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 consultee, commentator and public comments on the 2007 Appraisal Consultation Document (ACD)

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Alliance for Better Bone Health	**Appraisal Consultation Documents: primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women** Thank you for the two most recent ACDs dated February 2007 that elate to the ongoing osteoporosis appraisal. The Alliance for Better Bone Health, on behalf of sanofi-aventis and Procter & Gamble (The Alliance), is extremely concerned by the recent developments regarding these two appraisals and we wish to register these concerns. **Executive summary** 1. The development of the current ACDs has not been consistent with the Institute's published processes or standard procedures. As such, the validity of the recommendations and the current consultation process has been undermined. 2. Aspects of the recent appraisal process are not sufficiently transparent as to allow consultees and commentators to fully understand and critically appraise the consultation documents. 3. The preliminary recommendations would result in inappropriate treatment and potential harm to patients because they do not take account of key patient subgroups who cannot or, in the opinion of their physician, should not receive generic once a week alendronate as first line therapy. 4. The Alliance proposes, as in its previous response, that the guidance recommends the use of oral bisphosphonates as first line treatment for the prevention of osteoporotic fractures, and when the decision to prescribe has been made therapy should usually be initiated with a drug with a low acquisition cost.	Comment noted. 1. Consultees and Commentators have been regularly updated on the progress with this appraisal and the relevant processes of and consultation on evidence and Committee deliberation has been adhered to. 2. The Institute followed its published processes for consultation. 3. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. 4. Comment noted.

Consultee or Commentator	Comment	Institute Response
	1. <u>The development of the current ACDs has been inconsistent</u> *The development of the current ACDs has not been consistent with the Institute's published processes or standard procedures. As such, the validity of the recommendations and the current consultation process has been undermined.* The Alliance believes that recent changes to re-focus the preliminary recommendations for both appraisals to 'initiation of pharmaco-therapy' are inconsistent with the original scope of the appraisals. • The Institute's letter of 22 February 2007 identifies a recent decision by the Appraisal Committee to change the scope of the appraisals and transfer, to the osteoporosis Guideline Development Group, responsibility for guidance on treatment of women who have withdrawn from initial treatment. This is inconsistent with the original scope as defined for primary prevention in August 2002 following consultation. • Given that the most recent ACDs represent the fourth ACD issued in primary prevention and the third issued in secondary prevention, it is not clear why the scope has been changed at this stage. It is also inconsistent with the NICE appraisal process to make changes to the scope at this stage of an appraisal without appropriate consultation. • The appraisals have to date been informed by data and analyses conducted and presented to inform decisions in relation to the original scope of the appraisals. The Alliance therefore questions whether the Appraisal Committee has had sufficient information to make recommendations in line with the revisions to the scope. • The preliminary recommendations set out in the current ACDs propose that generic once a week alendronate is the standard of care against which all other treatment options are measured. This approach is inconsistent with the primary prevention appraisal scope which stated that head to head comparisons of "classes of interventions" would be undertaken rather than comparisons between interventions in the same class. As indicated in our response to previous ACDs, the distinction made between alendronate and risedronate is artificial and questionable since it is based solely on acquisition cost. **2. <u>Aspects of the recent appraisal process are not transparent</u>** *Aspects of the recent appraisal process are not sufficiently transparent as to allow consultees and commentators to fully understand and critically appraise the consultation documents.* • As indicated in the Alliance's response to the previous ACDs in October 2006, the ability of consultees and commentators to consult adequately on these appraisals has been significantly	1. The letter of the 23rd February 2007 sent to Consultees and Commentators states that the Appraisal Committee focussed its preliminary recommendations for both technology appraisals on 'initiation of therapy'. The NICE clinical guideline on osteoporosis will cover the treatment of women who are contra-indicated to, or have withdrawn from initial treatment. There has been no change to the scope of the appraisal. 2. The evaluation report includes evidence considered by the Committee and correspondence between the GDG and Committee. As stated in the 'Guide to Technology Appraisal Process', to

Consultee or Commentator	Comment	Institute Response
	impaired by the lack of transparency in the way that the information has been presented. Furthermore, despite our requests, we have not been provided with sufficient access to the health economic model to enable us to appreciate fully how the results were reached or how they should be interpreted. • The Institute's letter of 22 February 2007 suggests that significant dialogue has taken place between the Appraisal Committee and the Guideline Development Group, leading to the recent decision to change the scope of these appraisals. Neither the guide to the technology appraisal process nor the overview of the guideline development process defines, in sufficient detail, the parameters within which these groups interact with each other. It is therefore unclear to consultees and commentators what processes were in place for the osteoporosis appraisals. As a result, we are unable to judge whether the objectives have been met and whether the process has been fair.	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. The inclusion of the WHO risk algorithm within the Assessment Group models has been provided under an Academic in Confidence agreement and therefore the model cannot be released for consultation, which Consultees and Commentators were notified of in the letter dated the 23rd February 2007.
	3. <u>The preliminary recommendations would lead to inappropriate treatment</u> *The preliminary recommendations would result in inappropriate treatment and potential harm to patients because they do not take account of key patient subgroups who cannot or, in the opinion of their physician, should not receive generic once a week alendronate as first line therapy.* We recognise that the current ACDs do not cover the treatment of women who, for whatever reason, have withdrawn from osteoporosis therapy. However, even for treatment initiation, neither ACD addresses the significant subgroups of women who can be identified by physicians as being inappropriate for generic once a week alendronate. Women requiring osteoporosis treatment who may be inappropriate for generic once a week alendronate include patients who are: • Contraindicated for alendronate. Differences between alendronate and risedronate have been ignored in this respect. • Exhibiting gastrointestinal symptoms or receiving treatment for gastrointestinal conditions which might exacerbate the side effects of alendronate. The risks of gastrointestinal side effects associated with bisphosphonate treatment are acknowledged in paragraph 3.5 of both ACDs and there are important differences between risedronate and alendronate relevant to this	3. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. The clinical guideline will also examine treatment options for those who have withdraw from, are intolerant or not responding to initial treatment.

Consultee or Commentator	Comment	Institute Response
	subgroup. • Receiving treatment with non-steroidal anti-inflammatory drugs, with the attendant risk of gastrointestinal side effects. Differences in the evidence base between alendronate and risedronate in this population have been ignored. This is particularly important as a diagnosis of rheumatoid arthritis is specified as one of the self-identification criteria for secondary prevention in the November 2006 ScHARR report and chronic usage of NSAIDs in the rheumatoid arthritis population is high. • Unable to comply with the administration requirements for alendronate. Again, differences between alendronate and risedronate have been ignored, including the non-availability of a daily version of generic alendronate. We note the comments of the Royal College of Nursing on the September 2006 ACDs with regard to gastrointestinal symptoms. The College suggests that if there are "reasonable concerns" about poor tolerance of alendronate due to gastric disturbance risedronate, should be prescribed first line. Paragraph 3.5 of each ACD suggests that the Appraisal Committee has come to a conclusion on how to initiate some of the patients unable to take alendronate (those with oesophageal abnormalities and other factors that delay oesophageal transit or emptying). However, this information is not provided as part of the preliminary recommendations and is contradicted by paragraph 1.2 in each ACD. **4. <u>Proposed revision</u>** *The Alliance proposes, as in its previous response, that the guidance recommends the use of oral bisphosphonates as first line treatment for the prevention of osteoporotic fractures, and when the decision to prescribe has been made therapy should usually be initiated with a drug with a low acquisition cost.* In order to make the guidance capable of implementation in clinical practice, without giving rise to inappropriate treatment, we propose that in both primary and secondary prevention oral bisphosphonates are recommended as first line therapy for the patient populations identified in the most recent ACDs. Consideration should be given to acquisition cost, whilst recognising that alendronate does not always have the lowest cost e.g. for patients whose compliance is improved by daily dosing. Specification of alendronate in the recommendations is unhelpful. We would also like to see a stronger recommendation in each ACD on continuity of current treatment. Paragraph 1.5 of the primary ACD and paragraph 1.3 of the secondary ACD should make it clear that continuation of current therapy is not just an "option" but should be the default position. Discontinuation of current therapy associated with the introduction of the guidance would	4. Comments noted.

Consultee or Commentator	Comment	Institute Response
	be disadvantageous to many patients. However, we would like to emphasise that these proposals represent a response to the original scope of the appraisal. The most recent ACDs do not adequately address that scope, which was not limited to treatment initiation, and they impose limitations on the availability of appropriate and cost-effective treatments which if implemented would be detrimental to patients. **Summary** The Alliance trusts that the Committee will appreciate the concerns expressed in this response. We hope that the Committee will be minded to effect the revisions we have recommended in order to provide clear, pragmatic and implementable guidance for the NHS.	
Eli Lilly	**The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women** Thank you for the opportunity to comment on the ACD for the above appraisal. *i) whether you consider that all of the relevant evidence has been taken into account;* We believe that the relevant evidence was available to the appraisal committee. *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;* We continue to maintain that the breast cancer benefit of raloxifene is of relevance in any assessment of its cost effectiveness. Raloxifene with the full economic consequences of avoided cases of breast cancer was cost effective compared to proprietary alendronate in younger women, and may remain cost effective against non-proprietary alendronate. The guidance offers no analysis. *iii) whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.* By providing recommendations only on the 'initiation of pharmacotherapy', NICE has acted outside its remit and changed the scope of the review without consultation. We were unaware of this important change until the recent consultation. This is outside of NICE's published processes and	i. Comment noted. ii. Section 4.2.10 of the FAD explains the Committee's decision to exclude the modelling of breast cancer benefits for raloxifene in the cost effectiveness analysis. iii. The letter of the 23rd February 2007 sent to Consultees and Commentators states that the Appraisal Committee focussed its preliminary recommendations for both technology appraisals on 'initiation of therapy'. The NICE

Consultee or Commentator	Comment	Institute Response
	is fundamentally wrong. It is also detrimental to patient care.	clinical guideline on osteoporosis will cover the treatment of women who are contra-indicated to, or have withdrawn from initial treatment. There has been no change to the scope of the appraisal.
	Although a superficially attractive way to resolve the existing confusion between ongoing guideline and guidance processes, the decision is in fact poorly thought through. The proposed guidance offers no guidance at all for patients who are unable to tolerate or do not respond to alendronate, or those who are contraindicated to alendronate. It makes no attempt to offer guidance on when alternatives to non-proprietary alendronate might be used in a cost effective manner.	Recommendations are consistent with the original DH remit[1] in that the proposed guidance provides advice on the most cost-effective therapy and how recommended treatments are best targeted.
	There is not even an estimated date for consultation on and publication of the clinical guideline. In the meantime lack of guidance may be interpreted as negative guidance and used by cost-conscious healthcare trusts as an excuse to reduce funding for osteoporosis in general and for some therapies in particular. The worst scenario is that patients could be denied access to useful treatments, as such we feel sure that NICE would not want to be seen endorsing a reduction in choice of therapies.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline.
	Lilly believe there is a need to provide guidance on those withdrawn from initial treatment.	Treatment options for women who have withdrawn from initial therapy will be defined in the clinical guideline.

[1] Remit from Department of Health: To advise on the clinical and cost effectiveness of licensed treatments for the prevention and treatment of osteoporosis and prevention of osteoporotic fractures in post-menopausal women in the following pharmacological classes: Selective (o)estrogen receptor modulators (SERMs); Bisphosphonates; Parathyroid hormone (subject to licensing) relative to commonly-used treatments; and to advise if the evidence allows on how any recommended treatments could be best be targeted on those most likely to benefit.

Consultee or Commentator	Comment	Institute Response
	This decision appears to be motivated by the availability of generic alendronate and cost containment rather than providing assistance to those managing the disease in the NHS.	NICE technology appraisals contain recommendations on the clinical and cost effectiveness of technologies and NICE Clinical guidelines make recommendations on managing a disease in the NHS
Novartis	**Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women** **and** **Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women** I write in response to your letter of 23rd February 2007 inviting comments on the Appraisal Consultation Documents (ACDs) for the above appraisals. We have three main comments to make.	
	Firstly, we note with interest the focus of the ACDs on the initial treatment of post-menopausal osteoporosis (PMO) and that the forthcoming clinical guideline will cover the treatment of women who have withdrawn from treatment. Whilst this focus on initial treatment is not inappropriate, it cannot be assumed that all patients are either willing or able to take generic alendronate. For example, alendronate is contraindicated in patients with oesophageal problems and in those who are unable to stand or sit upright for 30 minutes. Furthermore, we know that approximately 20% of patients do not tolerate alendronate and that a further percentage will be unresponsive or unable to comply with therapy. Consequently, the draft guidances fail to recognise a small, but important, population of PMO patients for whom alternative treatment options are required.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline
	With this in mind, we would strongly suggest the wording of the guidances include a statement to indicate that there are a number of alternative oral, intravenous and subcutaneous treatments for PMO patients who are intolerant of, or unwilling/unable to receive, therapy with alendronate. Given that implementation of the forthcoming clinical guideline will not be mandatory, there is a real danger that PCT funding of alternative therapies to alendronate will be greatly reduced if the appraisal guidances do not refer to the availability of other treatment options. This will obviously be detrimental to patient care. Furthermore, the situation could be exacerbated if there was to be a significant delay between publication of the appraisal guidances and the clinical guideline.	Treatment options for women who are contra-indicated or intolerant to alendronate will be defined in the clinical guideline

Consultee or Commentator	Comment	Institute Response
	Secondly, comments relating to the previous ACD (September 2005) highlighted several concerns about applying an age 'cut-off' for eligibility of treatment for primary prevention. Section 1.1 of the current ACD suggests that no women under the age of 70 years without a fracture can be identified and treated. This age cut off is inconsistent with the available anti-fracture studies which included patients 65 years or above with or without a vertebral fracture at baseline. We would ask NICE to reconsider this 'ageism' as it does not allow appropriate treatment for those women with low BMD and multiple risk factors who may well be at high risk of fracture. Finally, we note that the timeline for review of the appraisals has increased to 3 years (in previous ACDs, the review time was 2 years). It would be helpful if the reasons for this change could be clarified. If you have any questions, please do not hesitate to contact me.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Technology appraisal guidance will be reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
Straken Group Plc.	We thank you for the opportunity to comment and provide input to the health technology appraisals for the primary prevention of osteoporotic fragility fractures in postmenopausal women. We will restrict our comments to the area of calcium and vitamin D supplementation. There is significant evidence to support the role of calcium and vitamin D3 (specifically 1200mg elemental calcium and 800IU vitamin D3 daily) in the primary prevention of fragility fractures in elderly institutionalised women,[iii],[iii]. This dose when compared with placebo, demonstrated a 43% reduction in hip fractures, and 32% reduction in non vertebral fractures (p values > 0.001 and 0.888 respectively) over an 18 month treatment period. These results were sustained over time, as was reported after a further 18 month treatment period. Considering the low acquisition cost of such treatment, and a favourable cost economy achieved with an NNT of only 20 [iv], we felt it important to raise this issue.	Comments noted. The required levels of calcium and vitamin D to be used will be covered in the clinical guideline on osteoporosis 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.

Consultee or Commentator	Comment	Institute Response
	We note in the appraisal committee's preliminary recommendations for the primary prevention appraisal, from the statement *'unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake, and are vitamin D replete, calcium and or vitamin D supplementation should be* ***considered'*** , that there is less emphasis placed on the need to provide supplementation than is currently the case in NICE TA 087. We concede that in section 4.3.28, the more directive word, 'provided' rather than 'considered' is used, however, the word 'considered' is likely to be incorporated in any abbreviated and concise guidance, or indeed in the preamble to the complete guidance once published. Less emphasis would therefore be placed on health care providers to actively view supplementation as adjunctive therapy with osteoporosis treatments. Most clinical trials with bisphosphonates were conducted in patients replete in calcium and vitamin D3[v], and the SmPCs for Fosamax once weekly 70mg tablets[vi], and Actonel [vii]specify that adequate calcium intake and vitamin D3 levels are essential as adjunctive therapy. Vitamin D levels in individuals aged 65 and older, in the community, were insufficient at 76%[viii], as is the case in 77% of institutionalised patients[viii]. 60% of working adults in the UK do not have sufficient vitamin D3[viii]. and 79% of patients on osteoporosis treatment referred to hospital were not replete in vitamin D3[ix]. With reported levels of vitamin D 3 insufficiency such as these, the need for adjunctive supplementation should be more directive than optional as is conveyed by the word, considered. We trust that our comments will be helpful during the process of developing guidance which will be appropriate to NHS. [References provided]	
Servier	Thank you for the opportunity to comment on the appraisal consultation documents for the HTA of	

Consultee or Commentator	Comment	Institute Response
	drugs for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. In summary, Servier Laboratories' comments on the revised documents are as follows.	
	• To recommend the use of only generic alendronate for all newly diagnosed patients is clinically inappropriate: o Patients who are unable to comply with the special administration requirements of alendronate, or for whom alendronate is contraindicated are not addressed in these ACDs. Strontium ranelate is appropriate for use in these patients and should be recommended as an initiating therapy. o Patients at risk of requiring a proton pump inhibitor (PPI) should not be prescribed alendronate. PPIs have been associated with an increased risk of fracture. Therefore, in these patients strontium ranelate is the most appropriate treatment.	Treatment options for women who are contra-indicated or intolerant to alendronate will be defined in the clinical guideline. Section 4.3.19 of the FAD explains the committee's consideration of the Strontium ranelate data. Committee did not think it appropriate to give further age-stratified recommendations for the women 80 years or older and thereby age-stratify the recommendations even further.
	• Only strontium ranelate has clinical evidence to support a recommendation for the prevention of both vertebral and peripheral fractures in patients 80 years and older. Special guidance in this group should be considered. • Strontium ranelate has robust evidence for hip fracture prevention as acknowledged by the EMEA.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	• Treatment should be targeted towards patients with osteoporosis at highest absolute risk of fracture irrespective of age. In contrast, the current draft guidance on primary prevention does not recommend treatment of patients under 70 years of age.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.

