 per year.	The cost effectiveness modelling has been updated to reflect the new price of weekly generic alendronate.
	5. Practical implications From a practical, clinical viewpoint, we do not believe the guidance is workable and think it will disadvantage and disenfranchise many patients.	
	We are concerned that the sole use of BMD measurement at the femoral neck ignores the significant proportion of patients who have large discrepancies between BMD at the spine and hip. We have previously examined data from 1586 clinical referrals to our centre aged between 40 and 95. Femoral neck BMD could not be measured in 73 individuals. Osteoporosis was diagnosed in 17.3% at both LS and FN, in 14% at FN alone, and 8.3% at LS alone. LS T score was lower than FN T score in 38% of individuals. Our data suggested that it is only beyond the age of 80 that LS measurement ceases to provide additional information.	More detail about measurement of BMD will be given in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'
	Most UK clinical services have used the Royal College of Physicians guidance (2002) to develop referral criteria and inform management decisions. We fully acknowledge the need to take resources into account, and to incorporate our increasing knowledge base around absolute fracture risk into our treatment decisions. Nonetheless, the current guidance is so far removed from the RCP guidance we have worked with for several years, we cannot see how we can alter the perceptions around management in a single dramatic step. We would argue that patients already on therapy for osteoporosis should be reassured that treatment will not be withdrawn. On the other hand, this would be perceived as unfair by patients who are not assessed until after the guidance is implemented.	NICE produces prospective guidance and this issue is clarified in the 2007 ACD section 1.5.
	Similiarly, we are astonished by the proposal that a patient has severe enough osteoporosis to warrant treatment but that if they cannot tolerate alendronate we may have to explain to them that they no longer have severe enough disease to warrant treatment with a clinically equivalent treatment. Ethically, we could not put this into practice.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and these have been based on clinical and cost effectiveness.
	Finally, whilst we agree that osteoporosis treatment should be targeted towards those at greatest clinical risk we do not believe that the primary prevention guidance will give clinicians the autonomy to identify those younger women with very low BMD who have not currently sustained a fracture. We feel it offers a very cynical approach to osteoporosis by implying that it does not exist if it has not yet resulted in a clinical outcome. The guidance also conflicts with recommendations issued about groups of patients such as those with liver or coeliac disease and women using the contraceptive agent, depo provera.	Comment noted
	We hope that these comments are felt to be constructive within the consultation process and look forward to seeing that they have been addressed in the revised draft of this guidance.	

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British Society for Rheumatology	The BSR is to glad to have the opportunity to comment on the most recent Appraisal Consultation Documents (ACDs) on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. The BSR has seen and strongly supports the comments made by the National Osteoporosis Society. However there are a number of points of concern in the guidance which we would like to draw your attention to: • In the new draft guidance it states a patient will only be prescribed a second line treatment if they do not tolerate a first line treatment or their condition becomes substantially worse. This significantly restricts treatment options available to patients. • We believe that it is inappropriate to position etidronate as an alternative to alendronate as a first line treatment on the basis of cost rather than clinical effectiveness. • By stating that young women with extremely low BMD will not receive treatment until they reach 75 unless they have a sustained fracture the guidance is effectively discriminating against younger patients even their absolute risk of fracture is identical to that of an older patient.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy
Helped the Aged	I am writing to express deep concern on behalf of Help the Aged over the recent recommendations made by NICE in their draft guidance for the primary prevention of osteoporosis. The recommendation that women under the age of 75 should not receive drug treatments to prevent broken bones due to osteoporosis is highly alarming. Help the Aged strives to prevent future deprivation and the withdrawal of primary prevention treatments from those under 75 will inevitably place greater financial strain on the healthcare system in years to come, whilst unnecessarily compromising independence and wellbeing in later life. Help the Aged works to remove the barriers to healthy successful ageing and we share your concern that NICE's latest guidance appears to be placing an obstacle to a healthy later life. Help the Aged is concerned about the direction that this guidance is taking and the effect it may have on the lives of older people and their carers. I hope that by adding our voice to your work on the guidance, we can secure a better deal for those with osteoporosis who are approaching, or in later life.	The age at which therapy can be initiated has been revised. Comment noted.

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Institute for Ageing & Health	I am happy to respond on behalf of the Institute for Ageing and Health to the latest report Appraisal Documents. I think that we all agree that there is a need to contain the drug budget for the NHS and the opportunity to promote rational prescribing is welcome. However these appraisal recommendations overstep the credibility mark. I would make a few points: 1. The methods of health economics are not applied in a consistent manner by NICE. a. Guidance on secondary prevention of myocardial infarction, specifies no specific ACE inhibitor(s). Despite the variation in costs between these agents being far greater than seen between bisphosphonates: http://www.nice.org.uk/page.aspx?o=352625 b. Concentrating on Appraisal Consultation Documents (ACD), the Breast cancer (early)- hormonal treatments ACD did not choose between available aromatase inhibitors: http://www.nice.org.uk/page.aspx?o=318564 c. Non drug-specific guidance has been provided for thiazolidinediones http://www.nice.org.uk/page.aspx?o=TA063guidance d. For dementia therapy, the cholinesterase inhibitors are treated as a class, with no direction about separate agents. http://www.nice.org.uk/page.aspx?o=322952 2. **For primary prevention of fracture** in osteoporosis, why do bisphosphonates come under such individual scrutiny? Alendronate and risedronate are effective and the former is currently cheaper. All available	The large differences in acquisition costs between the interventions made separate analyses necessary.

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	evidence suggests that Etidronate is less effective. However, there are no *head to head* studies, comparing bisphosphonates. a. *The HTA is redefining osteoporosis!* The patient with osteoporosis (t-score of –2.5) requiring treatment to prevent a first osteoporotic fracture must be over 75 to receive any treatment. b. Age is an important predictor of fracture risk but what about the 70 year old with a t-score of –3, -4 or –5? ***c.*** If patients are over 75, they receive Alendronate. However, if they cannot tolerate the drug, I must give a less effective alternative (Etidronate)! Meanwhile, risedronate is reserved for a t-score of –3. **How will I explain this to patients, rationally?** ***d.*** In all conscience, I am unable to offer an inferior drug (etidronate). Therefore, I will monitor the patient with a further DXA scan, to wait until their t-score falls below 3 (assuming that they have not had a fracture in the interim). ***What is the cost to the NHS of this strategy?*** 3. Strontium Ranelate appears to be as effective as Alendronate and Risedronate, particularly in the older age group. Purely based on average costs, I am expected to restrict prescribing of this medication 4. Finally, I am concerned that there is implicit ***ageism*** in analytical processes and the use of DALYs across the board in Technology Appraisals undertaken by NICE. For osteoporosis, affecting older people, there are fewer years available in prospect in which to limit disability! a. Comparison with the Breast cancer hormonal treatments is one example. The agents reviewed showed costs above £20,000/QALY except when considered using a 'benefits maintained' model that the benefit of the treatment is greater long after discontinuation. b. Has the application of a similar 'benefits maintained' model been considered for osteoporosis therapies, particularly in younger post-menopausal women?	The age at which therapy can be initiated has been revised according to the comments received. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy. Comment noted. Comment noted In the model the benefit of treatment carries on after treatment ceases.