Consultee or Commentator	Comment	Institute Response
	Patients in whom Alendronate is Contra-indicated Section 3.5 of both ACDs establishes that there are patients who are contra-indicated for bisphosphonate treatment. For alendronate this would include patients with abnormalities of the oesophagus or who are unable to comply with the special administration requirements for bisphosphonates. It is clear that patients in whom alendronate is contra-indicated must be prescribed an alternative medication first line where it is cost effective to do so. Since strontium ranelate has proved itself cost effective compared to no-treatment, it is appropriate for strontium ranelate to be the standard treatment for this patient group.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	Safety Signal for Bisphosphonate Use in Patients at Risk of Concomitant PPI Use NICE have undertaken a systematic review of bisphosphonate use that demonstrates that new bisphosphonate users are up to three times as likely as controls to require prescribed acid suppressant agents such as proton pump inhibitors (PPI). As previously stated, there is emerging evidence of increased risk of fracture associated with PPI use with three independent data sources that demonstrate statistically significant increases in the risk of fracture. 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. We would urge NICE to address this safety issue appropriately by requesting 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. Where possible, patients at risk of PPI use should be identified and allocated to strontium ranelate treatment instead.	Comment noted. The Committee considered a sensitivity analysis carried out by the DSU in Sept 2006.
	Treatment of Elderly Patients Section 4.1.2 of the Primary Prevention ACD states that there is 'little evidence' for the effectiveness of drugs in patients over 80 years. In fact, as stated in previous correspondence, strontium ranelate is the only treatment with robust proof of efficacy in non-vertebral fractures in patients 80 years and older. Other agents have been researched in this group and have been shown not to have evidence of effect. It is necessary for NICE to address this evidence base and consider the case for making separate	Section 4.3.19 of the FAD explains the committee's consideration of the Strontium ranelate data. The analysis considered all women over the age of 75 years as one group to avoid extrapolating the bisphosphonate data to women

Consultee or Commentator	Comment	Institute Response
	guidance for patients over 80 years. This guidance should account for the special capacity of strontium ranelate to protect patients in this age group from fracture.	aged 80 and older (see section 5.9.5 of 'Guide to the methods of technology appraisals').
	Hip Fracture Evidence Base for Strontium Ranelate Section 4.3.3 in the Secondary Prevention ACD and section 4.3.4 in the Primary Prevention ACD state that strontium ranelate has 'non-significant' evidence of prevention of hip fractures. In fact, strontium ranelate has significant evidence reducing the risk of a hip fracture by 36% in an appropriate patient population as acknowledged by the EMEA.	The Committee acknowledged the hip fracture effect by accepting the non-significant RR of 0.85 in the economic modelling.
	Age For Primary Prevention Initiation Treatment should be targeted towards those at highest risk. Excluding women under the age of 70 years, regardless of risk factors, from primary prevention treatment is entirely inappropriate. Indeed, in response to comments on the previous ACDs, NICE would appear to have acknowledged this fact by reducing the age for consideration of treatment and investigation from 75 to 70 years of age in the current draft guidance. However, this would still effectively discriminate against younger patients even if their absolute risk of fracture were identical or higher than that of an older patient.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years
	Additional Comments o We note that in section 3.12 the committee chose to highlight that patients with severe renal impairment are contra-indicated for treatment with strontium ranelate. It should be noted that alendronate also has a warning for patients with this condition and is contra-indicated in patients with hypocalcaemia**.**	Comment noted.
	o It is stated in section 4.1.5.3 that alendronate had demonstrated equivalent efficacy in fracture prevention between the daily and weekly doses. This is factually incorrect, as the study comparing these doses did not compare the doses on the basis of fracture prevention. The study compared the doses on BMD status and on the incidence of gastro-intestinal side effects.	Section 4.1.5.3 of the FAD states that equivalent efficacy between daily and weekly doses of alendronate were in terms of clinical fracture incidence and gastrointestinal adverse events.
	Thank you again for the opportunity to comment on these documents. Please contact me if you require further information about these comments.	Comment noted.

Consultee or Commentator	Comment	Institute Response
	[References provided]	
Nominated patient experts and clinical specialists		
Professor Juliet Compston Clinical Expert	**Comments on ACDs for primary and secondary prevention of osteoporotic fractures** Thank you for inviting me to respond to these documents. Most of the relevant comments have already been made in previous responses. I welcome the improvements that have been made in some aspects of clinical workability of the guidance. However, I remain concerned about the changes in model assumptions and the lack of transparency surrounding some of those assumptions. The absence of any access to investigation ± treatment in high-risk women aged less than 70 years also remains a major concern. Contrary to the original remit and scope of the guidance, the current ACDs are now restricted to the initiation of therapy with alendronic acid. Their recommendations do not cover the significant minority (30% or more) of women who cannot tolerate or who fail to respond to alendronate, nor do they cover individuals treated with oral glucocorticoids (estimated at 2.5% of the elderly population). The delegation of recommendations for these women to the Guideline Development Group is unsatisfactory, because of the difference in status between recommendations produced by the Appraisal Committee and those produced by the Guideline Development Group. In the present financial climate, many PCTs are funding only those treatments recommended by NICE in their guidance (and not even all of those are funded by all PCTs), and are removing other treatments from their formulary. As they stand, therefore, the ACDs provide incomplete guidance for women with osteoporosis and may result in failure to treat a significant proportion of women who sustain a fragility fracture or who are at high risk of their first fracture. A potential solution is the use of explicit wording in the Appraisal Committee guidance that endorses the Clinical Guideline recommendations and imposes a duty on the PCTs to follow these when initiation of therapy fails or when treatment is required to prevent fracture in patients taking glucocorticoids. In order for that strategy to succeed, the FADs	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years The letter of the 23rd February 2007 sent to Consultees and Commentators states that the Appraisal Committee focussed its preliminary recommendations for both technology appraisals on 'initiation of therapy'. The NICE clinical guideline on osteoporosis will cover the treatment of women who are contra-indicated to, or have withdrawn from initial treatment. There has been no change to the scope of the appraisal. Funding decisions of PCTs are not the responsibility of the Institute. The Healthcare Commission monitors the implementation of both technology appraisals and clinical guidelines.

Consultee or Commentator	Comment	Institute Response
	and the Clinical Guideline should be produced at the same time so that coherent and complete guidance is provided from the outset. In the absence of these actions, I fear that recommendations provided by the Guideline Development Group will be largely ignored by Primary Care Trusts and that many women with osteoporosis, particularly those who are frail and elderly, will be unfairly excluded from treatment.	
Professor Roger M. Francis	I am grateful for the opportunity to comment on the latest ACDs of the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. Although these have addressed some of the concerns expressed about the earlier draft guidance, many of the comments I made last October are still relevant. Rather than reiterate these comments under the headings adopted previously, I should like to highlight the following points: I am disappointed that although the cost of generic alendronate is now less than a third of branded alendronate, the draft recommendations on secondary prevention of osteoporotic fragility fractures are as conservative as the guidance in the Technology Appraisal published in January 2005. This encourages scepticism about the cost-effectiveness modelling, the presentation of which is unclear, lacks transparency and is inconsistent, as detailed in my response last year. In both the primary and secondary prevention ACDs, alendronate is recommended for the initiation of therapy, whereas etidronate, risedronate, raloxifene, strontium ranelate and teriparatide are not recommended in this situation. Although I accept that generic alendronate should generally be the treatment of choice on cost-effectiveness grounds, this is clearly inappropriate where the use of alendronate is contraindicated. Section 3.5 of both ACDs states that in people with oesophageal abnormalities and other factors that delay oesophageal transit or emptying, alendronate is contraindicated. I am therefore concerned that GPs following the proposed guidance may be encouraged to use alendronate in situations where it is contraindicated. This apparent ambiguity needs to be resolved in the FAD.	Comment noted. The Committee considered that there were a number of issues not incorporated specifically within the model. Although quantitative analysis of these uncertainties was not available, the Committee agreed that the sensitivity analysis for side effects could approximate these uncertainties. As recognised in the comment, alendronate (at an acquisition cost of £95) was deemed the most cost effective treatment and therefore recommended for treatment initiation. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.

Consultee or Commentator	Comment	Institute Response
	I am concerned that alendronate is recommended for the initiation of therapy, even in elderly women, as the major anti-fracture studies of alendronate only included women up to the age of 81 years. In contrast, risedronate has been shown to be safe and effective in reducing the incidence of vertebral fractures above the age of 80 years (Boonen et al, J Am Geriatr Soc 2004; 52: 1832-1839). Strontium ranelate has also been shown to be safe and effective in decreasing fracture risk in women above the age of 80 years (Seeman et al, J Bone Miner Res. 2006; 21: 1113-1120).	The Committee did not think it appropriate to give further age-stratified guidance for the women 80 years.
	Alendronate is not recommended in patients with a glomerular filtration rate (GFR) <35 mls/minute, a level of renal impairment which is not uncommon in elderly women. Although risedronate is not recommended when the GFR is <30 mls/minute, this bisphosphonate has been shown to be safe and effective in patients with mild, moderate and severe renal impairment (Miller et al, J Bone Miner Res 2005; 20:2105-2115).	Comment noted. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'
	I note that the NICE Clinical Guideline on Osteoporosis will address the treatment of women who have withdrawn from initial treatment with alendronate. Although I am confident that the Clinicians on the Guideline Development Group will provide appropriate advice on the management of osteoporosis, I am concerned that their recommendation may be unduly influenced by a cost-effectiveness model, which lacks transparency and is inconsistent. I therefore feel that stakeholders are being asked to comment on a 'pig in a poke', in that the management of a proportion of patients who withdraw from alendronate treatment will be determined by a Clinical Guideline we have not yet seen.	The GDG considers both clinical and cost effectiveness when developing the clinical guideline.
	I understand that failure of Hospital and Primary Care Trusts (PCTs) to implement NICE guidance in Technology Appraisals may be challenged in law, but a Clinical Guideline does not have the same mandatory status. I am therefore concerned that PCTs may use this as an excuse not to fund treatments other than alendronate. This is particularly the case with teriparatide, where some PCTs have been reluctant to implement Technology Appraisal 87.	Funding decisions of PCTs are not the responsibility of the Institute.
	I remain concerned that primary prevention of osteoporotic fragility fractures will only be considered in women aged 70 years and older, despite the fact that a younger woman with several risk factors and low bone density may be at greater risk of fracture than a 70 year old woman with one risk	Following consultation on the ACD, the Committee has included recommendations for women

Consultee or Commentator	Comment	Institute Response
	factor and a T Score of -2.5. The risk factors included in the primary prevention ACD are loosely based on those used in the as yet unpublished World Health Organization (WHO) model for predicting absolute fracture risk, but the use of these risk factors has been selective and the thresholds different to those advocated by the WHO. The ACD has increased the threshold for alcohol consumption from more than two units to four or more units daily, despite a recent meta-analysis of three prospective cohort studies, showing an increased risk of hip fractures with three units daily (Kanis et al, Osteoporosis Int, 2005; 16: 737-742). It is also unclear why the Appraisal Committee has continued to exclude smoking as a risk factor for fracture, despite its inclusion in the WHO model for prediction of absolute fracture risk. I am also uncertain why untreated premature menopause has been included as a risk factor for fracture in women above the age of 70 years, when I am unaware of data confirming that this is the case. Early menopause may lead to rapid bone loss and an increased risk of the development of osteoporosis in younger postmenopausal women, but I suspect that the magnitude of its effect on fracture risk diminishes with advancing age, as it would be diluted by other risk factors.	below the age of 70 years. Data available to the Committee showed no statistically significant effects for less than 4 units, and not for smoking in women. Risk factors used for opportunistic identification have been revised.
Dr Peter Selby Clinical Expert	***Appraisal Consultation Documents:*** ***Osteoporosis – Primary Prevention*** ***Osteoporosis – Secondary Prevention Including Strontium Ranelate*** Thank you for asking for my comments on these Appraisal Consultation Documents. The change in emphasis from considering all aspects of the use of these agents in the management of osteoporosis to merely considering the initiation of therapy with the other considerations being supplied by the clinical guideline is potentially a major improvement in the workability of the guidance to practising clinicians. On the other hand this does throw up problems of its own: 1. The difference of status of different types of guidance within the NHS means that many primary care trusts are likely to treat the technology appraisal guidance with more seriousness than the clinical guideline. This may result in expensive treatments such as teriparatide, which is currently mandated to primary care trusts under the guidance of TA87, no longer being made available to patients who could be cost effectively treated with it as the guidance regarding that technology will no longer be binding on primary care trusts. 2. Furthermore the guidance does not offer any option for initiation of therapy in those women for whom alendronate is contraindicated. At the very least there should be an explicit link to	Comment noted 1. Funding decisions of PCTs are not the responsibility of f the Institute. 2. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis:

Consultee or Commentator	Comment	Institute Response
	the clinical guideline for this group of women as well as those who have not tolerated or not respond to alendronate therapy. Although the difference in status between different types of guidance is the result of decisions taken outside the Institute it would be very helpful if there were some explicit wording within the technology appraisal guidance to establish the fact that by observing the recommendations of the clinical guideline a clinician was, in fact, complying with the technology appraisal guidance. If the intention of the Institute is that the technology appraisal and clinical guideline are so closely linked then I wonder whether it would be possible for the two pieces of guidance to be published simultaneously in order to emphasise the linkage between the documents? Although I have not rehearsed many of the comments that have been made previously regarding the earlier iterations of this guidance I would want to make one specific observation on the primary prevention document. At the moment the guidance would preclude the investigation and treatment of osteoporosis and any woman under the age of 70. This fails to recognize the fact that there will be a minority of such women who have a high risk of osteoporosis by virtue of the aggregation of several clinical risk factors. Indeed, these women may well be at higher risk of osteoporotic fracture than those women for whom treatment would be recommended by the ACD. I realise that the committee were anxious to avoid unnecessary and potentially costly investigation of women who were going to turn out to be at low risk of osteoporosis and subsequent fracture but am concerned that the current guidance would deny therapy to women who could be treated cost effectively with clinical benefit. Perhaps the committee could consider the use of multiple risk factors to identify such a group? I hope you find these comments helpful and look forward to our further collaboration on the development of this guidance.	assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. The Committee did not consider it appropriate to endorse guideline recommendations which are not yet finalised. Comment noted. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Comment noted.
Professional and Patient Groups		
Age Concern	Age Concern welcomes the opportunity to comment on the draft recommendations for this important issue. We understand the remit for this Appraisal; however, it would be a missed opportunity not to try to reduce fracture risks for older women whenever possible. We suggest including the recommendation to practitioners that all postmenopausal women with known modifiable clinical risk factors - high alcohol intake and low body mass index - receive advise and support on reducing	Comment noted. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.

Consultee or Commentator	Comment	Institute Response
	them. As women at risk of osteoporotic fragility fractures will not be able to benefit from therapy until they reach 70, we suggest that women below this age are asked to return around their 70th birthday for assessment.	
British Society for Rheumatology	**Appraisal consultation document on technologies for the primary and secondary prevention of osteoporotic fractures in postmenopausal women** The British Society for Rheumatology (BSR) welcomes the opportunity to comment on the appraisal consultation document (ACD) on technologies for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. We have had the opportunity to look at the comments submitted by the National Osteoporosis Society. We fully support the comments that they have submitted. We particularly share there concerns about the need to ensure that younger women also get the treatment they need.	Comment noted.
Helped the Aged (labelled as a public comment)	**Appraisal consultation document on technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women.** Help the Aged acknowledges the changes the Appraisal Committee have made to the draft guidance published in September 2006 by lowering the age threshold for primary prevention treatments amongst post-menopausal women from 75 to 70. However, whilst this revision will go some way to treat more women at potential high clinical risk of osteoporotic fractures, it remains discriminatory to younger post-menopausal women who are at a high clinical risk of sustaining a fracture. Help the Aged is concerned that these recommendations continue to use age as a barrier to preventive treatment. If NICE upholds the current age limit on access to primary prevention treatments, post -menopausal women under 70 may unnecessarily experience reductions in life expectancy and prolonged periods of ill health. Not only will this impact on the health and well-being of individuals at high risk, it will also increase the financial burden on the NHS. The resulting costs faced by the NHS of repairing hip fractures will be far higher than prescribing preventive treatments which can maximise the potential for a healthy later life. Help the Aged urges NICE to reconsider the use of age as the means of determining access to preventive treatments and instead to use clinical risk as a way of providing fair access to treatment.	Comment noted. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Health care costs avoided by treatment are taken into consideration in economic analyses. Recommendations based on absolute risk are not currently

Consultee or Commentator	Comment	Institute Response
	A failure to do so could spell an uncertain future for many women at high risk of sustaining an osteoporotic fracture purely based on their age. Help the Aged believes that age discrimination, in any form, is totally unacceptable. We do not believe that age should be a barrier to accessing vital services. Furthermore, such clear age discrimination is wholly at odds with Standard One of the National Service Framework for Older People, being guidance underpinned by statute, which demands the rooting out of age discrimination in services. We would also like to highlight our support for the National Osteoporosis Society; both organisations are committed to ensuring the health service supports those at risk and who live with osteoporosis. I hope that NICE will find our comments useful and are happy to discuss further if you would like more detail on this issue.	possible. Age and T-score (and prior fracture) are the most important factors to define risk of further fracture. Comment noted.
National Osteoporosis Society	**Appraisal consultation documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women** The National Osteoporosis Society (NOS) welcomes the opportunity to comment on the further Appraisal Consultation Documents (ACDs) on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. As we have done on previous occasions, we have incorporated our comments with respect to both ACDs in a single document to avoid duplication. We recognise that significant changes have been made to the draft guidance published in September 2006 and that some of those changes are consistent with comments made in our last consultation response. However, the Society remains extremely concerned that NICE has continued to set a treatment threshold for primary prevention based on age rather than by absolute risk of fracture. The result of this is that younger postmenopausal women, who are at a high risk of fracture, but have not yet experienced a fracture, will not be able to access treatment. Some of these women will have an absolute risk of fracture that is higher than individuals who would receive treatment under these draft recommendations. We are satisfied that the clinically unworkable recommendations for second line therapies have been removed and believe that the Guideline Development Group is well placed to consider the evidence and to make recommendations for second line treatments. However, we are concerned	Comment noted. Recommendations based on absolute risk are not currently possible. Age and T-score (and prior fracture) are the most important factors to define risk of further fracture. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.

Consultee or Commentator	Comment	Institute Response
	that, since Clinical Guidelines do not have a mandatory remit, second line therapies will not be prescribed in practice. Indeed we have already been contacted by health professionals who are extremely uneasy after being told that their PCT is currently preventing the prescribing of particular osteoporosis treatments until these Technology Appraisals are published. Since treatments other than alendronate are not included in the recommendations we believe that there is a significant risk that these restrictions will not be lifted after publication of the Final Appraisal Determinations (FADs). This consultation response focuses on our main areas of concern around the practical implementation of these recommendations. We make suggestions as to additions and changes to the recommendations to be included in the FADs relating to the following areas: • primary prevention for younger post-menopausal women • link to the Clinical Guideline on osteoporosis for recommendations on second line treatments and prevention of glucocorticoid-induced osteoporosis • initiation of treatment in women for whom alendronate is contraindicated • clarification of site used for bone mineral density (BMD) assessment • review date based on the likely changes in the field We have not reiterated, in detail, points of concern that have been raised in earlier submissions. However, we feel that it is necessary to note that, although it is unclear exactly which assumptions the Appraisal Committee have used in the economic model, we believe that some of the points of concern raised in previous submissions have not been satisfactorily resolved. These include, but are not limited to, the decision to use a disutility of vertebral fracture set to that of a hip fracture in the first year, the side effect disutility multiplied by 10 times and inequality in the acceptable cost per quality adjusted life year for primary and secondary prevention. For these reasons we remain extremely concerned about the transparency of the development process of these appraisals. **Primary prevention for younger postmenopausal women** The Society urges NICE to ensure that these recommendations allow younger post-menopausal women, who self-identify as being at a high risk of fracture, to be diagnosed and treated. Due to the lack of transparency in the economic model and the concerns that we have voiced in earlier submissions regarding the model assumptions we remain extremely concerned that the cost effectiveness threshold set at age 70 is too conservative. Indeed, early results from economic modelling that we are undertaking suggest that it is cost effective to treat younger women. Absolute fracture risk is derived from the existence of clinical risk factors, as well as age and bone mineral density. It is therefore possible for a woman of 59, who self identifies with several clinical risk factors and who is later found to have a very low bone mineral density, to have an absolute	Funding decisions of PCTs are not the responsibility of the Institute. FAD sections 4.2 and 4.3. describe the assumptions, The Committee considered that there were a number of issues not incorporated specifically within the model. Though quantitative synthesis of these uncertainties was not available, the Committee agreed that the sensitivity analysis for side effects could approximate these uncertainties. The Committee has included recommendations for women below the age of 70 years.

Consultee or Commentator	Comment	Institute Response
	fracture risk that is several times higher than a woman of 70 with a T score of -2.5 and one risk factor, for example. If the younger woman were to present to her GP, it would be negligent for them not to refer her for a DXA scan and if appropriate to offer her treatment. The ACDs make no provision for these cases. In the economic model, younger post menopausal women, who have not yet broken a bone but self-identify as being at a high absolute risk of fracture (because they have multiple risk factors), are inappropriately assigned opportunistic case finding costs. It seems perverse that, for these women, any identification costs should be included in the model and indeed it is these costs that have resulted in it not being cost-effective to diagnose and treat post-menopausal women under the age of 70. We believe that if these women were modelled in the same way as women who self identify by presenting with a prior fragility fracture it would be cost-effective to diagnose and treat them. The Society suggests that an additional recommendation be made regarding primary prevention for younger post menopausal women who self identify as being at a high risk of fracture to allow them to be assessed and treated. This would ensure that younger post menopausal women whose risk of fracture is equal to, or greater than, a woman aged 70 years or older (who would be eligible for assessment and treatment), can also access treatment. This change would remove unjustifiable age barriers (and hence age discrimination) to treatment for those at the highest risk. The age cut-off for treatment proposed in these and earlier ACDs has sparked outrage among our membership. Many of our older members have voiced that they felt disadvantaged during previous consultations as they have been unable to access the NICE website to comment on the ACDs. In response, the Society has offered a system to allow members, who do not have internet access, to express their views during this consultation period. We have received **5129** responses from members and stakeholders indicating their support for our view that drug treatments should be made available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. We have included an appendix showing the names and postcodes of all of the people who responded. **Recommendations to only include initiation of treatment** Although we believe that the inclusion of second line treatment recommendations in the Clinical Guideline on osteoporosis will result in comprehensive guidance on the care pathway for patients with, and at risk of osteoporosis, we are extremely concerned that this means that there will be no mandatory recommendations for treatments other than alendronate. We hear from patients on our helpline whose Primary Care Trust (PCT) has denied them access to teriparatide, even though they fit the criteria given in the mandatory TA87. Furthermore, during this	The Committee has taken the comments received into account (see FAD section 4.3.16). Issues arising from funding decisions by PCTs are not the responsibility of the Institute. Treatment options for women who

Consultee or Commentator	Comment	Institute Response
	consultation period we have received calls from several health professionals who have noted that strontium ranelate cannot be prescribed in their PCT until the recommendations we are consulting on have been published to give guidance on its use. Recently we have also heard from a professional whose PCT has a red light on prescribing of alendronate for glucocorticoid induced osteoporosis, because it is not being recommended by NICE. There is a real unease among the professional community that they will just not be allowed to prescribe treatments that are mandated by NICE. The NOS is therefore concerned that without their inclusion in mandatory guidance, teriparatide, raloxifene, strontium ranelate and risedronate may suffer from "NICE blight" until, and probably even after, recommendations are published in the Clinical Guideline. Our other concern regarding the move to include only treatment initiation is that there is a significant minority of patients for whom alendronate would be contraindicated or relatively contra-indicated as a first line treatment. This would include, for example, patients with dyspepsia or abnormalities of the oesophagus associated with delayed emptying, where alendronate is totally contra-indicated. Neither of the ACDs make provision for these patients. For recommendations in the Clinical Guideline on second line treatments and glucocorticoid induced osteoporosis to be implemented, the NOS believes that the guidance on osteoporosis must be published as a suite of guidance and that the Clinical Guideline must be subsumed in the TAs to ensure that clinicians follow the recommendations made in it. Ideally this would mean that the three documents are launched at the same time, unless NICE have an alternative solution to this particular problem. Furthermore, the Guideline Development Group must be allowed to make clinically workable recommendations that will ensure that a range of suitable and effective treatments are available to those patients who are unable to tolerate alendronate or for whom it is ineffective. In response to these two points the NOS would welcome the inclusion of the following two statements: • In section 1.1 of both ACDs: "When initiation of treatment with alendronate is contraindicated, treatment must be initiated using the recommendations for second line treatments included in the Clinical Guideline on osteoporosis" • Before section 1.3 (an additional recommendation) in both ACDs: "For recommendations on second line therapies and prevention of glucocorticoid induced osteoporosis, clinicians must implement those included in the Clinical Guideline on osteoporosis"	are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. The Committee did not consider it appropriate to endorse guideline recommendations which are not yet finalised. Committee considered alendronate at an acquisition cost of £95 per annum.

Consultee or Commentator	Comment	Institute Response
	Clarification of site used for BMD assessment An unwarranted change in both ACDs is the lack of specificity as to the site of assessment of BMD. Earlier ACDs have specified the femoral neck as the specific site to be used for reaching a diagnosis of osteoporosis. Whilst BMD can be assessed using DXA at peripheral sites (such as the forearm), axial (hip and spine) DXA is recognised as a better predictor of fracture than peripheral DXA. The NOS acknowledges that section 2.4 in both ACDs states that 'measurement of BMD at the femoral neck using DXA can estimate fracture risk'. However, we are concerned that without more specificity as to the site of assessment in the recommendations, NICE may inadvertently encourage widespread and inappropriate use of peripheral DXA. For this reason the NOS urges the committee to clarify its guidance in section 1 of the ACDs. We suggest the following wording: • "T-score relates to the measurement of BMD using axial ('hip and spine') dual energy X-ray absorptiometry (DXA) scanning and is expressed as the number of standard deviations (SDs) from peak BMD"	The wording in the FAD has been amended accordingly, see Section 2.4 and preamble.
	Review Date In the September 2006 ACDs, the review date included in both documents was 2 years post publication. However, in this most recent draft the review date is 3 years post the anticipated publication date. The NOS is not aware of significant changes in the field of osteoporosis to effect this change. On the contrary, since the start of this long development process 2 new osteoporosis treatments have been licensed (ibandronate and PTH 1-84) and a further treatment is being considered for a license (zolendronate) showing how quickly this field of medicine is moving. Furthermore, since the last ACD, the price of generic alendronate has seen a further small reduction to £7.22 for 4 weeks of treatment. Given the likely further reduction in price of alendronate in the coming months and the potential impact of the WHO fracture risk assessment tool in selective case finding, we believe that the increase in review time is neither appropriate nor evidence based. We urge the committee to reconsider the review date and would suggest that it should be a maximum of 2 years after the date of FAD publication.	Ibandronate, zolendronate and PTH 1-84 have not been referred to the Institute for Appraisal. Technology appraisal guidance is reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
	Summary of proposed changes In conclusion, the NOS remains extremely concerned about the development process for these Technology Appraisals. However, we hope that our comments will be facilitative to the development of FADs for primary and secondary prevention of osteoporotic fractures that meet the needs of all post-menopausal women who are at a high risk of breaking a bone. Specifically, we	Comments noted. See above responses.

Consultee or Commentator	Comment	Institute Response
	urge the committee to include the following additional points in the FADs: 1. A recommendation in the ACD for primary prevention which will ensure that younger women who self identify as being at a high risk of fracture are assessed and treated 2. In section 1.1 of both ACDs: "When initiation of treatment with alendronate is contraindicated, treatment must be initiated using the recommendations for second line treatments included in the Clinical Guideline on osteoporosis" 3. Before section 1.3 (an additional recommendation) in both ACDs: "For recommendations on second line therapies and prevention of glucocorticoid induced osteoporosis, clinicians must implement those included in the Clinical Guideline on osteoporosis" 4. The final paragraph of section 1 of both ACDs should be amended to: "T-score relates to the measurement of BMD using axial ('hip and spine') dual energy X-ray absorptiometry (DXA) scanning and is expressed as the number of standard deviations (SDs) from peak BMD" 5. In section 8.2 of both ACDs the review date should be amended to July 2009. With the inclusion of these points and the publication of a robust Clinical Guideline, we remain hopeful that a suite of guidance will be available to ensure that patients with, and at risk of osteoporosis, are able to access a range of suitable and effective treatments, regardless of their age. We very much hope that these comments are helpful and if you would like to discuss any of the points raised in more detail, please do not hesitate to contact me.	

Consultee or Commentator	Comment	Institute Response
NOS – Southampton and district group	We the undersigned members of Southampton and District Group of the National Osteoporosis Society are shocked to learn that N.I.C.E. is proposing to give post-menopausal women under the age of 70 no preventative treatment for osteoporosis, even when they are at high risk of breaking a bone due to the disease. By the time we have a DEXA scan taken we have already lost 25% of our bone mineral density. Indeed, for osteoporosis to show up on an X-ray 30 to 35% of bone mineral density has been lost never to be replaced. We therefore request that all postmenopausal women at risk should receive preventative treatment.	Comment noted. Please see above response to NOS comments.
Royal College General Practitioners 1 (Dr Sarah Jarvis)	As you will see, I have been asked to comment on these two appraisal documents in my capacity as women's health spokesperson for the RCGP. Briefly, my comments are as follows 1) I am delighted that the lower age limit for secondary prevention of osteoporotic fractures has been lifted- you will recall that in previous guidance (no87), the recommendation was that women under 65 should not be treated ever if they had had one or more fragility fractures, unless their T score was below -3. 2) I appreciate the rationale for initial treatment for all patients with alendronate, in view of cost effectiveness data. However, I am concerned that there is no mention of contraindications to bisphosphanates, or of the action recommended if patients are genuinely intolerant of bisphosphanates - the guidance concedes that there is ample evidence of a high incidence of intolerance and G-I side effects. 3) I am disappointed that previous clarification about the situations in which alternatives such as strontium ranelate and raloxefine should be prescribed (also in no. 87) has been omitted. This is particularly disappointing given that the cost effectiveness, at least for some of the alternatives in	1) Comment noted. 2) Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. The forthcoming NICE clinical guideline is expected to consider options for those women who are intolerant to alendronate 3) Treatment options for women who are contra-indicated to alendronate will be defined in the

Consultee or Commentator	Comment	Institute Response
	secondary prevention (4.2.3-4.2.5) is well below the £30,000 threshold sometimes used by NICE 4) I find it hard to justify the use of a £20,000 CQG cut-off for primary prevention, since the secondary prevention guidance refers to a £30,000 CQG cutoff. This was pointed out by the RCGP in its previous commentary	clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. 4) The Committee considered that women who have already sustained an osteoporotic fracture constitute a different population from the primary prevention population, who are well and asymptomatic
Royal College of Nursing	**Response to Appraisal Consultation Documents on the treatment of primary prevention and secondary prevention of osteoporotic fragility fractures in post menopausal women** The Royal College of Nursing welcomes these documents. These comments relate to both primary and secondary prevention The RCN notes that there will be an additional clinical guideline for 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' and welcomes this proposal. We would urge NICE to ensure that there are clear links between the clinical guideline and the technology appraisal guidance. The RCN notes, however, that the recommendations in both documents did not seem to cover in any way, the interest of postmenopausal women under the age 70 years, until they have experienced a fracture. This means for example that women with untreated early menopause (perhaps because of surgery or other medical conditions such as rheumatoid arthritis) who would currently be considered high risk for osteoporosis cannot be treated or even investigated by DEXA unless they have fractured. This is contrary to what is considered good practice in menopause care at present and will cause difficulties if implemented. By the time a fracture has occurred - it seems a little late to be considering investigations. In our view, this would create inequitable access to treatment and care for the women in this high risk population.	Comment noted. The preamble of the FAD states that the technology appraisal guidance should be read in context with the clinical guideline when it is published. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.