Consultee or Commentator	Comment	Institute Response

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National Osteoporosis Society	The National Osteoporosis Society (NOS) is glad of the opportunity to comment on the most recent Appraisal Consultation Documents (ACDs) on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. In view of the fact that our responses to each of these documents are substantially the same we have incorporated our comments with respect to both ACDs in a single document to avoid duplication. We recognise that some modifications to the draft guidance have been made consistent with our submission on the ACDs published in September 2005, including redefining intolerance to bisphosphonates and links to other relevant NICE guidance. However, we are extremely concerned that the current ACDs describe draft guidance that is even more restrictive than the ACDs on which we commented at the end of 2005. For example, the primary prevention ACD now only recommends treatment for the over 75s, and in both ACDs second line treatments are only recommended if a woman's' risk of fracture increases significantly. Concern regarding the implications of this draft guidance has been voiced to us directly by many of our members, members of the public and health professionals over the last three weeks. Medical staff managing patients with osteoporosis and treating the consequences of fracture tell us that these ACDs are clinically unworkable and will severely disadvantage patients at risk of first and second fractures as indicated in the examples below. Furthermore, in some areas these clinicians believe that the provision of treatment in accordance with the current guidance would be both unethical and inconsistent with their duty of care. This letter highlights our main points of concern under three separate headings; Process, Clinical Workability and Member and Patient Responses. In addition, we have provided comments, within the framework that you requested in your letter of 21st September, as a table, which is attached as Appendix I to this letter. In Appendix II there is a synopsis of just some of the comments that we have received by email from our members and members of the general public. They have been recorded verbatim on the whole, with careful editing to ensure anonymity of the author. Finally, Appendix III is a letter from a Director of Help the Aged to the NOS voicing their serious concerns on the ACDs. **Process** The NOS is particularly worried about the robustness of the development process of these Technology Appraisals. This follows on from, but is more serious than the points highlighted in our response to the DSU analysis dated 23rd August 2006. Since the last ACDs were published in 2005, the price of alendronate used in the most recent modelling has decreased by almost a half from £21.90 (in March 2006) to £13.27 (in July 2006). As there has been no new evidence reported on epidemiology, disutility caused by fractures, efficacy of the drug treatments or adverse events, we confidently expected that this would lead to improved cost effectiveness and thus more permissive guidance, particularly with regard to prescribing of alendronate. However, the result has been guidance that is even more restrictive. Initially we could not understand how reducing cost has resulted in further restricting availability of a drug treatment. The fact is that the increase in restrictiveness is due to other changes that have been made to the input parameters of the model. The reasons for incorporating these changes have not been explained and the evidence to support them has not been identified. This lack	The age at which therapy can be initiated and DXA requirements for older women have been revised following the comments received. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy. All individual comments noted. At the Committee meeting to agree on the content of the 2006 ACD, the Committee concluded that there was insufficient evidence that the drugs under consideration would reduce fracture risks that was not associated with low BMD, age, or prior fracture. The Committee noted that the distribution of additional risk factors was similar across all BMD sub-groups in the large FIT trial. If there was an effect for all clinical risk factors a greater drug effect would have been expected in the higher (less severe) BMD sub-group than was observed.

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	of transparency has severely limited our ability to consider the ACDs and to comment usefully upon the proposed guidance. The most important of the changes to which we refer are listed below and each of them will be considered in more detail in the relevant sections of this response. • The Appraisal Committee have assumed that drug treatments have no effect on the component of fracture risk contributed by independent clinical risk factors other than age, sex and BMD. The NOS does not believe that the evidence supports this assumption. Most phase III trials do not exclude women if they have risk factors other than age, sex and BMD (rheumatoid arthritis and glucocorticoid use are often exceptions). Thus, in these trials the efficacy estimates take into account any potential reduction in efficacy that is due to the presence of other risk factors. • The estimate used for efficacy of alendronate against hip fractures used by the Appraisal Committee to determine the cost effectiveness of treatment has been reduced from that relied upon for the purposes of TA 87 and through each of the different stages of modelling in this appraisal, even though each calculation is based on the same 16 studies. Therefore TA 87 used a relative risk of hip fracture associated with alendronate therapy of 0.49, while the current ACDs are based on a relative risk of hip fracture, calculated from pooled data relating to alendronate and risedronate of 0.71. The ACDs include no explanation or justification for the changes in approach which appears inconsistent with the evidence and intended simply to present alendronate as being as ineffective as possible. In particular, it is unclear why it is considered appropriate to combine the data for alendronate and risedronate to produce a combined figure for efficacy in view of the fact that the products are considered separately in the guidance and this strategy merely has the effect of diluting the benefits of alendronate. • The Appraisal Committee have chosen to set the disutility caused by vertebral fractures in the first year to 0.792, (which is the same as that reported for a hip fracture), rather than to the value reported in the literature of 0.626. No explanation for this approach is provided and the NOS is not aware of any evidence to support the figure chosen. This manipulation of the inputs to the economic model is inappropriate and has resulted in the Appraisal Committee presenting osteoporosis as a disease that is not cost-effective to treat in the majority of people. Although we feel that the model itself is robust, we would argue that the way that the Appraisal Committee has utilised the model - repeatedly "tweaking" the inputs without any explanation or evidence to support the changes - has now resulted in output and preliminary guidance that is fundamentally flawed and which downplays the cost of suffering experienced by our members. Since the ACDs have been issued for consultation the price for alendronic acid, 70 mg (4 tablets) set out in the NHS tariff has been further reduced to £7.30 (almost half the figure used in the modelling). It is self evident that, if the guidance is to be relevant to the treatment of patients with osteoporosis in England and Wales, it must be based on accurate current cost information. It is therefore clear that the recent price	Following consultation on the 2006 ACD, the Committee decided that the assumption of no efficacy on fracture risk associated with risk factors other than low BMD, age, or prior fracture (0% efficacy assumption) was probably too extreme. On balance, 50% efficacy for the fracture risk not associated with low BMD, age, or prior fracture was considered a reasonable, although necessarily approximate position. This position was taken as the Committee was still not persuaded that there was unequivocal evidence that the drugs alone would reduce the overall fracture risk for factors other than low BMD, age, or prior fracture.In addition, the Committee accepted an increased estimate for the RRs applied to the risk factors age, BMD, prior fracture to allow for this assumption. The analysis was carried out for combined (second generation) bisphosphonates on the advice of the Guidelines Development Group as it was considered that the second generation bisphosphonates had an overlapping efficacy range and could be considered a clinical class The Committee recognises that hip fracture is a major event and often argued to be a key goal for prevention of fractures. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that it was unlikely

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	reduction in alendronic acid must be reflected in the modelling, and the cost effectiveness of this product revised before the Institute's guidance is finalised. Furthermore, in view of the fact that the prices of all bisphosphonates may be reduced prior to March 2009, the date set for review, we would ask the Appraisal Committee to ensure that the guidance is "future proof" in terms of indicating the cost at which all such products would become cost-effective for all eligible patients.	that this would so greatly outweigh the utility decrement associated with a hip fracture. The Committee therefore considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip fracture The cost effectiveness modelling has been revised to the price of £7.31 for 4 tablets (November 2006). Potential future price reductions have not been included.
	The NOS firmly believes that osteoporosis should be considered in the same way as other diseases for which prevention is key, such as coronary heart disease or stroke. From these ACDs it appears that NICE are downplaying the significance of osteoporotic fractures by not even considering cost per QALYs (CPQs) above £20,000 in the ACD on primary prevention. No explanation for this approach is provided in the ACD and it appears inconsistent with NICE's own procedures, which do not impose a rigid cut-off value. The "Guide to the Methods of Technology Appraisal" provides at paragraph 6.2.6.10 that between ICER values of £20,000 and £30,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to certain identified factors, including the societal benefits of treatment. It is therefore clear that the Appraisal Committee is required to consider usage of technologies under consideration within this ICER range and to give reasons for or against recommending use in NHS patients. Such consideration is wholly lacking from the ACD dealing with primary prevention, which does not even identify ICER values associated with osteoporosis treatments, where these exceed £20,000/QALY. It is clear from the NOS's previous submissions, that we believe wider societal benefits in the prevention of osteoporotic fractures are enormously important. It is, therefore, essential that NICE explains fully its conclusions with respect to the ICER values associated with osteoporosis treatments and provides a reasoned justification for its refusal to consider recommending treatment in circumstances where it has calculated an ICER value of between £20,000 and £30,000/QALY.	The Committee applied the levels of cost effectiveness as outlined in the Guide to the Methods of Technology appraisal, section 6.2.6.10 and 6.2.6.11(Available from URL http://www.nice.org.uk/page.aspx?o=201974)
	Furthermore, for secondary prevention, although a CPQ of £30,000 was considered when modelling for alendronate, for all of the other drug treatments the cut off was set at £20,000/QALY and higher CPQs were again not even considered. In earlier ACDs higher CPQ were considered (and indeed accepted in TA 87). No explanation for this inconsistency is provided and again it does not reflect NICE's procedures. A clear Moving of the goal posts is demonstrated by these changes and this requires proper justification; this is lacking from the ACDs.	The 2007 ACD has been amended accordingly.