Consultee or Commentator	Comment	Institute Response
	General Comment In view of the above comments, we would urge the Committee to take this matter into consideration in determining the Final Appraisal Determination	
Society for Endocrinology	The Society welcomes the opportunity to comment on these revised proposals. Our response to these was developed by the Calcium and Bone Special Interest Group of the Society and has been approved by the Clinical Committee. Whilst we believe that the change in emphasis of the recommendations to deal only with initiation of therapy for both primary and secondary prevention of fractures means that the proposals are much more workable than previously we still have several concerns about the recommendations. 1. The different status afforded to Technology Appraisal guidance compared with Clinical Guidelines within the NHS raises concerns that those areas which have been delegated to the Guidelines Development Group might be ignored by local healthcare commissioners. In particular, we are concerned that the one expensive therapy, teriparatide, might be no longer available in the NHS as it would not be subject to Technology Appraisal guidance and therefore be considered an optional extra by most primary care trusts. 2. Linked to this is the problem that in those women who are not able to be given alendronate because of the presence of contraindications the proposed guidance offers no suggested therapy. Again we believe that this would leave these women open to a PCT making no therapy available. We believe that this problem could be forestalled by making very explicit reference to the upcoming Clinical Guideline within the guidance such that the guideline recommendations could be seen as fulfilling part of the role of the appraisal and hence be more likely to be adhered to by commissioners. 3. We realise that closer linkage between the technology appraisal and clinical guideline might be difficult given the different timetables for the two processes. In order to ensure that the Institute offers meaningful integrated guidance on the management of patients with osteoporosis we wonder whether it would be best to delay the release of the technology appraisal to coincide with the publication of the clinical guideline. 4. Whilst we appreciate the efforts made by the Institute to accommodate requests for sensible use of bone density measurements in frail elderly patients several of our members	Comment noted. Comment noted. 1. Funding decisions of PCTs are not the responsibility of the Institute. 2. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. 3. The preamble of the FADs states that the technology appraisal guidance should be read in conjunction with the clinical guideline when it is published. 4. The wording of the first bullet in FAD section 1.1 has been chosen

Consultee or Commentator	Comment	Institute Response
	feel that the guidance as currently written is likely to be interpreted as indicating no need for bone density measurement in these groups. Studies of patients following osteoporotic fractures show that even in elderly populations there is a substantial proportion of patients in whom bone density is not osteoporotic and therefore in whom therapy is not necessary. The data from the Glasgow Fracture Liaison Service (supervised by one of our members) demonstrates that among women with fractures of distal radius or ulna 45% aged 75-79 do not have osteoporosis; 35% of aged 80-84 do not have osteoporosis and about 28% of women age 85+ with these fractures do not have osteoporosis. Similar data are available for fractures at other sites. These data highlight: a. the costly misuse and futility of initiating treatment without prior DXA to a substantial percentage of women who are unlikely to derive benefit b. the clinical risk associated with such inappropriate initiation of drug therapies 5. We would therefore request the Institute to consider revision of the wording around the use of DXA in order to make it clear that it would be normally expected for bone density measurements to be undertaken before instituting therapy. The opportunity to institute therapy without such measurements should be reserved for those in whom there are good clinical reasons to proceed to treatment without the investigation. 6. We are concerned that the revised primary prevention guidance might preclude an important minority of patients from receiving appropriate therapy. In particular we believe that there are several postmenopausal women with high risk of osteoporotic fracture who could be cost effectively treated but who are overlooked by the current guidance. These are women who fall below the proposed age threshold for investigation and treatment but who have a high absolute fracture risk on the basis of the presence of multiple risk factors. Many of these patients will actually self present and therefore will have low identification costs. Within this group are many women who will actually be at a substantially higher risk of fracture than those who would be targeted by the proposed guidance. We would therefore ask the Institute to consider ways in which these women could be brought within the scope of the guidance. One possible mechanism would be to adopt a more stringent criterion for treatment in women with no previous fracture below the age of 70. This could either involve an increased number of clinical risk factors or a greater degree of bone loss measured by DXA than would be necessary for an older woman.	to allow clinicians the option to treat women, who are over the age of 75 and have with 2 risk factors, without DXA scan if they consider a DXA scan to be clinically inappropriate. This does not mean that in general, DXA scans should not be carried out in women over the age of 75. 5. See response to comment 4. 6. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
Royal College	Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of	

Consultee or Commentator	Comment	Institute Response
of Pathologists	osteoporotic fragility fractures in postmenopausal women And Alendronate, etidronate, risedronate, raloxifene and strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. The comments that follow are given in accordance with the general headings requested by the Appraisal Committee 1) It is surprising that the documents comment on the fact that the guidance should be read in the context of the clinical guideline which is not available. The exclusions are inappropriate especially since a large amount of literature is available on primary prevention in women who are osteopenic. 2) A number of studies now question the relevance of statements on adequate calcium/vitamin D intake and what constitutes being replete this needs addressed and a level of optimal supplement mentioned or this statement altered. 3) Work from Glasgow (McLellan AR et al Osteop Int 2003) questions the advisability of treating the elderly population without BMD measurements. Several other papers argue against this approach. I would recommend the committee read the work on the lack of age effects and fracture outcomes especially the NORA study which argued against an ageist approach (Siris E et al JBMR 2004). 4) HRT has been shown to be effective in several publications from the WHI study and yet has	1.) The guidance will remain in effect when the clinical guideline is published. Therefore reference to the clinical guideline is important – and has been considered by the Committee in response to consultation feedback. 2) The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on calcium and vitamin D. 3) The wording of the first bullet in FAD section 1.1 has been chosen to allow clinicians the option to treat women, who are over the age of 75 and have with 2 risk factors, without DXA scan if they consider a DXA scan to be clinically inappropriate. This does not mean that in general, DXA scans should not be carried out in women over the age of 75 4) HRT is not within the scope of this appraisal.

Consultee or Commentator	Comment	Institute Response
	been ignored in this analysis. 5) Alendronate has been made the drug of choice in primary and secondary prevention. This commentator would like to see the evidence from the literature that all generic forms of alendronate ("with the lowest acquisition price") have the same efficacy as Fosamax and evaluate the outcome data to support their use before such a recommendation is made. There is some data that suggests this may not be the case (see Epstein S et al Curr Med Res Opin 2003, Hough S. SAfr Med J 2006) 6) It is very surprising that other efficacious agents have been excluded from use by these documents or given lower ratings based purely on cost. It appears that cost considerations are dominating this appraisal document and pronouncement. Surely the value of second line agents with effectiveness against fracture in post-menopausal women who are unable to tolerate the first line therapy should be recognised by the appraisal group. 7) In making the cost comparisons the etidronate assessment includes the costs of calcium but the alendronate costing does not appear to include this. 8) It would serve patients better if the NICE panel recognised that all, bisphosphonates are best taken on an empty stomach where possible to aid absorption rather than between meals as stated in the document. 9) The type of screening programme that could be implemented should be re-considered. Costs effective analyses based on peripheral scanning and other approaches should now be assessed in the light of the published literature (Siris E et al Osteop Int 2006, Miller P et al J Clin Densitometry 1998, Miller PD et al Arch Int Med 2004)	5) Comment noted. 6) The Committee does not consider the costs of new technologies alone but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3). Second line therapies will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. 7) Comment noted 8) Comment noted. NICE guidance needs to be in line with the directions in the Summary of Product Characteristics (SPC). 9) The Committee has been advised by the GDG that peripheral scanning is currently not sufficiently validated. 10) Comment noted.

Consultee or Commentator	Comment	Institute Response
	10) Having identified the very serious nature of this condition within the document the current provisional recommendations are not a sound and suitable basis for the preparation of guidance to the NHS. Additional Comments Related to the Documentation The Committee have disregarded the evidence presented that shows ways of improving persistence and compliance with bisphosphonate therapy for either primary or secondary prevention. For a small amount of investment a significant return can be obtained by using biochemical markers of bone metabolism or nurse/physician led feed back to patients on compliance (Delmas P et al JCEM 2007, Eastell et al JBMR 2003, Clowes et al JCEM 2004). The committee should review the literature that exists in this area of the technology appraisal. The implications of this data should be included in the economic analyses with increased persistence factored into the calculations and assumptions made. Although hip facture is a “crucial goal” in the management of osteoporosis there is significant evidence pointing to the relatively “high cost” of vertebral fracture in terms of morbidity and the importance of reducing vertebral fracture incidence in patients with osteoporosis and this should not be underestimated by the committee (eg Borgstrom et al Osteop Int 2006). Once again the committee have ignored the science base on the effect of strontium on calcium measurement. Despite my previous responses on this matter the documentation still incorrectly has a statement that strontium can affect the measurement of calcium in the blood or urine. At the concentrations of strontium prescribed there is no statistically significant effect on calcium measurement in the blood. There can be an effect at high doses or immediately after a dose on urinary calcium excretion estimates but even this is a minimal effect. I would like to see a reference quoted that backs up the current incorrect statement on this in the documents. The continuing lack of expertise on the committee in this area of osteoporosis is resulting in ongoing problems related to the document.	Comments noted. Issues related to the management of persistence and compliance to bisphosphonates are outside the remit of the appraisal and may be included in the clinical guideline on ‘Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk’.
Society & College of Radiographers	**Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women** **and** **Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women** **Response from The Society and College of Radiographers**	

Consultee or Commentator	Comment	Institute Response
	The Society and College of Radiographers is pleased to have a further opportunity to comment on these important NICE appraisals. We welcome the extension to the consultation process following the first round of comment submissions and appreciate this indication that the Institute takes note of and responds to the views expressed at consultation. This response is informed by expert perspective provided from amongst our members in the field of bone densitometry. In particular, we are grateful for the contribution of Sue Barlow, Specialist Osteoporosis Radiographer at the Nuffield Orthopaedic Centre, Oxford. The Society and College of Radiographers notes the changes that have been made to both ACDs and welcomes them in so far as they go. However the **primary prevention** recommendations still indicate that women under the age of 70 who are at high risk but have not yet sustained a fracture are not eligible for treatment. We believe that clinicians and public will be at loss to understand how the title can be "Primary Prevention" when there is clearly no intention to support any attempt to be proactive in detecting and treating osteoporosis. We are pleased to note more significant positive changes on the **secondary prevention** recommendations , one being that if a patient is currently receiving treatment they can stay on it. However the treatment pathway seems to advocate Alendronic acid as the only option open. Many elderly frail patients are intolerant to this bisphosphonate. It is disappointing that no recommendations are made for any alternatives. It appears that this has been shelved on to the remit of the next stage, which is the publication of the Clinical Guidelines. These guidelines will also cover patients on steroids and those with osteopenia. We fear that, as guidelines, these will not be mandatory and that they can and will be ignored by the Primary Care Sector. In the view of the Society and College of Radiographers, NICE are missing an opportunity to take a more positive approach. For example, no mention is made of the effective use of teriparatide as an option in treating these patients. Under the current arrangements each patient has to prove eligibility before funding for the treatment is allowed. The lack of clarity implies that this situation will persist. In our view there are	Comments noted. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. The prevention and management of osteoporosis will be covered in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Comment noted. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Funding decisions of PCTs are not the responsibility of the Institute. Teriparatide is not recommended

Consultee or Commentator	Comment	Institute Response
	real risks that even with 2 or more spinal fractures, otherwise eligible patients will be denied this treatment on the grounds of cost. The Society and College of Radiographers notes with concern that some of the changes to the ACD since the last one issued in January 2005 seem to have been made without support of any clear evidence. The model used now has different, lower utility values for the spine. Without a clear commentary as to why this has been done, there are inevitable suspicions that values have been lowered to reduce the significance of spinal fracture. Where are the figures and evidence to support this change? Regarding the utility values for the hip, these should have been raised in our view, rather than the opposite. With regards to cost effectiveness of treatments, we are perplexed that, since generic alendronic acid is 2/3 lower in price than Fosamax there has been no change in the cost effectiveness over the last 2yrs. It must be more cost effective now to treat than before with that magnitude of savings. It is very regrettable that this process is taking so long. It has taken nearly 5 years to get to this stage and treatment options have evolved in that time, many more than in the first appraisal document. We are concerned that the final outcome cannot address comprehensively the best practice options in treatment of osteoporosis with treatment possibilities being excluded because they have not been assessed. Even existing recommendations are being passed over because they are still under review. The position of the Society and College of Radiographers remains unchanged. It seems obvious to us that the best case scenario and the one that should be striven for is that drug treatments be	as a treatment option for the initiation of secondary prevention of osteoporosis (see secondary prevention 2007 FAD section 1.4). The previous ACDs were issued in September 2006 and all evidence seen by the Committee was included in the evaluation report available on the NICE website. The Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, but it considered that it was not likely that this would so greatly outweigh the utility decrement associated with a hip fracture (see FAD section 4.3.10) The preliminary recommendations made for primary prevention before the substantial price change for alendronate (2005 ACD) were more restrictive than the recommendations in the current FAD (i.e. T-score thresholds were much more severe). The complexity of this appraisal, the changes in price for alendronate, and the parallel development of the clinical guideline has made additional analysis and extensive

Consultee or Commentator	Comment	Institute Response
	available for all post menopausal women who are at high risk of fracture, regardless of their age , **before** the incidence of the first fracture . Osteoporosis should be treated in the same way as other diseases for which prevention is key eg Heart disease and strokes and treatment should be freely available to all who need it regardless of age or gender. It is disappointing that, once again, NICE are stopping short of making effective recommendations to achieve this.	consultation necessary. Recommendations based on absolute risk of fracture are not currently possible. Age and T-score (and prior fracture) are the most important factors to define risk of further fracture, and consequently cost-effectiveness of treatment.
NHS Quality Improvement Scotland		
	Reviewer 1: **This document considers the use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.** The recommendations made differ from those made previously in NICE Technology Appraisal 87. These changes do have potential implications for NHS Scotland which require careful consideration. The main change in the recommendations has come about through the availability of generic alendronate. The price of this agent is significantly less than branded Fosamax. This means that the cost utility/effectiveness analyses have had to be revised. As a result of this it is recommended that generic alendronate is made available to all women over age 50 who have had a fracture and who have osteoporosis confirmed by DXA scanning. It is my view that this recommendation is appropriate and is consistent with the evidence base. Previously TA87 recommended that DXA scanning was not required after age 75. This document takes a position which is more in line with the evidence base (and SIGN Guideline 71) in that it is now stated that “a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible”. This by implication means that in other circumstances BMD assessment is recommended. This is appropriate for NHS Scotland as it means that patients who are resident in areas where DXA scanning is either limited or not available will still be eligible for treatment. It	Comments noted.

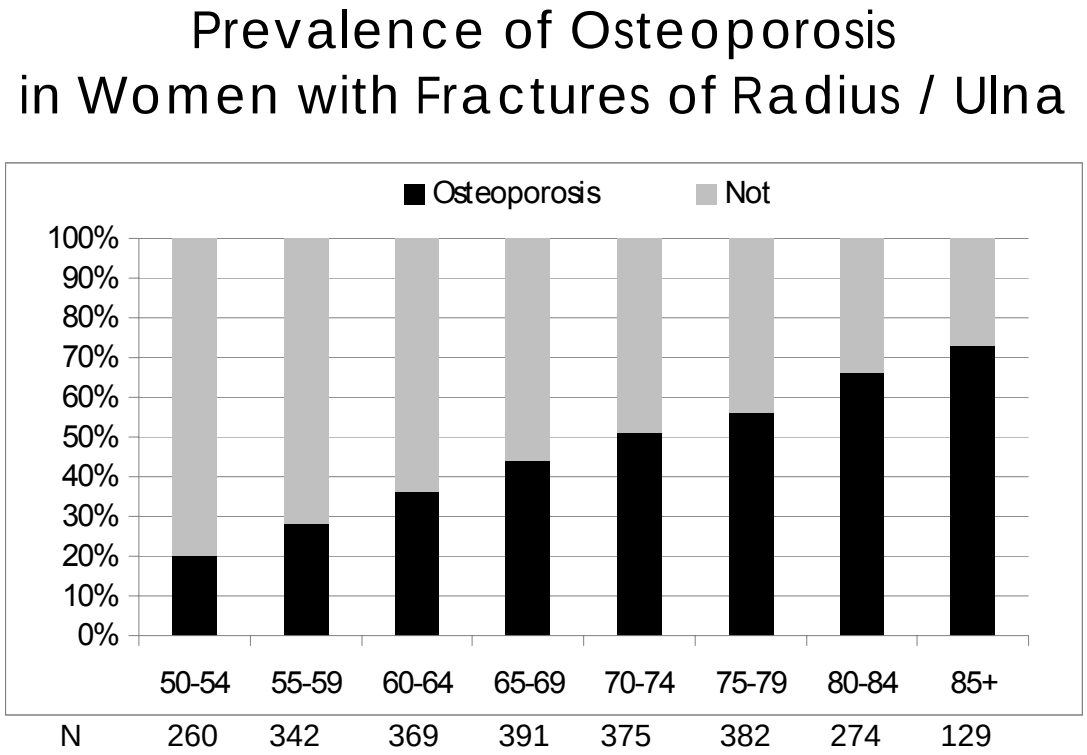
Consultee or Commentator	Comment	Institute Response
	should be recognised though that BMD assessment is still required for younger women and that in order to comply with this technology appraisal a number of Health Board areas in Scotland will need to invest in DXA facilities. There are a number of areas of this document however which I think are of concern and conflict with current policy in NHS Scotland: Firstly it is explicitly stated that outwith generic alendronate; no other treatments are recommended as primary therapies. The rationale behind this is not clear. In TA 87 other agents such as risedronate were cost effective in older patients. Since their costs have not changed significantly – they should remain cost effective in older (higher risk) patient groups. It is probably acceptable that drugs other than generic alendronate are generally not used under the age of 60. However in older patients or others at equivalent high absolute fracture risk then agents such as strontium ranelate and teriparatide should still have a role. These roles have already been defined by the Scottish Medicines Consortium (for strontium ranelate & teriparatide – and also ibandronate although this is outwith the scope of this document). I would recommend that the SMC guidance should remain in place for patients in Scotland. The principle here should be that any individual patient's absolute fracture risk should drive treatment decisions. Age is an important determinant of absolute fracture risk but not the sole determinant. A similar issue exists with respect to the use of treatments where generic alendronate is not tolerated. This document advises that the forthcoming clinical guideline "Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk" should be used. The concern here is that technology appraisals carry mandatory status whereas guidelines are advisory only. This could allow groups to choose not to follow the guideline recommendations. It is likely however that this is a more important issue in England where Primary care Trusts have commissioning status whereas this is less likely to be important in Scotland. However this is also an argument to say that SMC guidance should remain in place. **This document considers the use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the primary prevention of osteoporotic fragility fractures in postmenopausal women.** The principal recommendation in this document is that generic alendronate (and no other agent) is recommended for use in women over the age of 70 who have osteoporosis and at least one other	Comment noted. Because of the changes in price for generic alendronate, the other drugs are economically dominated by generic alendronate. Recommendations based on absolute risk of fracture are not currently possible as an absolute risk of fracture algorithm is not available. Age and T-score (and prior fracture) are the most important factors to define risk of further fracture, and consequently cost-effectiveness of treatment. Funding decisions of PCTs are not the responsibility of the Institute. Following consultation on the ACD, the Committee has included recommendations for women

Consultee or Commentator	Comment	Institute Response
	risk factor for fracture. This however is taking a very simplistic view of fracture risk. Whilst I am happy to accept that this is an appropriate population to treat I am concerned about potentially excluding very large numbers of high risk patients who are younger than age 70. This recommendation is not consistent with SIGN Guideline 71 or SMC guidance. The overarching principle here should be that treatment decisions should be based on a patient's absolute risk of fracture. Patients under age 70 who are ***at equivalent risk*** to those over age 70 should also be considered for treatment. Reviewer 2. i) Whether you consider that all the relevant evidence has been taken into account. This is a narrow HTA since it is designed to be complemented by NICE's Clinical Guideline. I am not sure about the positive predictive power of DXA scans but the sensitivity analysis does seem to take some variation into account. 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. Primary prevention as described could be interpreted as a large additional workload for primary care. I note this is noted but I am not sure it has been fully considered iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. If in the absolute sense of doing what is says, then yes although will be difficult. i) Whether you consider that all the relevant evidence has been taken into account. As far as I can tell, yes this seems so. ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on	below the age of 70 years. Comment noted. Comment noted. Comment noted. Comment noted.

Consultee or Commentator	Comment	Institute Response
	the resource impact and implications for the NHS are appropriate. Yes although since the two TA documents are similar and without accompanying models, it is difficult to say whether there has been adequate separation of the models. A concern is the costs of DXA scans v GP time – both models (primary and secondary) say they differ in these but that the sensitivity analyses for drug side effects should cover them – I hope so. iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Yes probably. My concern is that since this guidance differs considerably from current NICE guidance and SMC advice, it will be useful possibly to expand the group of people aware of this guidance. . Reviewer 3. i) Whether you consider that all the relevant evidence has been taken into account. The failure of the Primary Prevention ACD to adequately address the needs of patients arises from data that I have generated from the North Glasgow Fracture Liaison Service – a service that routinely assesses patients age 50 and over who present with new clinical fractures; the purpose is to assess them for osteoporosis and for the need for treatment for secondary prevention. 73% of patients(age 50 and over) who undergo full assessment by this service have not sustained a prior fracture. In other words 73% of new fracture patients present with their first fracture. The opportunity to impact on the public health problem of osteoporotic fractures requires not just systematic secondary prevention but identification of those at high risk without prior fracture who will benefit from primary prevention. The authors correctly acknowledge in section 4.3.7 of the secondary prevention document that 'there was not sufficient evidence of a proven treatment effect on fracture risk related to risk factors other than BMD, age and prior fracture'. In that context the potential to initiate alendronate for fracture primary prevention in 75+ year old women with 2 or more risk factors without DXA 'if the responsible clinician considers it to be clinically inappropriate or unfeasible' is bewildering and	Comment noted. Comment noted. Comment noted. Comment noted. The wording of the first bullet in FAD section 1.1 has been chosen to allow clinicians the option to treat women, who are over the age of 75 and have with 2 risk factors, without DXA scan if they

Consultee or Commentator	Comment	Institute Response
	utterly without evidence. Failure to identify a BMD threshold for initiation of alendronate under 70yr - of course is designed to discourage case-finding of patients with osteoporosis using DXA, but also neglects fracture risk reduction opportunities in our population who are at substantial fracture risk because of the extent of the reduction in their BMD. The primary prevention ACD fails to address adequately the needs of patients who are at high risk of sustaining their first fracture and is unacceptably restrictive. A compromise might be to incorporate a lower BMD for initiation of Rx – say ≤-3 for patients who are assessed by DXA based on 1 risk factors in age band 60-70. But for those over 75, DXA is essential to decide who can be treated appropriately, with acceptable risk benefit and cost benefit. 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. No – see above iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. No – see above i) Whether you consider that all the relevant evidence has been taken into account. The authors correctly acknowledge in section 4.3.7 that 'there was not sufficient evidence of a proven treatment effect on fracture risk related to risk factors other than BMD, age and prior fracture'. Having acknowledged that they then chose to make key recommendations that disregard that; in that context and given the necessity to assess BMD in younger postmenopausal women with fracture, the potential to initiate alendronate for fracture secondary prevention in 75+ year old women without DXA 'if the responsible clinician considers it to be clinically inappropriate or unfeasible' is bewildering. I enclose most recent data on the prevalence of osteoporosis in ~2500 postmenopausal women age 50 and over with the commonest fractures (of distal radius / ulna (fig 1). I am able to share with	consider a DXA scan to be clinically inappropriate. This does not mean that in general, DXA scans should not be carried out in women over the age of 75. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Comment noted. Comment noted. The wording of the first bullet in FAD section 1.1 has been chosen to allow clinicians the option to treat women, who are over the age of 75 and have with 2 risk factors, without DXA scan if they consider a DXA scan to be clinically inappropriate. This does not mean that in general, DXA scans should not be carried out in women over the age of 75.

Consultee or Commentator	Comment	Institute Response
	the committee, similar data for patients with fractures at any site, if that would be helpful. It should be noted that among women with fractures of distal radius or ulna 45% of women age 75-79 do not have osteoporosis; 35% of women age 80-84 with these fractures do not have osteoporosis and about 28% of women age 85+ with these fractures do not have osteoporosis. This data highlights: 1) the costly misuse and futility of initiating treatment without prior DXA to a substantial percentage of women who are unlikely to derive benefit 2) the clinical risk associated with such inappropriate initiation of drug therapies. Judicious, safe and cost efficient prescribing necessitates prior DXA assessment irrespective of the age of the patient with the fracture. Figure 1	Comment noted. Comment noted. Comment noted.

Consultee or Commentator	Comment	Institute Response
	 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. The authors have chosen to focus exclusively now on initiation of treatment for secondary prevention of osteoporotic fractures. Generic alendronate is correctly and unequivocally first choice therapy – and this will be tolerated by the vast majority of patients. The authors have now, however, not included alternative treatment options for patients who are intolerant of this. Omission of clear recommendations of alternatives for this small percentage of patients will leave their management open to wide variation in practice – perhaps postcode prescribing, depending on local	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Comment noted. Comment noted.

Consultee or Commentator	Comment	Institute Response
	financial pressures. If NICE is to achieve its aims this document must include endorsement of the priniciple or give guidance on judicious use of alternatives to alendronate, for the occasional patients where alternatives are necessary. It should be noted that the issues raised in section 1 would lead to less prescribing of drugs for osteoporosis, but notably more appropriate, safer and targeted prescribing. The document is otherwise acceptable. iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. If the above issues are addressed adequately then the document is appropriate as guidance for the NHS. Reviewer 4. [Reviewer 4 resubmitted the NOS response letter in full]	
Department of Health		
	No comment	
Guideline development group		
	<u>GDG response to ACDs for primary and secondary prevention of osteoporotic fractures</u> **Executive Summary** The GDG welcomes many of the changes made by the Appraisal Committee, in the light of previous GDG comments, particularly those changes relating to clinical workability. The GDG has given clear and detailed responses on the remodelling assumptions, and our views on this remain unchanged. In this document, we have chosen to focus on two main aspects of the ACDs (primary	Comment noted.

Consultee or Commentator	Comment	Institute Response
	and secondary), which are applicable to both ACDs. We recognise that there are significant areas of agreement, and urge the Committee to resolve several issues before clinically workable guidance for the NHS can be provided. The only way to achieve this, is through a carefully managed approach by NICE, encompassing the two appraisals and the clinical guideline as a suite of guidance. The GDG preferred option would be for synchronous publication of both appraisals and the guideline, forming a suite of guidance. In the absence of this, the potential for the guidance to be seen in isolation and not part of the whole clinical pathway and patient experience is a significant risk. Key to consistency in recommendations across the suite of the guidance, are clear linking statements between the appraisals and the guideline. The GDG has suggested appropriate linking statements in order to negate this risk. We are concerned that one group of patients have not been adequately covered: post-menopausal women under 70 years of age, without a prior fracture, but who are at high risk of fracture. This creates inequitable access to treatment across the high risk population.	Comment noted. Section 1 of the FAD states that the guidance should be 'read in the context of the clinical guideline' Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	Detailed GDG response. **1. Second line therapies** Patients who have started on generic alendronate, but then are intolerant of this should, without reservation, be offered one of the second line therapies. Both advisory groups are consistent on this.	Comment noted.

Consultee or Commentator	Comment	Institute Response
	Responsibility for second line therapies has been passed to the GDG, in order to provide guidance to the NHS. Whilst the GDG welcomes this responsibility, we recognise the importance of clear unambiguous linking statements from the Appraisals to the Clinical Guideline. This will establish that: • second line therapies are offered to those found to be intolerant of alendronate • clinician/patient guidance regarding the nature of the second line therapies is provided by the Clinical Guideline. Both of these points should be included in the appraisals. The following linking statement is suggested: **"For those patients who are intolerant of generic alendronate, second line therapies should be prescribed, and the recommendations in the clinical guideline on osteoporosis should be followed."**	Section 1 of the FAD states the clinical guideline will cover the treatment of women who are contraindicated to alendronate at initiation, have withdrawn from initial treatment, who have osteopenia, and who are on long-term corticosteroid therapy' and that the guidance should be 'read in the context of the clinical guideline'. See above.
	In the current NHS climate, there is high risk associated with the absence of explicit linking to the complementary guidance. This is further explained in the following risk assessment.	The Healthcare Commission monitors the implementation of both technology appraisals and clinical guidelines. See section 1 of the FAD, as above. 1.) Funding decisions of PCTs are not the responsibility of the

Consultee or Commentator	Comment	Institute Response
	Risk identified *No linking statement to the clinical guideline re second line therapies* Risk potential 1. *PCTs not funding 2nd line therapies because these are not mandated by inclusion in the Appraisals.* 2. *Second line therapies being 'red-lighted' and not prescribed (evidence of this already, see appendix)* 3. *Patients are started on generic alendronate, but then denied the treatment benefits if the drug is not tolerated* 4. *Clinician confusion* 5. *National variation in practice and post code access to NHS services*	Institute. 2.) The Healthcare Commission monitors the implementation of both technology appraisals and clinical guidelines 3.) The forthcoming NICE clinical guideline is expected to consider options for those women who are intolerant to alendronate. 4.) The 2007 FAD concentrates on treatment initiation, and clearly states circumstances where the forthcoming clinical guideline will provide recommendations. 5.) The Healthcare Commission monitors the implementation of both technology appraisals and clinical guidelines
	The following linking statement is suggested: **"For the management of patients on oral glucocorticoids, the recommendations in**	Comment noted.

Consultee or Commentator	Comment	Institute Response
	the clinical guideline on osteoporosis should be followed." A similar risk assessment has been produced for patients on oral glucocorticoids, another area of responsibility for the Clinical Guideline. Risk identified *No linking statement to the clinical guideline for treatment interventions in related populations (patients taking glucocorticoids)* Risk potential 1. *The two sets of guidance, which are complementary, are seen as separate rather than part of a suite of NICE guidance for the NHS in related populations.* 2. *Patients only receive part of the benefit of parallel guidance, with some patients potentially not receiving cost effective treatment.* 3. *Clinician confusion* 4. *National variation in practice and post code access to NHS services*	Section 1 of the FAD states that the clinical guideline will cover the treatment of women 'who are on long-term corticosteroid therapy' 1–2) Section 1 of the FAD states that the guidance should be 'read in the context of the clinical guideline' 3.) The 2007 FAD concentrates on treatment initiation, and clearly states circumstances where the forthcoming clinical guideline will provide recommendations. 4.) The Healthcare Commission monitors the implementation of both technology appraisals and clinical guidelines.
	2. Special groups of postmenopausal women The two ACDs state that they cover postmenopausal women who have osteoporosis, with the	Section 1 of the FAD states the clinical guideline will cover the

Consultee or Commentator	Comment	Institute Response
	exception of those on oral glucocorticoids. The ACDs have split this group of women into those who have a prior fracture (secondary prevention) and those that do not (primary). It is assumed that the former group are self-identifying and the latter are identified opportunistically when they visit a GP for any reason. Accordingly, allowance has been made for identification costs in the latter group. There is, however, a further group of postmenopausal women who are not covered by either appraisal, and they are the high risk, self-identifying group, aged less than 70 years, without a prior fracture. This group comprises those with rheumatoid arthritis and other medical conditions that have an associated increased risk of osteoporosis (e.g. ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility). Women with untreated premature menopause are also included in this group. In the Assessment Report, these have been rightly identified as at-risk patients belonging to the self-identifying group, but how they are managed is unclear in the ACDs. For this group, there is no need to include identification costs and the thresholds for secondary prevention should therefore apply. We recognise that such patients also fall within the remit of primary prevention, and, as such, will be assigned a maximum cost per QALY of £20,000. The GDG recognises that from economic modelling, it is cost-effective to send for DXA scans all women between 60 and 70 years who have any one of the above risk factors, and treat with alendronate if appropriate. Below this age range, it is cost effective for a woman with 3 clinical risk factors (including the main presenting factor). We recognise that there are relatively few women in	treatment of women who are contraindicated to alendronate at initiation, have withdrawn from initial treatment, who have osteopenia, and who are on long-term corticosteroid therapy'. Comment noted. Following consultation on the 2006 ACD, the primary prevention 2007 FAD includes recommendations for women below the age of 70 years. Treatment for women with untreated premature menopause may be further specified in the forthcoming clinical guideline. Comment noted. See above for

Consultee or Commentator	Comment	Institute Response
	this special group. The clinically workable solution for this group is to recommend that all postmenopausal women with other relevant conditions are sent for DXA, provided they have one other clinical risk factor (from: family history of osteoporotic fracture, high alcohol level, low BMI). The GDG recommends that the primary prevention appraisal inserts the following linking statement to the guideline: **"Women less than 70 years with rheumatoid arthritis, or other medical conditions that carry a risk of osteoporosis, or untreated premature menopause should be considered for DXA scanning and subsequent treatment, provided they have one additional clinical risk factor. Recommendations in the clinical guideline on osteoporosis should be followed."**	primary prevention recommendation for women less than 70 years of age. Comment noted. See above.
	3. Other The GDG accepts the Committee's statement that the appraisals and guideline need not use the same assumptions in the respective modelling. We recognise that complementary NICE guidance should be consistent. As this position has been reached, we do not consider it appropriate for either type of guidance to openly criticise the assumptions of the other in their documents. Therefore the GDG requests that the words, "*Although the Committee recognised that 50% was necessarily an arbitrary figure, the use of either 0% or 100% were both considered extreme and implausible*." be replaced with, "*The Committee recognised that 50% was necessarily an arbitrary figure*." The GDG believes that, with these modifications to the ACDs, workable guidance for the NHS in the osteoporosis community will be achieved.	Comment noted. Comment noted.