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	The Appraisal Committee has become gradually more conservative in its treatment of osteoporosis. The committee has also suggested that the prevalence of osteoporosis is much lower than has been previously reported (see sections 2.5 in both ACDs). This conclusion appears to be based on a single study (Holt et al., 2002) which did not adequately recognise all cases of osteoporosis. It is therefore likely to be a substantial underestimate. The overall result is that it appears to our members that NICE are trivialising the cost and personal impact of osteoporotic fractures. While the NOS recognise that limited resources should be used in the most cost effective way, we also believe that all disease areas should be considered on an equal basis. If it is cost effective to treat osteoporosis according to current CPQ thresholds (and we believe it is), it is not within NICE's remit to make decisions on whether or not there are sufficient NHS resources to accommodate the costs. This is a matter of affordability which is a decision properly reserved to the Secretary of State. In the response to the DSU analysis in August, the NOS raised concerns over the Appraisal Committee's move to self-identifying and opportunistic assessment. The NOS believes that this change further reflects the fact that the Committee are becoming increasingly conservative in their approach to osteoporosis. Within these ACDs the cost of BMD assessment of the entire potential population for treatment are included in the economic model. By doing this, NICE are effectively screening for osteoporosis and including the cost of this in the assessment of the cost effectiveness of osteoporosis treatments. We are not aware of any other NICE TA that has included the cost of screening, but note that there are a number of recent TAs which do exclude the costs of screening (for example, TA's 52 and 47 for myocardial infarction and acute coronary syndromes and TA 36 for rheumatoid arthritis). The cost-effectiveness of screening does not lie within the scope of this TA and we are therefore extremely concerned at the negative impact that this has had on the economic modelling. These ACDs do not include recommendations for women with clinical risk factors whose bone density falls into the osteopenic range. It is implicit from the introductions to the ACDs, which refer to women with osteoporosis, that patients with osteopenia are not considered, although this is not clearly stated. However, the results of the economic modelling suggest that in some cases it would be cost-effective to treat osteopenic patients. The NOS are concerned that the division of the original scope which was going to consider primary and secondary prevention in the same appraisal, into separate appraisals for primary and secondary prevention and the addition of the TA on strontium ranelate for secondary prevention, may have produced confusion as to the remit of the Appraisal Committee and whether the situation of osteopenic patients should be considered. The original scope notes that; *"although current diagnostic definitions for osteoporosis are based around BMD, other factors need to be considered when assessing overall risk of fracture"*	The Committee did not take affordability into account when making its decision. The Committee agreed that all costs should be included in the assessment of the cost effectiveness or primary prevention strategies; this includes this cost of opportunistic identification of women who can benefit from primary prevention therapy. The Institute has decided that the technology appraisal will only consider osteoporosis (a T score of equal to or below -2.5 SD), and that osteopaenia (a T score between -2.5 and -1.0 SD) will be considered in the clinical guideline 'Osteoporosis: assessment of fracture risk and the

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	suggesting that osteopenia should be part of the appraisal, in circumstances where other clinical risk factors were present. Furthermore, the population to which the scope refers includes post-menopausal women at risk of developing osteoporosis. For these reasons we are concerned that the Appraisal Committee now seems to have relegated osteopenia to the remit of the Guideline Development Group (GDG). The evidence suggests that most fragility fractures occur in women whose bone density is not in the osteoporotic range and there is also considerable evidence that shows that bisphosphonates are effective in reducing the risk of non-vertebral fractures in patients whose bone density is not osteoporotic. It is therefore essential that the position of such patients is considered by the Appraisal Committee and appropriate guidance on treatment issued to avoid confusion in doctors and patients.	prevention of osteoporotic fractures in individuals al high risk'. It should be noted that weekly alendronate and risedronate, strontium ranelate and raloxifene have a marketing authorisation for the treatment of osteoporosis, and not osteopenia. This would have hindered the development of recommendations by the Appraisal Committee for the use of these drugs in osteopenia.
	In previous submissions, we have commented that the evidence supports the inclusion of alcohol consumption and current smoking as risk factors for fracture. The evidence demonstrates that alcohol consumption of more than 2 units per day significantly increases the risk of fracture. However, although alcohol consumption has been included as a clinical risk factor in these ACDs we are concerned that it is included at daily intakes of 4 units or more. Furthermore, the Appraisal Committee continue to exclude smoking as a risk factor, despite their being evidence to support its inclusion. The NOS are concerned that the recommendations made by the Appraisal Committee are not based on the evidence and that there is no transparency in the reasoning behind this.	The Committee has reviewed the evidence available to it and did not see any evidence that daily intakes of alcohol of less than 4 units increase fracture risk.
	The proposed guidance for primary prevention does not permit any change in therapy for patients who fail to respond to alendronate and etidronate but who are able to comply with the instruction for administration and are not intolerant of these treatments. Similarly the proposed guidance for secondary prevention will not allow for any alternative treatment for patients who fail to respond to alendronate and etidronate but are able to comply with the instruction for administration and are not intolerant of these treatments unless such patients are eligible for teriparatide. This situation, which represents a significant change from the 2005 guidance (TA 87) is not explained and appears irrational.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy.
	Clinical Workability If this guidance is published without major revision, it will result in a huge number of patients who are currently being treated for osteoporosis being denied treatment after its implementation. This concern has been voiced by many callers on our helpline and via emails and phone calls to our Policy Department. Clinicians would have to explain why a treatment, which is clinically effective (and for secondary prevention, cost effective based on NICE's own assessment in TA 87), may no longer be prescribed. The NOS urges NICE to ensure that both the primary and secondary prevention ACDs include a statement that will ensure that all of those people who are currently taking a treatment would not have their treatment withdrawn on implementation of this new guidance, as it does in other TAs.	NICE produces prospective guidance and this issue is clarified in the 2007 ACD section 1.5.

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	Under this new draft guidance, if a patient does not tolerate a first line treatment, their condition would have to become substantially worse before they could be prescribed a second line treatment. A GP called us to discuss a hypothetical patient and how he would treat her under the new guidance. The patient he described was a 65 year old woman with vertebral fractures and a T-score of -2.6 SD to whom he had prescribed alendronate. When one month later she presented with oesophageal symptoms he would be unable to prescribe her a second line treatment. He said that this would be inconsistent with his duty of care and unethical. We believe that there is no other disease area or healthcare system where there are 5 or 6 treatment options (and where there are only modest differences in cost in most cases) that have had second line treatments restricted in this way and we urge the Appraisal Committee to reconsider its conclusions.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy.
	The positioning of etidronate as an alternative to alendronate as a first line treatment has also caused much clinical concern. We accept that etidronate is low cost and that given the disutility of vertebral fracture comes out as competitive in the model scenario. However, there is no RCT evidence for non-vertebral and hip fracture risk reduction and we strongly question its prominence as an alternative first line treatment simply on economic grounds. It is perhaps for this reason that etidronate was never approved in the USA because the FDA did not consider the evidence of its effectiveness to be good enough. We do not believe that the inclusion of data from an observational study for one drug treatment is appropriate. Several of our clinical advisors have voiced that the prescription of etidronate to many of their patients would be inconsistent with proper clinical care.	The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy.
	Under this guidance, younger women with extremely low BMD will not receive treatment until they reach the age of 75 unless they have sustained a fracture. The NOS are extremely concerned that these ACDs are ageist in the way in which they discriminate against younger patients even if their absolute risk of fracture is identical to that of an older patient. For example, a clinician reported that a 68 year old woman scanned recently at their specialist centre, had osteopenia noted on X-ray. She was a recurrent faller but had no fractures when seen. Her T-score at the hip was -4.0 SD and at the spine -5.9 SD. Her absolute risk of experiencing a fracture was higher than most of the patients over 75 that present to their clinic, yet under this guidance she would not be offered a treatment. The NOS are disappointed that the recommendations that are being made in these ACDs will not allow all women who are at a high enough absolute risk of fracture to have access to a treatment.	The age at which therapy can be initiated has been revised according to the comments received.
	In practice, clinicians currently consider the BMD at both the hip and spine when considering treatment options. Indeed, we know that there are many younger or middle aged women who present with normal BMD at their femoral neck, but very low T-scores at their lumbar spine. We cite as two examples i) a lady of 72 scanned in the past month at one of our recognised centres who had sustained an early menopause at the age of 40 and whose hip T-score was -1.6 while her lumbar spine was -3.8. and ii) a lady of 62 who presented with a Colles fracture and has chronic liver disease who had not received corticosteroid therapy	More detail about measurement of BMD will be given in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'

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	whose hip T-score was -1.7 and spine score -3.9. Neither of these women who are at a high risk of vertebral fracture would receive treatment under this new draft guidance. The NOS would like to make the suggestion that the Appraisal Committee re-phrase section 2.4 in both ACD documents to *"T-score measurements vary by site and method. It has been recommended that BMD should be measured at the femoral neck and/or lumbar spine using DXA to estimate fracture risk and that treatment decisions should be based on the lowest value".* The NOS has begun to try to develop algorithms from this guidance which would allow clinicians to follow the recommendations in practice. However, in particular for the guidance on secondary prevention of osteoporotic fractures, it is almost impossible to produce a clinically useful tool. We believe that this draft guidance, if implemented as it stands would cause widespread confusion. The vast change in attitude towards primary prevention from the current RCP guidelines, which are widely used, will add to this particularly in the primary care setting. The direction taken by the Appraisal Committee on this guidance will put England and Wales, and assuming further acceptance by NHS Quality Improvement Scotland and the Northern Ireland Health Boards, the UK, in a position that stands it apart from the rest of the world. The NOS remains concerned that these draft ACDs, if published in their current form, do not allow the GDG enough freedom to produce a clinically robust osteoporosis guideline that is useful in clinical practice. **Member and Patient Responses** The NOS is a patient organisation with more than 23,000 members. We believe that we are in a unique position to provide a patient perspective on this draft guidance. In developing this response we have been overwhelmed by emails and phone calls both directly to our Policy Department, but also through our nurse-run Helpline from concerned NOS members and the public. We have included a selection of the comments we have received by email during the public consultation, on this document in Appendix II. We strongly believe that these concerns represent the concerns of our 23,000 members and hope that they help to illustrate to the Appraisal Committee that osteoporosis is certainly not a disease that should be trivialised and treated conservatively. Quotes from NOS members, including patients, carers and health professionals are included to support other sections of this submission. In conclusion, the field of osteoporosis has seen huge advances in diagnostic risk assessment and therapy in the last 20 years. The NOS feels that the draft guidance upon which we have been asked to consult	Comment noted. Comment noted. Comment noted. Comment noted.