Consultee or Commentator	Comment	Institute Response
	Appendix Quote from Dr Sally Hope, RCGP member of osteoporosis GDG: *" In Oxfordshire and Buckinghamshire, strontium ranelate had been 'red light' designated by the Oxfordshire + Bucks prescribing advisors on the grounds it was waiting for NICE [from end of 2005-2006]. This red light means GPs were not able to prescribe it. They claimed they were waiting on NICE for a position statement. An appeal was launched by Professor John Wass, endocrinologist, to get this overturned on the grounds that the NICE statements and drafts were in the public domain and it might still be some time before the final documents were published. This has been reversed very recently [Feb 2007]. I know GPs in Kent still cannot prescribe Strontium and I'm trying to find out the national picture: the problem is there is no consensus."* Further evidence from within primary care in Cambridgeshire, has also indicated that there is a red light for bisphosphonates in all steroid treated patients because this is not in current NICE appraisal guidance.	Comment noted.

Reply received but no comments:

- DH
- Merck, Sharp & Dohme Limited

Comments received from website consultation:

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Patient 1	1	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 2	2	drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 3	–	I was diagnosed with osteoporosis at the age of 42 (I am now 44) and I firmly believe treatments should be available to younger women. Osteoporosis should also have been part of the QoF targets in general practice which it was going to be. There is definitely not nearly enough done for younger women with osteoporosis. After all they have a lot of years ahead of them with fragile bones	Comments noted. Recommendations for people with pre-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. It is outside the Institute's remit to make recommendations on what should be included in the QoF targets.
	2	there should be far easier access to DXA scanning than there currently is	Recommendations on the provision of DXA scanning are outside the scope of this appraisal.
	3	There should be vigorous lobbying of the government to make drugs zero rated for VAT then people would be less likely to be denied them. (I personally have been denied all the above treatments)	Comments noted.
Patient 4	5	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 5	1	There should be a caveat that if Alendronate is not tolerated the other medications should be considered, not just on a cost basis - as the costs of treating the fracture due to no drug being prescribed will be greater than the cost of using an alternate, better tolerated drug. It is very difficult for clinicians to assess calcium dietary intake and vitamin d status as they do not have the relevant skills to do this and this document section does not set out what the calcium and vit d requirements are or good dietary sources of calcium (in mg/day)	Recommendations for women who cannot tolerate alendronate and on the use of calcium and vitamin D supplements will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	4	see comments re vit d and calcium made in section 1	see above
	6	is there a plan for separate guidance re premenopausal osteoporosis?	Recommendations for people with pre-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Patient 6	–	I am currently receiving treatment for osteopenia which has helped increase my bone density. My mother suffered from osteoporosis and had two fractures, one of which meant she was in hospital for three months. I am concerned that women under 70 will have to break a bone to get treatment, even though preventative treatment is not expensive, and even though they have risk factors and a scan shows they have bone loss. This seems to be the only condition where one cannot receive treatment for a diagnosed condition until it becomes life-threatening--many elderly people die following a fracture. It also seems a gender issue, as there are many men (and women)who receive medication for raised blood pressure or high cholesterol, even though they have not yet had a stroke or a heart attack, but most of those suffering bone loss are women. Also one does not have to go blind in order to receive diabetic medication. I would urge a rethink on this, as I would think the cost involved in fractures, especially in those with bone loss and the elderly must be considerable, quite apart from the pain and anxiety	Comments noted. The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		cause to the patients.	
	4	I am currently receiving treatment for osteopenia which has helped increase my bone density. My mother suffered from osteoporosis and had two fractures, one of which meant she was in hospital for three months. I am concerned that women under 70 will have to break a bone to get treatment, even though preventative treatment is not expensive, and even though they have risk factors and a scan shows they have bone loss. This seems to be the only condition where one cannot receive treatment for a diagnosed condition until it becomes life-threatening--many elderly people die following a fracture. It also seems a gender issue, as there are many men (and women)who receive medication for raised blood pressure or high cholesterol, even though they have not yet had a stroke or a heart attack, but most of those suffering bone loss are women. Also one does not have to go blind in order to receive diabetic medication. I would urge a rethink on this, as I would think the cost involved in fractures, especially in those with bone loss and the elderly must be considerable, quite apart from the pain and anxiety cause to the patients.	Comments noted. The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 7	1	I do not understand your terminology when you write: “This guidance does not cover the following." and subsequently you write ""The NICE clinical guideline on osteoporosis will cover the treatment of"" This does not make any sense.	The technology appraisal makes recommendations for specific technologies (alendronate, etidronate, risedronate, strontium ranelate and raloxifene) and the circumstances under which they may or may not be used. The clinical guidelines make recommendations on how to manage the condition of osteoporosis.
	2	It is all very well commenting that Osteopenia: T-score of between -1 and -2.5 SD but I was diagnosed osteopenic, then 4 years later after the use of alendronate my DXA scan was normal T-score, with Fractures, and following a bone biopsy shown to have severe Osteopenia.	Recommendations for people with osteopenia (defined as a T-score of between -1 and -2.5 SD) will be covered by the clinical guideline on ‘Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk’.
	3	It is always good to look at reducing the cost of treatment; however some products are	The responsible clinician will

Consultee or Commentator	Section of ACD (if specified)	- Comment	Institute Response
		not going to work with some people due to the fact that their body reacts to the constituents or due to other medical needs such as dyspepsia may be unable to take that medication. What happens then? What happens with people with Learning Disabilities who may not understand the need to take the appropriate amount of water, 30 mins before the food or not lie down before eating? This damages the need for Consultants to look at each patient as an individual. Are they going to be preventative and proactive or treat the result?	discuss with the patient (and carer) the most appropriate available treatment option. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	4	I have done Statistical analysis when I was at university on research groups for scientific study. It appears that only people who are motivated can be persuaded to take part in research studies. Many people whose first language is not English refuse to take part. It would therefore be more appropriate for your statistics to show the number of people who were in the population, who refused to be part of the trial or who were not allowed to be part of the trial because of certain conditions. Than when you have put that statistical analysis in do you come to the same conclusion? I don't think so. I know so many people who have given up on alendronate because of the pain and nausea that it gave them. They ended up becoming a secondary group because their bones fractured. What are you doing to prevent this from happening? If DXA is being reduced then more people may fracture. What about the people who get on with their lives without them going to the doctor with pain etc and don't want to bother the GP? Wouldn't it be more appropriate to set up as part of the requirement for people to go to a well person centre and have advice & checks to ensure they don't need treatment?	Comment noted.
	6	Would it be possible for someone to Research: What research is done following cessation of the contraceptive pill that there is not a decrease in turnover of bone cell activity and that decrease starts at an earlier age than previously thought, and this in conjunction with the ever increasing weight and height of the population? And Secondly the factor that when people have Polycystic ovarian disease that at present there is no proof of the turnover of bone cell activity when the Follicle Stimulating Hormone and Luteinising Hormone are not within the correct ratio and periods are not regular, T-scores may be within normal limits but are they accurate?	Comment noted. This is outside the remit of the appraisals. It maybe appropriate to reiterate this comment during the consultation of the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Patient 8	–	Drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
			treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 9	–	I currently take one of the drugs under discussion. I am 54 and have never had a fracture. However, I witnessed the pain and distress of osteoporosis and fractures in my late mother and do not wish to suffer in the same way. Surely money spent now in prevention will result in lower costs to the NHS in the future in treating fractures etc.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 10	1	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age even if they have not yet broken a bone. I have osteopenia but am only 57 years old. Common sense tells me prevention is better than cure & I do not want to be disabled & in pain as a friend in her early 70s is with osteoporosis. By the time I & many, many others are in our 70s we too could be disabled if you go ahead with this ill-thought out proposal. You are very short-sighted & it will cost the country much more money in the long run if you go ahead with these proposals.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 11	1	Drug treatments should be available for all post menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	Drug treatments should be available for all post menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 12	–	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
Patient 13	1	In my opinion, the case is not made to restrict primary preventive measures to women aged 70 years or older.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	4	Having read the evidence presented above relating to clinical effectiveness, I am still of the view that the case is not sufficiently robust to deny treatment to post-menopausal women under 70 years of age with a diagnosis of osteoporosis at risk of breaking a bone, regardless of whether or not they have already experienced a fracture.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 14	1	I believe that drug treatments should be available for all people who are at high risk of breaking a bone, regardless of age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 15	–	I agree with the point made by NOS, as follows	Comment noted.
	1	1.2 I have benefited from taking Risedronate for 2 years since diagnosed with osteoporosis of lumbar region and osteopenia of the hips. I am grateful that in early February I suffered only from compression fracture of lumbar 2 and not more damage.	Comment noted.
	2	I suffer from no other medical condition. I drink 4-6 units of alcohol per week and have never smoked. My diet is good and I take sufficient calcium and vitamin D. My BMI is within normal limits. I do not diet excessively. I have never taken steroids.	Comment noted.
	3	I take Risedronate weekly without difficulty.	Comment noted.
	4	I cannot comment.	Comment noted.
	6	Could you involve Professor Eastell "work of the Northern General Hospital Sheffield?	Clinical experts who are involved with this appraisal were nominated by Consultees and Commentators.
	7	I think that drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, whether or not they have yet done so.	The recommendations in section 1 of the FAD reflect when the

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	8	I cannot comment.	
Patient 16	1	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 17		I was diagnosed aged 50 with a T score of -3 and a mother who had been severely affected by osteoporosis. I have benefited from treatment for the last 10 years and my bone density has increased and I have not fractured. I am dismayed to think that others in my position will now have to wait 20 years till they were 70 to get treatment to prevent/reduce the risk of fractures. Loss of bone density is very significant in the post menopausal years and they are going to get worse as they wait. Surely that is the very time to try to reduce the loss so as to avoid the expensive and painful fractures of the spine and hip that my mother had to endure and following which she died.	Comment noted.
		Why are you not willing to consider treating those with defined osteoporosis simply because they haven't reached 70. Why do they have to wait to get worse before you start to try to reverse the problem. Other conditions such as high blood pressure and cholesterol you try to identify early and provide preventative treatment.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years (see section 1.1 of primary prevention FAD).
		I find it extraordinary that generic Alendronate costs under 100 a year. I find it unbelievable that this is not considered ""cost effective"" to give to those under 70 with very low bone density and fracture risks even if they haven't yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 18	1	Drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	Drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 19	2	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 20	1	Drug treatment should be available for all men and post menopausal women who are at high risk of breaking a bone, regardless of their age even if they have not yet broken a bone. Prevention of fractures should be a top priority.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 21	1	Drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 22	5	I submit that Drug Treatments should be made available to all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone, on the premise that preventative action must be more advantageous than ""its too late to do anything now""	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 23	2	DRUG TREATMENTS SHOULD BE AVAILABLE FOR ALL POST-MENOPAUSAL WOMEN WHO ARE AT A HIGH RISK OF BREAKING A BONE, REGARDLESS OF THEIR AGE, EVEN IF THEY HAVE NOT YET BROKEN A BONE.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 24	–	I have had osteoporosis for a number of years. My GP prescribes Alendronic Acid and Adcal-D3 as treatment. I had an early hysterectomy (and therefore an early menopause) but was not prescribed anything to help with maintaining bone density at this stage. Both my mother and grandmother had osteoporosis; both lost height. My mother was not diagnosed with osteoporosis until she was in her 80s. By then she had lost over 8 inches in height and her spine was curved causing her to lean forward; these problems led in turn to problems with balance, mobility and being able to swallow food, etc. Only after I went with her on a visit to her GP and mentioned these points did the GP agree that she should have a scan and this confirmed osteoporosis. My GP informs me that my osteoporosis is genetic (inherited genes), and I am concerned that my daughter and granddaughter may also inherit the disease.	Comment noted.
	1	I strongly feel that drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	Clinicians and GPs need to have sufficient training, information, and guidance throughout their medical careers to enable them to detect, diagnose, prescribe treatment for, and review treatment for osteoporosis, both early stages and severe stages of the disease. There must be adequate diagnostic facilities to detect and monitor the disease(with the aid of reducing unnecessary broken bones and maintaining and/or improving quality of life for those suffering from osteoporosis)in all areas of the country.	Comment noted.
	3	GPs and clinicians need to have a thorough knowledge of the various treatments available and their side effects and contraindications, and whether patients might have difficulty taking some of the medications in the correct way. They should be prepared to offer an alternative treatment if a patient continues to suffer severe side effects with a particular drug. There should be opportunities to review medication/ treatment after a set period (e.g. every 5 years).	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
	8	I would agree that the guidance for the diagnosis and treatment for osteoporosis should be reviewed in 2010.	Comment noted.
Patient 25	1	I believe that drug treatment should be available for women like me who are post menopausal yet have not broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 26	2	I am 64 yrs of age, my mother suffered from osteoporosis. I consider it is essential that drug treatments be made available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 27	–	Background: I am a sufferer of osteoporosis aged 57. My mother had one of the worst cases of osteoporosis my doctor daughter had ever seen. Despite recognised risk factors (maternal osteoporosis and loss of periods at age 18 for 2 years), I was denied a DEXA scan, being too young (a postcode issue). After diagnosis I was recommended to go onto Fosamax by the private consultant rheumatologist. My mother suffered for nearly 30 years with breaks of wrists, back, sternum and hip. Her pain was incessant. Methods of risk assessment must be made more sophisticated so that those who are at risk can be treated preventatively before they break bones - weak bones are more of a problem with mending than good ones. They cannot always be pinned if the state of the bones is so poor already.	Comment noted.
	1	Clinicians often believe that women do not have adequate calcium intake and suggest supplementation first for confirmed osteoporosis. I think I recall that this has also been underlying the previous draft guidelines. The first step should be to check calcium and vitamin D levels and for coeliac disease using blood tests. By doing so underlying metabolic problems can be eliminated. My doctor initially suggested calcium - the blood tests showed I was suffering from Hyperparathyroidism - blood tests showed a raised but marginally high level of calcium in the blood, despite having an enormous adenoma on one of the glands - probably thee for at least 10 years according to the top parathyroid surgeon in the UK. Possible causes of the osteoporosis should be eliminated before the treatment is proposed - this should happen for all women - not just the young.	Comment noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
	2	Please see comments above about improved risk assessment and also examining the causes of the osteoporosis to see if any underlying problems can be addressed. Improved risk assessment should also take into account known/researched increased risks. e.g. I understand that there is a threefold greater risk for a daughter having osteoporosis, where a mother had a non impact wrist fracture at a relatively early age - as was the case with my mother.	Comment noted.
	4	The potential side effects of the drugs, whilst understood by clinicians, are not necessarily dealt with adequately , particularly for the very elderly. My mother list between 8 and 10 inches of height. Consequently she was very bent. She eventually had dementia and yet the nursing home where she was for nearly a year before she died and the GP never considered taking her off Fosamax. For the last four months of her if she showed signs of gastrointestinal problems but these were ignored. Ten days before she died she started bleeding somewhere in her digestive system. The gastro registrar suggested an ulcer/side effects of alendronate was the cause. She died shortly thereafter. This suggests that there comes a point where the use of the drug can be counterproductive in certain circumstances and therefore careful clinical consideration of its continuation in the elderly should be preferred. My mother's case suggests that the preferred way forward - and the economically beneficial route - would have been to have prescribed the drug sooner rather than later in order to prevent fractures in the first place.	Comment noted. Guidance on the withdrawal from treatments for individuals with post-menopausal osteoporosis may be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	6	Given that life expectancy varies so much, is it possible to determine an age at which to stop giving the drug? If there is evidence that there is a ""hangover2 effect of the drug, is there a case for looking at a combined measure of age and T score to decide at what point to stop giving it? If an active 80 year old is likely to live to 90 plus, should she not continue on the drug for a further period if she has confirmed osteoporosis?	See above
Patient 28	1	If this appraisal document goes through there will be no prevention at all for women under 70 - what will consultants and GP's say to their patients to go away and only return when they have fractured. I think its very short sighted to save just a couple of pounds a month and heaven forbid you fracture a hip with a cost to the NHS of about 20,000 - please reconsider and take on board the amount of younger patients there are with very active lives often working full time and even caring for elderly parents or grandchildren. With diets and life styles of the younger generation the number of cases of Osteoporosis will only increase, I would like my daughters and granddaughters to have some prevention available to them rather than treatment after they have fractured.	Guidance on the management of post-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Patient 29	–	I am extremely grateful that my osteoporosis was diagnosed early (age 55) before the word was even a part of my vocabulary, giving me the chance to explore all possible	Comment noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		means of treatment (nutritional, hormonal, pharmaceutical, exercises, etc) so as to inform my decisions regarding how I live and what I eat and do so as to have the best possible effect in slowing the progress of the deterioration in bone strength, and even possibly turning things around. (Bless the NOS!) I avoid taking drugs as much as possible, for a number of reasons pertinent to my own situation, but strongly believe that every woman (or man) should have free choice as to what therapeutic approaches she (he) takes, and that exploring what is most suitable should be between the patient and her/his GP or Consultant. People's tolerance to pharmaceutical interventions varies widely, and depends on variations in individual biochemistry (for which the patient should NOT be PUNISHED!) The best weapons on the patient's side are EARLY DIAGNOSIS (prompted by screening for risk factors), a WELL-informed GP or nurse (point of first contact), and referral to the NOS for further help and information and support and encouragement. My GP has a peripheral DEXA which is used as a relatively low cost preliminary screening device after patients have been selected for risk factors. Early diagnosis followed by dietary and lifestyle advice can be extremely cost effective! Osteoporosis is a cruel condition, causing people to spend the last years of their lives in pain and utter misery. Not to diagnose and treat as early as possible is extremely short sighted and inhumane. You too will grow old one day!	
	1	The NOS wishes to ensure that NICE makes drug treatments available for all post menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. I support the NOS position. It has been my experience that spinal fractures are often not even noticed until deterioration has progressed so far that radical measures are the only option available.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	2.2.....after the menopause because of a decrease in the production of both estrogens AND PROGESTERONE.	Comment noted.
	3	It is a serious indictment of our whole medical system that we have nothing more wholesome, and far less harmful, to offer patients with osteoporosis. Somehow we have to create a system that researches how to work WITH nature instead of always patenting poisons.	Comment noted.
	4	4.3.23--DEFINITELY! And what about all the other minerals that play a part - Boron, Magnesium, Manganese, Strontium, etc!!! 4.3.5--Seems to me you are missing a key possibility. If you screen the patients in a practice for risk factors, and then use a peripheral DEXA as a preliminary relatively low cost screening device for those at risk, and then TELL THEM WHAT THE DRUGS AVAILABLE REALLY DO TO ONE, You might be able to catch people early enough and FRIGHTEN them into taking positive	Comment noted. Guidance on the management of post-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		action about diet, supplementation, lifestyle and exercise, to have a positive, EXTREMELY BENEFICIAL and VERY LOW-COST EFFECT on their bone density and long term prognosis, thus saving the NHS ""pots of money""! (Well, it works for SOME heart attack patients - Why not consider it?) Waiting until the ""horse has bolted"" is extremely costly in the long run!	osteoporotic fractures in individuals at high risk'.
	6	I appreciate the lack of knowledge of long-term effects of these treatments and applaud the above recommendations. It may be entirely possible that long-term use causes more problems than it solves. I also feel that far more research should be carried out into non-pharmaceutical treatments, human-bio-identical hormone supplementation in physiologic doses, optimum nutritional approaches, and genetic analysis and treatment. (By the time the field of Genetics tells us what we really NEED to know, I will probably be a Poltergeist!) Meantime, it is Hobson's Choice! My heart goes out to any compassionate doctor faced with a patient with acute spinal fracture (and of course to the patient). The ""weapons"" currently at his/her disposal are an appalling choice. I have a young acquaintance who was diagnosed with osteoporosis at the age of 5, and have met a young man who, at the age of 19, had already had 40 fractures. I have also seen 3 relatives through the late stages of osteoporotic degeneration, and we still seem to be no nearer understanding the true root causes. There is a DESPERATE NEED for NON DRUG-RELATED BASIC RESEARCH!	Comment noted.
	7	I support the NOS in their submissions.	Comment noted.
	8	Do you expect this ""Guidance"" to be PUBLISHED before 2010? (Sorry, I DO appreciate the amount of work involved.) (Nightmare!)	Subject to an appeal the date of the technology appraisal publication is planned to be 2007.
Patient 30	1	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. Drug treatment must be available for those under 60 who have been diagnosed with osteoporosis.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
	3	See above comments	Comment noted.
	6	See above comments	Comment noted.
	7	Drug treatment should be available for all those of any age who have been diagnosed with osteoporosis, whether or not they have broken a bone. It should also be available for all post-menopausal women who are at high risk.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	8	see comments above	Comment noted.
Patient 31	–	Drug treatments should be available for all post menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	1	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 32	–	I support this submission I believe drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 33	–	I strongly believe that drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. I am currently receiving treatment and have been very worried that this would be withdrawn, so I am relieved that I can remain on it.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	1	I Strongly believe that drug treatments should be available for all post-menopausal	The recommendations in section 1

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. I am currently receiving treatment and have been very worried that this might be withdrawn, so I am greatly relieved to learn that I will be able to remain on it.	of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis. Comment noted.
Patient 34	1	Drug treatment should be made available to women of any age who are post-menopausal, have a high risk of breaking a bone and have a confirmed osteoporosis diagnosis from a DXA scan, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Patient 35	1	At 41 yrs of age I suffered an ectopic pregnancy This led to an immediate menopause At 52 yrs of age I slipped and fractured my hip An emergency pin operation followed - when the surgeon suspected osteoporosis. Osteoporosis was indeed confirmed and within 12mths I received a full hip replacement as the pin was wearing into the cup I am now 62 yrs of age, and have spent the last 10yrs spreading awareness of osteoporosis and campaigning for preventative treatment and improved treatment for postmenopausal women If this ACD becomes guidelines - I will wait and worry that my daughter, sisters, nieces and many friends will go through the traumas and restrictions in life that I have had to suffer All the strategies being developed by the NHS/Local Authorities to minimise the long term effects of osteoporosis to the individual, and cost to the nation, will become utterly meaningless and pointless Only those able to access private treatment will keep the disease at bay NICE was not formed to create inequalities it is supposed to eliminate them	Comment noted.
Carer 1	–	drug treatments available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			initiation of treatment for primary prevention of osteoporosis.
Carer 2	–	My wife had a hysterectomy at age 42 years. It also happened to be an oopherectomy although we were not made aware at the time. She had received spinal damage at age 20 as a result of a farming accident and initial spinal aches and pains some ten years later were put down to that. After two rib fractures due to no more than pressure from ironing she was referred by an alive young GP to a research programme with access to a DEXA scan some 18 years later and treated with HRT. However she has never recovered the lost bone density and has since fractured ribs, wrist, feet and pelvis and is currently undergoing reconstruction of one foot to allow her to walk better. One of her rib fractures resulted in pneumonia and she now suffers badly from shortage of breath due to lung damage and kyphosis. I would hope that one day anyone who might be susceptible in the same way might have a better chance of staving off the effects of hysterectomy/oopherectomy.	Comment noted.
	1	No mention is made of those women put at risk by oopherectomy.	Comment noted. This is outside the remit of the appraisals. It may be covered in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	2	It might be clearer if the untreated premature menopause were stated to include the effects of oopherectomy since it is not included in medical conditions.	See response to section 1 above.
	4	None of the studies appear to me to adequately encompass the younger woman whose menopause may have been accelerated by whatever means. Nor do I believe that 4.3.14 adequately highlights these factors and the distortion of age relevance that is so underlined in every other aspect of studies and treatment considerations. Whatever, I consider that more significance to availability of Bone Density measurement to all cases of induced risk at younger ages needs emphasis and that treatment should be available for all women at risk of breaking a bone post menopause or induced early menopause without regard to age and even evidential breaking of bones.	See response to section 1 above.
	7	I hope 7.3 contains some treatment of induced early menopause.	See response to section 1 above.
Carer 3	1	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. DXA scans should be available throughout the UK.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
			clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Carer 4	2	I urge that these technologies be made widely available and in a un-grudging way. It should not be necessary to wait until there has been a skeletal damage/failure to administer this kind of help. What is required is PREVENTATIVE pre-emptive action not post-injury response.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	4	None except as my above comment applies.	Comment noted.
Carer 5	1	The Government consistently tell us that prevention of disease is their prime consideration. Surely, the prevention of fractures in postmenopausal women who have been diagnosed with osteoporosis by DXA scan, or who have a clinical risk factor, should not have to wait until they have a fracture or reach the age of 70 years before being offered any preventative treatment. What price can be put on premature death, severe pain, loss of independence and loss of self-esteem through height loss, curvature of the spine and bulging stomachs that sometimes accompanies spinal fractures and creates difficulty in finding suitable fashionable clothing?	Comment noted. Guidance on the management of post-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	4	As a layman, it appears to me that that NICE seem to be making many assumptions in their recommendations, which do not appear to be backed by hard evidence. The pieces of research quoted seem to be based on various parameters that make it difficult/impossible(?) to compare. Research seems to be based on assessing the efficacy of a particular drug compared with a placebo or no treatment. I cannot see any that compares the efficacy of different drugs head to head. Nor can I see any research comparing side effects of different drugs and their regimes for taking them.	The Guide to the Methods of Technology Appraisal specifies that indirect methods can be used to compare drugs when there is no evidence for head to head comparisons.
	6	While research into the long term effects of bisphosphonates on bone quality is important, so is research into side effects and regimes for taking the drugs. I assume that research has determined that non-proprietary Alendronate is as efficacious as propriety brands and has no worse side effects and is not more difficult to take.	Comments noted.
Carer 6	1	These recommendations are contrary to world opinion. Every other organisation recognises the importance, to the individual and to the economy, of effective prevention. Adopting these recommendations will stall all the good work being achieved to minimise the long-term effects of osteoporosis in England/Wales by Trusts/ medical professionals/pharmaceutical companies and volunteer organisations The Post Code Lottery will most positively be ended NO ONE WILL BE TREATED FOR PREVENTION	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		UNDER 70YRS. OF AGE NICE has yet again strayed from its reason de etre Whatever the reasons behind these absurd recommendations are, they are not acceptable to the citizens of England/Wales, and must be modified to encourage responsible prevention of the disease So adversely severe are some of the implications of NICEs recommendations that I believe the time has come to abolish the organisation and allow medical advances to proceed, as they used to, under a free market ethos	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
Carer 7	1	I believe drug treatments should be available for all post menopausal women who are at risk of breaking a bone, regardless of their age even if they have not yet broken a bone. I have experience of the consequences of lack of treatment sufficiently early to reduce the risk of fractures	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Carer 8	1	I am totally shocked and saddened that NICE has decided that the preventative treatment of osteoporosis for those under 70 is not important The pain to individuals and the financial cost to the nation will be enormous My father has recently been diagnosed as diabetic and is attending an Xpert Patient course aimed at preventing the development of diabetes why such a different approach to osteoporosis? NICE is showing, yet again, that they do not consider the health and well being of the population of this country to be of primary concern I am a daughter who has watched her mother go through a hip fracture and its traumatic consequences and then seen the physical and mental improvements associated with correct drug treatment A hip replacement does not stop with the operation confidence and belief are essential tools for recovery medication has been proven as essential for this recovery Prevention is better than cure please explain why NICE does not realise this I do not want my taxes to be wasted on treatment after the damage has been done	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 1	1	Drug Treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. Later potential costs to the NHS of treating fractures together with a person's diminished quality of life should be taken into account.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	2	Repeat comments as section 1.	Comment noted.
Public 2	1	I would like drug treatments available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 3	–	drug treatments should be available for all post menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. Prevention of only a small percentage of breakages and the complications which follow both for the health service and families and carers would more than cover drug costs. No-one is going to want these drugs unless they really need them. Consider the vast expenditure each year on antibiotics when there is evidence that outside hospital only a small percentage of people complete courses and the wasted drugs cost hundreds of millions of pounds. Closer supervision of all prescribed drugs would save enough to fund many newer and more effective treatments.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 4	–	I believe that all drug treatments for osteoporosis should be available to all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	1	A criterion for primary treatment based on qualifying ages seems entirely inappropriate when the major risk factors appear to be heredity, BMD and lifestyle. Also some women suffer side-effects with other drugs which make their use problematical. If these women can more easily tolerate alendronate, etidronate, risedronate, raloxifene or strontium ranelate, and treatment is clinically necessary, then these drugs should be made available by the NHS to women of any age.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 5	1	I believe that drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	3	The annual costs of some of these treatments appear high. Obviously non-branded drugs should be the first choice if they suit the individual concerned. The possible pain and restricted life chances of those who suffer fractures, together with the extra costs of care also must be considered.	All health effects including pain are included in the economic modelling (see section 5.5 of the 'Guide to the methods of technology appraisal'.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Public 6	1	I believe drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. In many communities it is post-menopausal women who take on key roles supporting and caring for other elderly people as well as young families. It is surely a good investment to keep these women as active as possible for as long as possible. When these women are incapacitated by osteoporotic fractures the cost to the community is more than just the cost their care and should be set against the cost of primary prevention drugs.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 7	1	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 8	1	Drug treatments should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of their age, even if they have not yet broken a bone. It is ridiculous to refuse treatment to women at risk and incur the costs and personal trauma of breaking a bone before treatment can be given. Prevention of a first fracture should be a primary concern.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 9	7	Drug treatments should be available to all post-menopausal women who are at risk of breaking a bone, regardless of age, and regardless of whether they have broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
Public 10	1	In Section 1, the last statement requires clarification over the site of DXA scan. I would like to see the word axial before DXA to ensure that pDXA is not used inappropriately. The recommendations in this section miss a significant minority of patients who are at a high risk of fracture. They are postmenopausal women under the age of 70 who self identify with risk factors - these may be premature menopause, conditions associated with low BMD or women who present to their GP with other risk factors. There are now tools available to calculate a woman's risk of fracture and NICE should be directing treatment to women at the highest risk and not to women by their age. The current	The wording in the FAD has been amended accordingly. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		recommendations need to contain an additional statement that will ensure that these women who have no identification costs, where appropriate can be assessed and treated. To ensure that prescribing authorities do not red light treatments that are not mandated by NICE, this guidance needs to be more clearly linked to the Clinical Guideline to ensure that its recommendations are implemented	
	7	Does the guidance need to refer to TA87 and the new secondary prevention guidance - if this ACD and the secondary prevention one are published as FADs at the same time, then surely 7.1 and 7.2 can be combined?	The primary and secondary preventions FADs are standalone documents therefore it is not possible to combine 7.1 and 7.2 of the respective FADs.
	8	Why has the review date changed to 3 years post publication - this change is unwarranted and is not evidence based.	Technology appraisal guidance will be reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
Public 11	1	My mother and grandmothers were crippled by osteoporosis. My BMD T score has been measured as 2.6 but I have not to my knowledge had a fracture. I am 62. Whilst I appreciate the need for a population-wide approach to efficacy things look different through my end of the telescope. I avoid doctors and look after my health; I don't smoke, drink little alcohol and try to get a balanced diet and adequate exercise. If I had a family predisposition for diabetes, heart disease or stroke and asked my GP for appropriate tests to determine my risks I would expect a diagnosis of high blood sugar, high cholesterol or high blood pressure to lead to prescribed medication to reduce these levels. Why should osteoporosis be different? It is evil and unfair that people like me with low bone mineral density and a family history of osteoporosis but no fracture yet should be denied appropriate treatment. I have seen the consequences of fractures. Living with osteoporosis can be as difficult as living with diabetes, heart disease or stroke. Please reconsider your recommendations for the primary prevention of osteoporosis in women under 70 and take an equitable approach to this disease area.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
Public 12	1	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age,- even if they have not yet broken a	The recommendations in section 1 of the FAD reflect when the