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	represents a serious step back from the achievements that have been made.	
Royal College General Practitioners 1	<u>General</u> • I feel that the advice will be difficult to follow. Different bone mineral densities are to be used as thresholds for prescribing different drugs. This is too complex within a busy clinic setting. • It has been recommended that only the T score at the hip is to be used. Lumbar bone mineral density is conventionally also reported. A proportion of vertebral fractures will be missed if this guidance is followed. • Etidronate has been recommended. There is no randomly controlled trial evidence that this drug prevents hip fracture. The newer aminobisphosphonates have much greater clinical effectiveness. Clinical experts do not recommend the use of this medication. • The issue of compliance has been discussed and yet no mention has been made of the differences between daily or weekly administration of these drugs. There is a significant difference in both adherence and persistence between the dosing regimes. • Intolerance has been redefined and the patient no longer needs a gastroscopy. This is sensible. <u>Primary Prevention</u> • There seems to be an assumption of 0% efficacy of clinical risk factors to fracture risk other than age, BMD and previous fracture. This seems to be in contrast to the international evidence.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy. More detail about measurement of BMD will be given in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' Comments noted. Following consultation on the 2006 ACD, the Committee decided that the assumption of no efficacy on fracture risk associated with risk factors other than low BMD, age, or prior fracture (0% efficacy assumption) was probably too extreme. On balance, 50% efficacy for the fracture risk not associated with low BMD, age, or prior fracture was considered a reasonable, although necessarily approximate position. This position was taken as the Committee was still not persuaded that there was unequivocal evidence that the drugs alone would reduce the overall fracture risk for factors other than low BMD, age, or prior fracture. In addition, the Committee accepted an increased estimate for the RRs applied to the risk factors age, BMD,

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	• Only patients 75 yr and older have been considered. Younger patients at high risk, calculated using other risk factors are not considered. This is in conflict with the World Health Organization algorithm that is being developed. • • • Patients who suffer with dyspepsia and cannot tolerate bisphosphonates will need to have much worse osteoporosis before strontium can be used. I feel that this is in conflict with our 'duty of care'. Patients with dyspepsia are being penalized. In conclusion I do not feel that these documents will be respected by the clinical experts in osteoporosis.	prior fracture to allow for this assumption. The age at which therapy can be initiated and DXA requirements for older women have been revised following the comments received. This guidance does not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. Comment noted
Royal College General Practitioners 2	The RCGP has highlighted before the need for an algorithm or other tool for quantifying the absolute risk of osteoporotic fracture on the basis of risk factors. The NICE guidance alludes to the development of such an algorithm by the WHO (section 2.12) It is essential that this algorithm is widely publicized for GPs who use the NICE guidance as soon as it is available,. And I would like to see an undertaking on the part of the committee to add it electronically to their guidance as soon as it is available, even if they insist on including a proviso that it has not been formally included in their considerations because it was not available at the time of drafting of the final guidance There are obvious gaps in the guidance for women over 75 with T scores between -2.5 and -3 who cannot tolerate alendronate, or for women over 75 with T scores between -2.5 and -4 who cannot tolerate bisphosphanates - the guidance recommends that they need treatment (section 1.1) but do not offer an alternative if they cannot tolerate alendronate or bisphosphanates, as its criteria for the use of risedronate and strontium ranelate are different for those for alendronate. This is an obvious inequity of provision	The Institute has received the data related to the WHO algorithm under a confidentiality agreement and therefore cannot publish it with the guidance. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment.
Royal College of Nursing	**Primary Prevention of Osteoporosis in Post-menopausal Women** The Royal College of Nursing welcomes the opportunity to review this document. We welcome the extensive work and research undertaken in this appraisal. We are pleased to see in the document and welcome the self identified /GP opportunistic assessment of osteoporosis risk which is a significant step forward in pro-active management to reduce the risks related to osteoporosis. However, we consider that some of the recommendations in the document if adopted will result to a backward step in the care of patients with osteoporosis and suggest that they be given further consideration. In our view, the appraisal has serious omissions in relation to primary prevention in the under 75's and	The age at which therapy can be initiated has been revised following the comments received.

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	believe that the guidance should and must address early primary prevention for these groups of patients. We note that generic alendronate is the primary bisphosphonate but would point out that not all patients can tolerate it due to gastric disturbance. In practice, if there are reasonable concerns about this, Risedronate is prescribed first line. Also, it is somewhat confusing when identifying etidronate as less clinically useful, why then is it being indicated as second line after alendronate? The interventional T-scores are also confusing, when patients fail on alendronate. Is it then appropriate to change the patients to risedronate / strontium with a T score of -2.5 or do they then have to have lower T scores - this relates to the t-scores stipulated for each individual therapy, i.e. it states that a patient should have a lower score before commencing on different therapies, this needs clarifying within the document. We also believe that the risk of failing to continue treatment (persistence) is quoted at 50% (although other data have suggested 75%) However, the issue is how this data can be improved with the production of the NICE Osteoporosis Guidance. Currently many patients are prescribed bisphosphonates without sufficient education/information given to ensure they have fully understood the reasons for their treatment, information on how to take the medication etc. This can be significantly improved with appropriate focus on nurse/pharmacist input. This is a vital component that must be accounted for and stressed in any guidance. With regards to compliance, although it has been mentioned in the ACD, there is no real strategy built in to assess compliance. Prescription event monitoring does not really assess if the patient has taken their medication, only that it has been collected. For those patients with dyspepsia, what happened next? Who assessed them? We consider that the CNS has a role here. We are pleased to see the assessment of risk factors in the GP opportunistic review and welcome the inclusion of conditions such as Rheumatoid Arthritis (but also recognise there are other conditions that need to be included - such as those that significantly reduce functional ability etc or have been shown to pre-dispose to osteoporosis). We would also welcome a global approach to identifying those taking high doses of steroid (more than 7.5mg a day) being discussed and referred to relevant guidance (this is in relation to the risks associated with steroid dose in the context of the overall assessment). However, we do recognise that there will need to be greater clarity about these risk factors and how an algorithm is prepared for instance on treatment options. We hope that this would include failure to tolerate bisphosphonates and options to have other treatment choices (based upon appropriate counselling and review process to promote adherence).	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. This will be addressed in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' The 2007 ACD recommendations explicitly do not cover the treatment of people who are on long-term systemic corticosteroid therapy. The NICE clinical guideline will cover the treatment of the group of people.

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	We support the reduction in criteria that dictates a DEXA scan is required when clinical judgement shows a high index for treatment. With regard to calcium and vitamin D, we consider that a universal assessment within the clinical guideline is an excellent move forward. **<u>General comments with respect to both ACDs</u>** We reiterate that denying treatment to the under 75years age group until they have sustained a fracture is the most worrying aspect of these documents. The increased number of fractures that will occur can not be justified on the basis of cost effectiveness. Fractures are costly both in financial and human terms and any measures that can be taken to avoid their occurrence has been the focus of 'osteoporosis' and other clinics, together with the National Osteoporosis Society for many years now. Having a choice of treatments in recent years has helped with patient compliance/concordance and we are concerned that a patient maybe advised to continue taking generic alendronate even if they have persistent side effects.	Comment noted. The age at which therapy can be initiated has been revised following the comments received
Society for Endocrinology	The Society is grateful for the opportunity to comment on this proposed guidance. This is especially relevant, as we believe that the new proposals will lead to guidance which is more restrictive and less clinically workable than the existing recommendations on the secondary prevention of osteoporotic fractures. We were amazed to see that despite the considerable fall in the acquisition cost of alendronate the secondary care guidelines are more conservative. In the absence of any new information on clinical effectiveness or disutility this must mean that the modelling assumptions have been changed between the two sets of recommendations. Although these assumptions are briefly described no justification for them is offered and we seriously question whether any such justification can be made; rather it appears that they were arbitrary decisions made by the committee perhaps with a view to minimising the cost of utilisation of the technologies in question. Of these assumptions the ones most open to question are: • The assumption that there was “an absence of evidence to demonstrate that treatment with any of the drugs under consideration would reduce fracture risk that was not associated with low BMD, age or prior fracture”. This is simply incorrect. There is abundant evidence that all the treatments will reduce vertebral fracture risk whatever the source of that risk and increasing evidence that the same is true for non-vertebral fracture (except for etidronate and raloxifene, where there is no non-vertebral efficacy anyway). Exclusion of these risks will seriously underestimate the true efficacy of these treatments and hence suggest that they are less cost effective than is really the case.	Comment noted. Following consultation on the 2006 ACD, the Committee decided that the assumption of no efficacy on fracture risk associated with risk factors other than low BMD, age, or prior fracture (0% efficacy assumption) was probably too extreme. On balance, 50% efficacy for the fracture risk not associated with low BMD, age, or prior fracture was considered a reasonable, although necessarily

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	• The committee appear to have arbitrarily set the disutility value associated with vertebral fracture to a level which they think is "right" rather than that described in the literature. The justification for this is facile; especially from a group of non-experts, who are ill qualified to make this judgment. This appears to be a total travesty of evidence based medicine. We believe that the effect of both of these is to devalue the treatment effects in this patient group hence leading to the recommendation that the treatments be denied to many women who could cost effectively have been treated. We believe that there is an underlying assumption against the clinical reality and consequences of osteoporosis in the recommendations. Examples of this include: • The downplaying of the prevalence of osteoporosis in both ACDs by suggesting that the prevalence is lower than usually accepted. We believe that this may be the result of accepting a study which was primarily based in East Anglia and only examined bone density at the hip. The consequence of this is that not only did this survey grossly underestimate the prevalence of the condition; it also may not apply generally to the UK. • The change in MAICER between the secondary prevention ACD and the previous guidance. We do not understand why a MAICER of £30 000 was used for alendronate and £20 000 for other interventions. • The arbitrary changes in disutility referred to above. We are also concerned that the guidance recommended by these proposals is totally unworkable in clinical practice:	approximate position. This position was taken as the Committee was still not persuaded that there was unequivocal evidence that the drugs alone would reduce the overall fracture risk for factors other than low BMD, age, or prior fracture.In addition, the Committee accepted an increased estimate for the RRs applied to the risk factors age, BMD, prior fracture to allow for this assumption. The Committee recognises that hip fracture is a major event and often argued to be a key goal for prevention of fractures. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that it was unlikely that this would so greatly outweigh the utility decrement associated with a hip fracture. The Committee therefore considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip fracture. The 2007 ACD has been amended accordingly. This was a misunderstanding and the 2007 ACD has been amended to increase the clarity.

Consultee or Commentator	Comment	Institute Response
	• The move from alendronate to other therapies seems a very cumbersome process and is likely to be difficult to achieve in clinical practice. In particular the injunction to obtain BMD in elderly patients who have already fractured seems to us to be cruel and unnecessary as well as being wasteful of scarce NHS resources. • Furthermore, we believe that the tiered approach to treatment with different thresholds for different interventions will be difficult to implement and likely to cause discontent amongst patients who are denied a second treatment having had problems with alendronate. • The placing of etidronate as a joint first line therapy indicates how the committee have allowed cost effectiveness considerations to over rule clinical effectiveness. The evidence that this agent is of any use against non-vertebral fractures is so scant that we should not be recommending its use if there is serious concern about non-vertebral fracture occurrence. • We are concerned that the recommendation is to use femoral neck BMD. This is often no longer reported by many scanning units, having been superseded by total hip measurements. By excluding lumbar spine measurements many patients with spinal osteoporosis, at risk of vertebral fracture, will be excluded from this guidance. • There is inconsistency in the place of intolerance and ineffectiveness in the movement between treatment modalities • The choice of risk factors appears to be capricious and at variance with the literature, particularly the meta analyzes that have been published in the lead up to the WHO technical bulletin on fracture risk prediction. We fear that when this document is published (and we believe this to be imminent) there will be great confusion in the clinical community as to the correct basis on which to assess fracture risk.	The 2007 ACD gives recommendations only for the initiation of primary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. More detail about measurement of BMD will be given in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' The 2007 ACD recommendations do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The Committee has considered risk factors carefully and its considerations are in the 2007 ACD section 4.3.5. The background section in the ACD has been amended to increase clarity.

Consultee or Commentator	Comment	Institute Response
	• It might have been easier and would "future proof" the guidance against the WHO document if the committee were to express its recommendations in terms of absolute fracture risk and whilst waiting for the WHO document produce indicative guidance using age, fracture history, BMD ± other clinical risk factors. We hope that the committee will be able to incorporate these comments into the next stage of development of their guidance. Without major changes we fear that the proposed guidance will be clinically unworkable and will set back the management of women with osteoporosis in the NHS.	Because of the absence of a published and accepted algorithm to which clinicians can refer to, the Committee is not in a position to quote absolute risk figures.
Society & College of Radiographers	The Society and College of Radiographers together form the professional body and representative organisation for the radiography workforce in the UK. The organisations' public responsibilities lie in the development of professional and practice policies, educational standards and the promotion of research in the science and practice of radiography in both the radiotherapy and diagnostic imaging disciplines. These principles are mirrored within our policies and support for members within their professional practice and in their need for support and representation in the workplace. The Society and College of Radiographers is pleased to have the opportunity to comment on the Health Technology Appraisal through a consultation process. In making this response we have taken views from expert members within the field of osteoporosis evaluation. I am afraid that the two documents are generally regarded as disappointing in the view of the Society and College of Radiographers. We find that they are far from encouraging in the level of support given to clinicians and patient in the uphill task of prevention and treatment to the debilitating effects of osteoporotic fractures. The primary prevention consultation outlines NICE recommendations for the use of agents in patients at risk of osteoporotic fragility fractures. However the recommendations seem to be at	Comments noted.

Consultee or Commentator	Comment	Institute Response
	variance with the objective of presentation. The documentation does not advocate the need for primary prevention until the age of 75 years, by which time it is too late for any treatment to have any appreciable time to show an advantageous effect. High risk should in our view be the trigger for treatment, just as it is in heart disease or stroke. It is not appropriate for "primary prevention" to in reality imply a catch up treatment once a fracture has been documented. In our opinion the presence of an osteoporotic fracture signals failure to prevent the disease and its effects. It is inappropriate for this to be the trigger to prevent the condition which in effect has caused the fracture in the first place. Turning to the secondary prevention of osteoporotic fracture appraisal document, we find that this is far too complicated in the scenarios concerning when and what treatment might be offered once a fracture has occurred. In our view it has too many sections of thresholds, with and without concomitant risk factors and ever changing levels of Bone Mineral Density. There is a risk that all those concerned are going to be confused about prescription recommendations. We fear that this will result in inappropriate treatment choices or no treatment at all. In conclusion we can only assume that the reasons for recommending delay until first fracture must be concerned with cost saving. This in our view defeats the objective and does nothing to alleviate the pain and anguish of each patient who has an unnecessary fracture. It is documented that every single hip fracture costs the NHS a minimum of £12,000. This does not take into account the cost of social care post operatively where I believe the national daily cost runs at £5 million. In our view, the NICE recommendations fail to take a significant opportunity not only in ensuring patients and practitioners are supported by sound guidance but also in making a significant change to cost effective health care. I trust that this response is useful to you in concluding the consultation process. Please do not hesitate to get in touch if we can be of any further help or if you require clarification of any of our points.	The age at which therapy can be initiated and DXA requirements for older women have been revised following the comments received. The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy. Comment noted.

<table>
<tr><th>Consultee or Commentator</th><th>Comment</th><th>Institute Response</th></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Southwark PCT</td></tr>
<tr><td></td><td>Southwark Primary Care Trust generally agrees with the ACD and has outlined our comments below.

<table>
<tr><th>Headings</th><th>Comments</th></tr>
<tr><td>Primary prevention</td><td>We generally agree with the ACD</td></tr>
<tr><td>Relevant evidence</td><td>• Yes but there has been a further reduction in the drug tariff price of Alendronic Acid. This will strengthen the case for Alendronic Acid.
• Calcium and Vitamin D supplementation. The recommendation for supplementation is welcomed although there is a need for guidance to be included in the technological Appraisals. We also feel that the language needs to be stronger to encourage prescribing of supplements. (Unless clinicians are confident of adequate intake supplementation should be provided rather than considered).</td></tr>
<tr><td>Clinical & cost effectiveness
Resource impact and implications on the NHS</td><td>Although Clinical and cost effectiveness have been taken into consideration, the ACD did not contain any information on Resource impact and implications on NHS resources. We are therefore unable to comment on this.</td></tr>
<tr><td>Are provisional recommendations of the appraisal committee are sound and constitute a suitable basis for the preparation of guidance to the NHS</td><td>We are unable to respond to this point as we have not been able to respond fully to the second point above</td></tr>
<tr><td></td><td>Use of language.</td></tr>
</table></td><td>Comment noted.

The price reduction for Alendronate to £95.03 per year has been included in cost effectiveness modelling on which the recommendations are based.

The Committee is not in a position to recommend the provision of Ca/ Vit D, as this was not included in its remit for this appraisal.

A costing report and template will be available separately when the guidance is published.

Comment noted.

The word persistence has been used.</td></tr>
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<table>
<tr><th>Consultee or Commentator</th><th>Comment</th><th>Institute Response</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>• Use of comply in 1.3,1.4,4.3.21 compliance in 4.1.11.4. The preferred choice is adhered to
• 3.6 “Specific instructions” is preferred to “complex instructions” &” special instructions” in 4.3.21</td></tr>
<tr><td>Other comments</td><td>Use of language.
1.3,1.4, 4.1.12.4,4.3.21,4.3.19,4.3.22 uses comply while adhered to is used in 1.7. The preferred choice is adhered to
3.6 “Specific instructions” is preferred to “complex instructions” &” special instructions” in 4.3.19,4.3.21</td></tr>
<tr><td>Consistency</td><td>3rd point of 1.1 Should read post menopausal and below 65 as in 1.3</td></tr>
</table>
There may be other areas of the documents where the terms comply and adhere have been used has been used</td><td>The word persistence has been used.

The word persistence has been used.

The 2007 recommendations have been amended.</td></tr>
<tr><td colspan="3">NHS Quality Improvement Scotland</td></tr>
<tr><td></td><td>Reviewer 1

General feedback
Health economic analysis
Overall, these two documents advocate a very conservative approach to fracture risk reduction; this arises from the ICER which, somewhat arbitrarily, has been set at £20K. Use of £20K contrasts with the recommendations of Dept of Health in 1998/9 when the RCP guideline on the management of osteoporosis was written, it contrasts with the original analysis by NICE in 2005 and appears to treat osteoporosis differently from other disease areas.

We must recognise that the health economic analysis is a somewhat less precise science than the presented analysis might lead us to believe - the outcomes being entirely a function of the assumptions that have been created. It is striking that the health economic modelling generates a figure to the single pound and not a range within which the true value might actually lie!

Inconsistencies between the ACDs in how treatment is targeted
Contrasting approaches to the identification of modifiable fracture risk have been adopted in the two documents; the primary prevention guideline correctly endorses the principle of needing to confirm the presence of osteoporosis (in the context of age) as a prerequisite for targeting and initiating treatment, whereas the secondary prevention document recommends that patients over 75yr with past fracture should</td><td>The Committee applied the levels of cost effectiveness as outlined in the Guide to the Methods of Technology appraisal, section 6.2.6.10 and 6.2.6.11(Available from URL http://www.nice.org.uk/page.aspx?o=201974)

The Committee is familiar with the uncertainties involved in economic analysis.

Comment noted.</td></tr>
</table>

Consultee or Commentator	Comment	Institute Response
	be treated without prior DXA (a recommendation that will result in 20-25% of these fracture patients being treated ineffectively as they have BMD that is above the osteoporosis threshold). **Assumptions about persistence with drugs for osteoporosis** Adoption of persistence of 50% at this stage in our understanding is again conservative. Our own data - that have not been published suggest compliance rates of 80-86% at about 12months and this may relate to the education we provide at time of initiation of treatment and how we link assessment to understanding of fracture risk. The published literature in this area has become clouded by industry sponsored studies and are designed to pave the way for novel treatment regimens with newer bisphosphonates. **The site for DXA measurement** The recommendation to use femoral neck DXA is too restrictive. DXA providers invariably perform scans at two sites. Clinical trials have also used DXA measurements at spine and have shown that use of a LS T-score can be used to successfully target alendronate to reduce non-vertebral fracture risk; in the study by Pols et al (Pols et al Osteoporosis International 1999;9:461-8) they used a LS T-Score of below -2 to initiate treatment. NICE should consider adoption of DXA at spine & hip with decisions for initiation of treatment made on the basis of the lower of the two measurements. They should consider levels of BMD for initiating treatment of FN less than or equal to -2.5 or LS less than or equal to -2.0. **The falling cost of alendronate** Since alendronate came off patent its price has been falling. Unfortunately, currently the fall has been relativey modest, but with several manufacturers the price will inevitably fall further, and prbably soon. Given that treatment costs are the substantial determinant of cost-effectiveness these documents need to incorporate models that can be adopted based on future potential drug costs - that quite conceivably may end up at less than 50% of the costs that underpin the current NICE treatment recommendations. **Duration of treatment** There is no consensus as to how long treatment should be continued. Antihypertensive treatment is generally continued life-long. There is nothing to suggest that treatment to reduce fracture risk should not be used similarly. The innate conservatism of clinicians has resulted in a variety of approaches - 5yrs and stopping (as recommended by NICE with subsequent offset of action) is by no means universal. NICE should consider modelling alternative approaches such as continuous treatment say for 10yrs and initial 5yrs continuous and alternate yearly thereafter. **Implications of differing BMD thresholds for initiating treatment**	Comment noted. The clinical trial evidence used in this appraisal uses mainly the femoral neck as the site for DXA scanning. More detail about measurement of BMD will be given in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' The cost effectiveness modelling has been revised to the price of £7.31 for 4 tablets (November 2006). Potential future price reductions have not been included. More detail about the duration of treatment may be given in the NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.

Consultee or Commentator	Comment	Institute Response
	The different thresholds for using risedronate and strontium are impractical and will generate uacceptable anomalies. Patients who are intolerant of alendronate, may find themselves above the treatment thresholds for risedronate and strontium. Patients would, understandably. find denial of access to these alternative treatments for fracture risk reduction somewhat unacceptable.	The 2007 ACD recommendations do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment.
	Comments specifically relating to NHSQIS: My comments above raise concern about the health economic analysis, inconsistencies in how the evidence has been translated into recommendations, omission of some relevant evidence and the impracticality of some aspects. If these are addressed then The NICE osteoporosis ACDs may be applicable in Scotland as in England. In the meantime, in Scotland, we have the SIGN guideline on osteoporosis management - a guideline that is much more conservative in its recommendations than others such as the RCP guidelines.	Comment noted.
	Reviewer 2. **i) Whether you consider that all the relevant evidence has been taken into account.** This is a generally useful document which does appear to have considered the relevant evidence appropriately. Overall there are a number of improvements in the recommendations made. This is especially true in the Secondary Prevention document (compared with Technology Appraisal No 87). There are however a number of inconsistencies in the interpretation of the evidence (particularly in the Primary Prevention document) that would make implementation of all of this guidance flawed. Furthermore significant parts of this guidance are not consistent with SIGN Guideline 71 (Management of Osteoporosis).	Comment 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. One of the fundamental areas where this guidance strays from the evidence base is where recommendation is made to start treatment in patients over age 75 and age 80 on the basis of the number of fracture risk factors they have without recourse to BMD assessment. This contradicts recommendations made to NHS Scotland through SIGN 71. The basis of the problem here is that there is no evidence in the literature to indicate that a treatment strategy based on prevalent risk factors will be associated with a reduction in fracture risk. The guidance at one point acknowledges this (Primary Prevention 4.3.5 …..any recommendation for the use of drugs would be less soundly based in people with osteopenia than in people with osteoporosis). This clearly implies that knowledge (as defined by BMD) of osteoporosis status is required	Comment noted. The DXA requirements for older women have been revised according to the comments received.
	The stance on this in the Secondary Prevention guidance has clearly softened compared with before in that	Comment noted.

Consultee or Commentator	Comment	Institute Response
	4.3.10 suggests that there is still a role for DXA scanning in patients over age 75 after fracture. The evidence does not support the assertion made that "it is very likely that women who have sustained a fragility fracture will have a low BMD (T-score of -2.5 or below). Our own data shows that only around 60-65% of this population have a BMD of <-2.5. Furthermore in spite of this statement in Primary Prevention 4.3.5; the guidance recommends treatment for women at age 75-79 and over 80 with a T-score of -1.5 (In over 80s this will make up a large proportion of the population). The Risedronate Hip Trial showed that this strategy is not associated with fracture risk reduction. Having said this, where bone densitometry is not available a strategy based upon risk factor assessment may be a pragmatic approach but at best should be considered temporary while bone densitometry services are being developed. I would suggest for NHS Scotland that this aspect of the guidance should not be adopted.	Comment noted.
	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. See comments above. Whilst it is clear much of this guidance has been updated some of the costs have not. This is especially relevant with respect to the assessment relating to alendronate. This drug is now available as a generic and the cost continues to fall. This will alter the cost-effectiveness thresholds considerably. Specifically this means that the treatment thresholds now being suggested are very conservative.	The cost effectiveness modelling has been revised to the price of £7.31 for 4 tablets (November 2006). Potential future price reductions have not been included.
	Reviewer 3. We recognise that some modifications to the draft guidance have been made consistent with submissions on the ACDs published in September 2005, including redefining intolerance to bisphosphonates and links to other relevant NICE guidance. However, we are extremely concerned that the current ACDs describe draft guidance that is even more restrictive than the ACDs on which we commented at the end of 2005. For example, the primary prevention ACD now only recommends treatment for the over 75s, and in both ACDs second line treatments are only recommended if a woman's' risk of fracture increases significantly.	The age at which therapy can be initiated has been revised according to the comments received.
	Concern regarding the implications of this draft guidance has been voiced by members of the public and health professionals over the last three weeks. Medical staff managing patients with osteoporosis and treating the consequences of fracture advise that these ACDs are clinically unworkable and will severely disadvantage patients at risk of first and second fractures as indicated in the examples below. Furthermore, in some areas these clinicians believe that the provision of treatment in accordance with the current guidance would be both unethical and inconsistent with their duty of care.	Comment noted.
	Process There is concern regarding about the robustness of the development process of these Technology	The remaining of Reviewer 3's comments are identical to the NOS

Consultee or Commentator	Comment	Institute Response
	Appraisals. This follows on from, but is more serious than the points highlighted in our response to the DSU analysis. Since the last ACDs were published in 2005, the price of alendronate used in the most recent modelling has decreased by almost a half from £21.90 (in March 2006) to £13.27 (in July 2006). As there has been no new evidence reported on epidemiology, disutility caused by fractures, efficacy of the drug treatments or adverse events, we confidently expected that this would lead to improved cost effectiveness and thus more permissive guidance, particularly with regard to prescribing of alendronate. However, the result has been guidance that is even more restrictive. Initially we could not understand how reducing cost has resulted in further restricting availability of a drug treatment. The fact is that the increase in restrictiveness is due to other changes that have been made to the input parameters of the model. The reasons for incorporating these changes have not been explained and the evidence to support them has not been identified. This lack of transparency has severely limited our consideration of the ACDs and to comment usefully upon the proposed guidance. The most important of the changes to which we refer are listed below and each of them will be considered in more detail in the relevant sections of this response. • The Appraisal Committee have assumed that drug treatments have no effect on the component of fracture risk contributed by independent clinical risk factors other than age, sex and BMD. Most phase III trials do not exclude women if they have risk factors other than age, sex and BMD (rheumatoid arthritis and glucocorticoid use are often exceptions). Thus, in these trials the efficacy estimates take into account any potential reduction in efficacy that is due to the presence of other risk factors. • The estimate used for efficacy of alendronate against hip fractures used by the Appraisal Committee to determine the cost effectiveness of treatment has been reduced from that relied upon for the purposes of TA 87 and through each of the different stages of modelling in this appraisal, even though each calculation is based on the same 16 studies. Therefore TA 87 used a relative risk of hip fracture associated with alendronate therapy of 0.49, while the current ACDs are based on a relative risk of hip fracture, calculated from pooled data relating to alendronate and risedronate of 0.71. The ACDs include no explanation or justification for the changes in approach which appears inconsistent with the evidence and intended simply to present alendronate as being as ineffective as possible. In particular, it is unclear why it is considered appropriate to combine the data for alendronate and risedronate to produce a combined figure for efficacy in view of the fact that the products are considered separately in the guidance and this strategy merely has the effect of diluting the benefits of alendronate. • The Appraisal Committee have chosen to set the disutility caused by vertebral fractures in the first year to 0.792, (which is the same as that reported for a hip fracture), rather than to the value reported in the literature of 0.626. No explanation for this approach is provided and we are not aware of any evidence to support the figure chosen. This manipulation of the inputs to the economic model is inappropriate and has resulted in the Appraisal	comments. Please therefore refer to the response to NOS comments above. Please see response to NOS comments above.

Consultee or Commentator	Comment	Institute Response
	Committee presenting osteoporosis as a disease that is not cost-effective to treat in the majority of people. Although we feel that the model itself is robust, we would argue that the way that the Appraisal Committee has utilised the model - repeatedly "tweaking" the inputs without any explanation or evidence to support the changes - has now resulted in output and preliminary guidance that is fundamentally flawed and which downplays the cost of suffering experienced by patients. Since the ACDs have been issued for consultation the price for alendronic acid, 70 mg (4 tablets) set out in the NHS tariff has been further reduced to £7.30 (almost half the figure used in the modelling). It is self evident that, if the guidance is to be relevant to the treatment of patients with osteoporosis in England and Wales, it must be based on accurate current cost information. It is therefore clear that the recent price reduction in alendronic acid must be reflected in the modelling, and the cost effectiveness of this product revised before the Institute's guidance is finalised. Furthermore, in view of the fact that the prices of all bisphosphonates may be reduced prior to March 2009, the date set for review, we would ask the Appraisal Committee to ensure that the guidance is "future proof" in terms of indicating the cost at which all such products would become cost-effective for all eligible patients. Osteoporosis should be considered in the same way as other diseases for which prevention is key, such as coronary heart disease or stroke. From these ACDs it appears that NICE are downplaying the significance of osteoporotic fractures by not even considering cost per QALYs (CPQs) above £20,000 in the ACD on primary prevention. No explanation for this approach is provided in the ACD and it appears inconsistent with NICE's own procedures, which do not impose a rigid cut-off value. The "Guide to the Methods of Technology Appraisal" provides at paragraph 6.2.6.10 that between ICER values of £20,000 and £30,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to certain identified factors, including the societal benefits of treatment. It is therefore clear that the Appraisal Committee is required to consider usage of technologies under consideration within this ICER range and to give reasons for or against recommending use in NHS patients. Such consideration is wholly lacking from the ACD dealing with primary prevention, which does not even identify ICER values associated with osteoporosis treatments, where these exceed £20,000/QALY. It is clear from previous submissions, that we believe wider societal benefits in the prevention of osteoporotic fractures are enormously important. It is, therefore, essential that NICE explains fully its conclusions with respect to the ICER values associated with osteoporosis treatments and provides a reasoned justification for its refusal to consider recommending treatment in circumstances where it has calculated an ICER value of between £20,000 and £30,000/QALY. Furthermore, for secondary prevention, although a CPQ of £30,000 was considered when modelling for alendronate, for all of the other drug treatments the cut off was set at £20,000/QALY and higher CPQs were again not even considered. In earlier ACDs higher CPQ were considered (and indeed accepted in TA 87). No explanation for this inconsistency is provided and again it does not reflect NICE's procedures. A clear moving of the goal posts is demonstrated by these changes and this requires proper justification; this is lacking from the ACDs.	Please see response to NOS comments above.

Consultee or Commentator	Comment	Institute Response
	The Appraisal Committee has become gradually more conservative in its treatment of osteoporosis. The committee has also suggested that the prevalence of osteoporosis is much lower than has been previously reported (see sections 2.5 in both ACDs). This conclusion appears to be based on a single study (Holt et al., 2002) which did not adequately recognise all cases of osteoporosis. It is therefore likely to be a substantial underestimate. The overall result is that it appears to our members that NICE are trivialising the cost and personal impact of osteoporotic fractures. Whilst limited resources should be used in the most cost effective way, we also believe that all disease areas should be considered on an equal basis. If it is cost effective to treat osteoporosis according to current CPQ thresholds, it is not within NICE's remit to make decisions on whether or not there are sufficient NHS resources to accommodate the costs. This is a matter of affordability which is a decision properly reserved to the Secretary of State. In the response to the DSU analysis in August, concerns were raised over the Appraisal Committee's move to self-identifying and opportunistic assessment. This change further reflects the fact that the Committee are becoming increasingly conservative in their approach to osteoporosis. Within these ACDs the cost of BMD assessment of the entire potential population for treatment are included in the economic model. By doing this, NICE are effectively screening for osteoporosis and including the cost of this in the assessment of the cost effectiveness of osteoporosis treatments. We are not aware of any other NICE TA that has included the cost of screening, but note that there are a number of recent TAs which do exclude the costs of screening (for example, TA's 52 and 47 for myocardial infarction and acute coronary syndromes and TA 36 for rheumatoid arthritis). The cost-effectiveness of screening does not lie within the scope of this TA and we are therefore extremely concerned at the negative impact that this has had on the economic modelling. These ACDs do not include recommendations for women with clinical risk factors whose bone density falls into the osteopenic range. It is implicit from the introductions to the ACDs, which refer to women with osteoporosis, that patients with osteopenia are not considered, although this is not clearly stated. However, the results of the economic modelling suggest that in some cases it would be cost-effective to treat osteopenic patients. The NOS are concerned that the division of the original scope which was going to consider primary and secondary prevention in the same appraisal, into separate appraisals for primary and secondary prevention and the addition of the TA on strontium ranelate for secondary prevention, may have produced confusion as to the remit of the Appraisal Committee and whether the situation of osteopenic patients should be considered. The original scope notes that; *"although current diagnostic definitions for osteoporosis are based around BMD, other factors need to be considered when assessing overall risk of fracture"* suggesting that osteopenia should be part of the appraisal, in circumstances where other clinical risk factors were present. Furthermore, the population to which the scope refers includes post-menopausal women at	Please see response to NOS comments above.

Consultee or Commentator	Comment	Institute Response
	risk of developing osteoporosis. For these reasons we are concerned that the Appraisal Committee now seems to have relegated osteopenia to the remit of the Guideline Development Group (GDG). The evidence suggests that most fragility fractures occur in women whose bone density is not in the osteoporotic range and there is also considerable evidence that shows that bisphosphonates are effective in reducing the risk of non-vertebral fractures in patients whose bone density is not osteoporotic. It is therefore essential that the position of such patients is considered by the Appraisal Committee and appropriate guidance on treatment issued to avoid confusion in doctors and patients. In previous submissions, comment has been made that evidence supports the inclusion of alcohol consumption and current smoking as risk factors for fracture. The evidence demonstrates that alcohol consumption of more than 2 units per day significantly increases the risk of fracture. However, although alcohol consumption has been included as a clinical risk factor in these ACDs we are concerned that it is included at daily intakes of 4 units or more. Furthermore, the Appraisal Committee continue to exclude smoking as a risk factor, despite their being evidence to support its inclusion. There is concern that the recommendations made by the Appraisal Committee are not based on the evidence and that there is no transparency in the reasoning behind this. The proposed guidance for primary prevention does not permit any change in therapy for patients who fail to respond to alendronate and etidronate but who are able to comply with the instruction for administration and are not intolerant of these treatments. Similarly the proposed guidance for secondary prevention will not allow for any alternative treatment for patients who fail to respond to alendronate and etidronate but are able to comply with the instruction for administration and are not intolerant of these treatments unless such patients are eligible for teriparatide. This situation, which represents a significant change from the 2005 guidance (TA 87) is not explained and appears irrational. **Clinical Workability** If this guidance is published without major revision, it will result in a huge number of patients who are currently being treated for osteoporosis being denied treatment after its implementation. This concern has been voiced by many callers on our helpline and via emails and phone calls to our Policy Department. Clinicians would have to explain why a treatment, which is clinically effective (and for secondary prevention, cost effective based on NICE's own assessment in TA 87), may no longer be prescribed. The NOS urges NICE to ensure that both the primary and secondary prevention ACDs include a statement that will ensure that all of those people who are currently taking a treatment would not have their treatment withdrawn on implementation of this new guidance, as it does in other TAs.	Please see response to NOS comments above.

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	Under this new draft guidance, if a patient does not tolerate a first line treatment, their condition would have to become substantially worse before they could be prescribed a second line treatment. For example, a 65 year old woman with vertebral fractures and a T-score of -2.6 SD who had been prescribed alendronate presenting one with oesophageal symptoms a clinician would be unable to prescribe her a second line treatment. This would be inconsistent with his duty of care and unethical. There is no other disease area or healthcare system where there are 5 or 6 treatment options (and where there are only modest differences in cost in most cases) that have had second line treatments restricted in this way and Appraisal Committee is urged to reconsider its conclusions. The positioning of etidronate as an alternative to alendronate as a first line treatment has also caused much clinical concern. We accept that etidronate is low cost and that given the disutility of vertebral fracture comes out as competitive in the model scenario. However, there is no RCT evidence for non-vertebral and hip fracture risk reduction and we strongly question its prominence as an alternative first line treatment simply on economic grounds. It is perhaps for this reason that etidronate was never approved in the USA because the FDA did not consider the evidence of its effectiveness to be good enough. We do not believe that the inclusion of data from an observational study for one drug treatment is appropriate. Several clinical advisors have commented that the prescription of etidronate to many patients would be inconsistent with proper clinical care. Under this guidance, younger women with extremely low BMD will not receive treatment until they reach the age of 75 unless they have sustained a fracture. There is concern that these ACDs are ageist in the way in which they discriminate against younger patients even if their absolute risk of fracture is identical to that of an older patient. For example, a clinician reported that a 68 year old woman scanned recently at their specialist centre, had osteopenia noted on X-ray. She was a recurrent faller but had no fractures when seen. Her T-score at the hip was -4.0 SD and at the spine -5.9 SD. Her absolute risk of experiencing a fracture was higher than most of the patients over 75 that present to their clinic, yet under this guidance she would not be offered a treatment. Recommendations that are being made in these ACDs will not allow all women who are at a high enough absolute risk of fracture to have access to a treatment. In practice, clinicians currently consider the BMD at both the hip and spine when considering treatment options. Indeed, we know that there are many younger or middle aged women who present with normal BMD at their femoral neck, but very low T-scores at their lumbar spine. We cite as two examples i) a lady of 72 scanned in the past month at one of our recognised centres who had sustained an early menopause at the age of 40 and whose hip T-score was -1.6 while her lumbar spine was -3.8. and ii) a lady of 62 who presented with a Colles fracture and has chronic liver disease who had not received corticosteroid therapy whose hip T-score was -1.7 and spine score -3.9. Neither of these women who are at a high risk of vertebral fracture would receive treatment under this new draft guidance. would like Could the Appraisal Committee re-phrase section 2.4 in both ACD documents to	Please see response to NOS comments above.

Consultee or Commentator	Comment	Institute Response
	"T-score measurements vary by site and method. It has been recommended that BMD should be measured at the femoral neck and/or lumbar spine using DXA to estimate fracture risk and that treatment decisions should be based on the lowest value". The NOS has begun to try to develop algorithms from this guidance which would allow clinicians to follow the recommendations in practice. However, in particular for the guidance on secondary prevention of osteoporotic fractures, it is almost impossible to produce a clinically useful tool. believe This draft guidance, if implemented as it stands would cause widespread confusion. The vast change in attitude towards primary prevention from the current RCP guidelines, which are widely used, will add to this particularly in the primary care setting. The direction taken by the Appraisal Committee on this guidance will put England and Wales, and assuming further acceptance by NHS Quality Improvement Scotland and the Northern Ireland Health Boards, the UK, in a position that stands it apart from the rest of the world. These draft ACDs, if published in their current form, do not allow the GDG enough freedom to produce a clinically robust osteoporosis guideline that is useful in clinical practice. In conclusion, the field of osteoporosis has seen huge advances in diagnostic risk assessment and therapy in the last 20 years. This draft guidance represents a serious step back from the achievements that have been made. An extensive table of patient comments can be made available to support these points.	Please see response to NOS comments above.
Department of Health		
	Thank you for inviting the Department of Health to comment on the above Appraisal Consultation Documents. We do not have any specific comments to make on these appraisal as they sit well with current Department of Health policy and also with our publication 'A New Ambition for old age: next steps in implementing the NSF for older people', bone health (including prevention/treatment of osteoporosis and falls prevention. Prescribing in general practice of drugs affecting bone metabolism is already rising sharply (up 20% from 2004 to 2005) and the NHS is working hard to improve access to bone density scans and shorten waits as part of the wider 18-week programme. There may be additional drug costs, but there may equally be offsets as new, more effective drugs are substituted for those that are currently used.	Comment noted.

Consultee or Commentator	Comment	Institute Response

Reply received but no comments:

- Novartis