Consultee or Commentator	Section of ACD (if specified)	- Comment	Institute Response
		bone.	treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
NHS Professional 1	1	1) It is possible for patients younger than 70 years to face the same 10 year fracture risk, as those above this age, if their Z score is low enough. This why it is important that absolute risk rather than age thresholds be used to advise and select patients for therapy. 2) The long biologic half life of alendronate (11 years), and growing reports of the potential adverse effects of long term bisphosphonate therapy (osteonecrosis, impaired fracture healing, increased bone fragility) , make it important to consider which bisphosphonate a patient should receive, and how long they should receive it for, rather than simply selecting the lowest acquisition cost. 3) Ibandronate should be considered, and etidronate probably withdrawn due to lack of non vertebral anti fracture efficacy. Teriparatide should be considered for primary treatment in individuals with highest 10 year fracture risks (?>30%).	1. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. However, recommendations based on absolute risk of fracture are not currently possible. Age and T-score (and prior fracture) are the most important factors to define risk of further fracture, and consequently cost-effectiveness of treatment. 2. Treatment duration will be covered in the clinical guideline. 3. Technology appraisal can only include technologies that have been referred by the Department of Health, and Ibandronate has not been referred for Appraisal. At the time of this appraisal, teriparatide was not licensed for use in women without prior fracture.
	2	1) There is substantial heterogeneity in the published estimates of the incremental risk of fracture after an initial fracture. 2) Site specific measures of BMD generally give best site specific fracture risk estimates 3) Radiologic osteopenia is a well documented risk marker for measured low bone density	Comment noted.
	3	See comments above re half life of various bisphosphonates and potential adverse effects with prolonged usage. Long term safety of Strontium is uncertain	Comment noted.
	4	The FIT 2 study not only showed that alendronate did not work in those subjects without osteoporosis, but was associated with an increased risk (significant at the wrist) in these patients. As the modelling clearly assumes 5 year treatment periods (which I agree	Duration of treatment will be covered in the clinical guideline.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		with), the TA should make it clear to prescribes that they should plan to stop therapy electively at 5 years. I have had one NHS complaint this year, this from a patient who was upset that I wanted her to stop alendronate after 7 years of therapy, for primary prevention. as mentioned above, it is not sensible to impose an age limit of 70 years for primary preventive prescriptions, as identical absolute risks can be faced by younger patients whose BMD is extremely low	
	6	Agree with these proposal	Comment noted.
	7	Very much support absolute fracture risk assessment, but treatment allocation needs to consider treatable risk	Comment noted.
NHS Professional 2	1	You do not cover the need for younger women to have bone protection when their 10 year risk of fracture is high (e.g. 15-20% or greater). this is not unusual in those with an early menopause or significant comorbidity. Do you propose excluding these women from treatment until they fracture?	Recommendations for women with pre-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	3	Risedronate has a better GI tolerance profile and should therefore be drug of choice in those with GORD or other oesophageal problems. strontium ranelate is useful in the elderly who may have trouble with the dosing regime required by the bisphosphonates. Nursing homes can find it very difficult to comply with the dosing requirements of bisphosphonates. patients with oesophageal stricture, at high risk of fracture, should have strontium ranelate as first choice. I would recommend that you incorporate recommendations for alternative first choices to alendronate in your appraisal.	Comment noted. The recommendations in section 1 of the FAD include alternatives to alendronate at the point they become cost effective to use for women who have contradictions to alendronate.
NHS Professional 3	2	a few of my patients with very severe OP are HIV/AIDS +. Would it be possible to include them in your list of risk factors Other problematic young and old institutionalised patients are those with severe mental/physical disabilities - could you mention them?	The Committee was not presented with any evidence about HIV/AIDS being risk factors for osteoporotic fractures.
	4	Why do you insist on putting Etidronate as a first line treatment? you will be really hard pressed to find a clinical trial that shows efficacy at the hip and the efficacy at the spine is limited. You talk about evidence-base but you agree on anecdotal evidence that it is well tolerated; my experience shows that it is not and that the few patient I have who are still on it are delighted to swap over to a weekly/monthly medicine. This is the first time that I have seen any data indicating that there is an 80/100% compliance with	Following consultation on the ACD, the Committee has revised its recommendations for etidronate. Etidronate is now recommended as an alternative to alendronate in section 1.1 of the

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		bisphosphonates after 1 year of treatment; from all the literature I have seen it is more likely to be between 40 and 60%. In my department we tend not to treat women in their 50/60ies at risk of OP but it does not mean that in some cases treatment should be forsaken until a fracture occur. Do the health economists who wrote this recommendation ever have to face an irate patient at high risk of breaking a bone after being told that she has to wait until after the break to be treated? what has happened to health promotion? I	FADs under specific circumstances and consideration should be given when choosing between risedronate and etidronate on the balance of overall proven effectiveness profiles, tolerability and adverse effects of the drugs in individual patients this should be done.
	5	On the whole those recommendations will be quite helpful in dealing with worried women concerned about OP and who have no risk factors; however, I think that the prevention should be considered for women who have a number of risk factors (I don't consider smoking important enough to be included); some of them have had private DXAs that do show severe OP (as low as -5.3 at the spine in a patient of mine in her early 50ies)and treatment should not be withheld for this patients, especially with regards to vertebral OP.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	6	It appears that many fractures occur in women who are osteopenic for whom, prevention pre-fracture treatment was not given for lack of evidence that it works. I would therefore suggest that proven efficacious treatment for osteopenia would be most welcome	Guidance on the treatments available for individuals with osteopenia (defined as a T-score of between -1 and -2.5 SD) will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	7	As an aside, why are there consultants in psychiatry, vascular medicine etc on the panels but no orthopaedic surgeons, ortho-geriatricians?	The Appraisal Committee comprises of a range of professions including consultants, GPs, nurse advisors, pharmacists, lay members, pharmaceutical industry representatives, medical statisticians, health economists and NHS management. The Appraisal Committees are standing committees and hear evidence from clinical specialists

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
			within the respective field for each appraisal.
NHS Professional 4	–	Have spent twelve years trying to establish an osteoporosis service which finally commences next month!	Comment noted.
	1	The guidelines apply to only a tiny percentage of the population - probably in the region of under 5% - as they relate just to women over 75 not on steroids and with no prior fracture. We are missing the boat here as there are many other groups who are also at risk but not covered by the guidelines	The primary prevention recommendations are for post menopausal women aged 70 years old with one or more clinical risk factors. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	4	What about the better safety evidence in the over 80 year olds the guidelines include? there is good evidence that Risedronate is safer than Alendronate here especially with regard to the upper GI intolerance which is so common in this age group. Surely patients with a prior history of this would be better using Etidronate or Risedronate first off?	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'
NHS Professional 5	4	CESSATION OF THERAPY: NICE should provide guidance on whether one needs to stop the Bisphosphonates in those on treatment but sustain a fragility fracture i.e. distal radius and hip etc during the healing process of the bone to allow those fractures to heal.	Guidance on the cessation of therapy will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
NHS Professional 6	1	I support the views of the National Osteoporosis Society that drug treatments should be made available to all post-menopausal women at high risk of fracture, regardless of their age, even if they have not yet broken a bone.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
NHS Professional 7	1	I strongly disagree with the fact that you have NOT recommended active osteoprotective treatment for women on corticosteroids, when this is standard clinical practice, bearing in mind the effects of long-term steroid use on the bone structure. expression of such	Guidance on treatment options for patients on corticosteroids will be covered by the clinical guideline

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		views by NICE is only going to make, thousands of vulnerable patients more prone to sustaining otherwise preventable fractures, as the GPs are more than likely stop bisphosphonate therapy in patients who are, on steroids, and are receiving this, therapy as a preventive measure , Secondly i am not quite sure why just one generic preparation has been recommended, when clinical experience , and controlled studies have shown that there is variability in the gastrointestinal side effects seen with different bisphosphonates available	on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
NHS Professional 8	–	I have received honoraria for lectures and advisory work for Roche, Servier, Proctor and Gamble, Shire and Menarini	Comment noted.
	1	There is a problem here. Absolute fracture risk is driven by a complex interaction between bone mineral density, age and clinical risk factors (CRF) that act as proxies of those characteristics of bone quality that we cannot routinely measure. It is quite possible for a woman <70 to have a combination of these predictors that put her fracture risk several times higher than a woman >70 with one CRF and a T score of -2.5. An example would be a 60 year old T -3.8, FHx parental hip fracture, BMI 19. It would be negligent and cost ineffective not to offer treatment. While also wishing to discourage inappropriate treatment of low risk patients, I think a statement is necessary e.g. ""Rarely younger women may have sufficient risk of fracture that in the opinion of a specialist, treatment is warranted"". This will anticipate the WHO fracture risk guidance that will identify a small number of younger people with sufficient risk.	Recommendations based on absolute risk of fracture are not currently possible. Age and T-score (and prior fracture) are the most important factors to define risk of further fracture, and consequently cost-effectiveness of treatment. Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	4	There is a problem here. Absolute fracture risk is driven by a complex interaction between bone mineral density, age and clinical risk factors (CRF) that act as proxies of those characteristics of bone quality that we cannot routinely measure. It is quite possible for a woman <70 to have a combination of these predictors that put her fracture risk several times higher than a woman >70 with one CRF and a T score of -2.5. An example would be a 60 year old T -3.8, FHx parental hip fracture, BMI 19. It would be negligent and cost ineffective not to offer treatment. While also wishing to discourage inappropriate treatment of low risk patients, I think a statement is necessary e.g. ""Rarely younger women may have sufficient risk of fracture that in the opinion of a specialist, treatment is warranted"". This will anticipate the WHO fracture risk guidance that will identify a small number of younger people with sufficient risk.	see above
NHS Professional 9	–	Consultant rheumatologist with special interest in osteoporosis and management of the condition by my local PCT	Comment noted.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
	1	Most fractures occur in women with BMD better than -2.5 Fracture risk increases well below age 70; if asked by a patient or relative if I am doing everything possible to reduce fracture risk after the menopause (from around age 50 in UK) I can't in all honesty say "yes" if I wait to age 70 to investigate and treat should it be necessary No alternative is given for those in whom a bisphosphonate is contraindicated or who develop ADR's. This makes the guidance difficult to use and in particular to "sell" to GP's to implement Needs a system in place in each GP practice to assess such women; this does not exist currently and will not unless osteoporosis is a QOF target (so my GP colleagues tell me) so the guidance alone will have limited use in reducing fractures, deaths and use of NHS resources If an untreated early menopause, why wait 20+ years till age 70 to investigate? The same applies, with less importance to the other risk factors. Is a woman of 70 really to be asked about her mother's or father's health 50 years earlier and if so how is ""I don't know"" to be interpreted?	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Recommendations for women with osteopenia (defined as a T-score of between -1 and -2.5 SD) will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	2	Yes, an increase in older women and thus fractures and deaths is inevitable. Costs to NHS and Social Services will increase. The only age group increasing over next 30 yrs is those over 65 (DHSS own figures). I struggle with age 70 as a threshold; why, with such low cost now of generic alendronate and greater availability of dexa (with NHS tariff 49 i.e. just 3-4 months treatment with a bisphosphonate) do we wait till then and not find and treat those aged 50-70 and reduce their fracture risk by half?	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	3	Fine; but all options should be discussed with patients, as we do with drugs for other conditions. Not all can tolerate a bisphosphonate and some should not start one at all. Some prefer monthly dose, whose persistence appears to be better than that of alendronate, but you have not even mentioned oral ibandronate. Strontium needs a pt who understands exactly how to take it but it"s a useful alternative if risk high and a bisphosphonates is not tolerated	The Institute understands that patients and their clinicians will discuss the available treatment options for the prevention of osteoporotic fractures. Ibandronate has not bee referred for appraisal By the Department of Health to the Institute.
	4	Your only suggestion for women at risk is generic alendronate. This is not appropriate for all and what does the GP do if not? The answer is not set out in terms an average GP will understand and primary prevention will be wholly in the PCTs/primary care court so clear statements are needed with alternatives if drug No 1 is not tolerated. Preference of monthly dosing shown in recent studies may then favour ibandronate, which you have not considered. Ibandronate may not reduce hip fractures as well as alendronate but treatment is continued by more patients; a case for discussing carefully	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		and offering choice; in those at risk I'd rather have the pt take monthly ibandronate than nothing Please stress more calcium and Vit D as companies promoting the other agents fail to do so (as they don't market Ca + vitD) even though it's used in almost all trials and absolutely essential with strontium (whose trials gave all Ca+vitD alone for at least a month before adding strontium itself and you omit to mention this) Raloxifene remains an attractive option for ladies who cannot tolerate a bisphosphonate and particularly if spine BMD is lowest and FH of breast cancer	risk'. The clinical guideline will include guidance on calcium and vitamin D.
	5	All practices, large and small, interested and not interested need to implement this and without clear guidance on whom to look for and in whom to do dexa and no inclusion in QOF, I worry that this guidance will have little impact on fracture rates. With the cost reduction of alendronate I expected treatment thresholds to be reduced but by using age 70 as cut-off many preventable fractures will occur This guidance heavily favours generic alendronate but gives no alternative. In those with v low BMD, why not teriparatide first and then alendronate to stabilise bone gained? To use teriparatide after a bisphosphonate reduces its efficacy; it may then not be cost-effective at all! The evidence base for teriparatide is in bisphosphonate naive pts; alendronate, held in bone for years after treatment, blunts effect of PTH. Why should GP's wait till 70 age to implement this? Practices should instead consider osteoporosis as well as cardiovascular risk factors at the menopause.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	6	Agreed, and doctors have been asking for this but who to fund?? Strontium does affect BMD and thus nomograms to compensate have been produced	Comments noted.
	8	Too late. Much new is planned before then, incl the WHO guidelines cited above. 2009 at latest	Technology appraisal guidance will be reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
NHS Professional 10	1	The guidance is inflexible and should allow all post-menopausal women who are at high risk of breaking a bone - regardless of age - to commence treatment at a specialist's discretion.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			prevention of osteoporosis.
NHS Professional 11	–	Medical Adviser to Durham Osteoporosis Patient Support Group (local branch of NOS) Member of Regional Advisory Board for Osteoporosis (North East) (supported by a grant from the Alliance for Better Bone Health)	Comment noted
	1	1.The clinical guidelines need to be developed and ready to be published alongside this one to reduce confusion 2.The change in the values for the clinical risk factors has not been explained (e.g. higher BMI and higher than recommended alcohol intake)	1. Comment noted. 2. The inclusion of clinical risk factors was based on the evidence available to the Committee.
	2	2.4 Using only hip T score is appropriate where degenerative changes invalidate the spine score- but low spine scores do occur in the presence of a normal or low normal hip score. This statement suggests only hip T score estimates fracture risk 2.12 Risk factors - again change in values from currently accepted	The FADs have been amended; using an axial BMD to measure BMD is suggested. Risk factors have been discussed with the clinical specialists and the Guideline Development Group.
	3	3.5 In view of this (reference to contraindications to alendronate), where generic alendronate alone is recommended subsequently, shouldn't this be followed by reference to this section, and an alternative allowed?	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	4	4.2.8 Unless this discussion is limited to women >75 years, follow up scans are the norm in some units. 4.2.11 Clinical risk factors in this section are those currently in use, cf those above 4.3.12 there are differences between bisphosphonates and degree of retention in bone; the committee does not appear to have concerns at advocating one to the exclusion of all others, where this one is permanently incorporated into bone, and the long term effects of this are as yet unknown.	Comments noted.
	5	4.3.13 I am very concerned that women younger than 70 years who may at be high risk of fragility fractures will be denied primary prevention. Effectively, this group will have to sustain a fracture before being treated. This is akin to saying that a patient has to have a stroke or myocardial infarction before having antihypertensive or lipid lowering drugs respectively. Consider taking a lower cut off point for BMD if 2 + CRF's are positive (e.g.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		T-3.0, or even -3.5) -and stress the importance in the younger osteoporotic patient of looking for treatable causes (e.g. coeliac disease etc).	
	6	6.1 Agree; there are now a substantial number who will have been taking a bisphosphonate for >10 years. We, and particularly GP's, need advice about who and when to stop; without evidence patients will be anxious that stopping therapy will put them at (increased)risk of fractures, when the reverse may be true. 6.3 If DXA is needed once a patient is on strontium, correction factors can be applied.	Duration of treatment will be addressed in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include withdrawal from treatment.
	7	7.3 It will be difficult to implement either of the technical appraisal guidance documents in the absence of the clinical guideline; recommend that they are published as a package if confusion is to be avoided. They cover much the same ground, surely?	The technology appraisal makes recommendations for specific technologies (alendronate, etidronate, risedronate, strontium ranelate and raloxifene) and the circumstances under which they may or may not be used. The clinical guidelines makes recommendations on how to manage the condition of osteoporosis.
	8	8.2 The rate of new developments may dictate the most appropriate review date. Already, since this document first saw light, there are newer bisphosphonates which have not been considered at all, and which potentially have advantages over those discussed, e.g. in delivery. As compliance is a major issue with this group of drugs this is important.	Comment noted.
NHS Professional 12	1	Is alendronate recommended for initiation of treatment in all women who meet the criteria, for instance those with oesophageal stricture? We need options for those in whom alendronate contraindicated or used with caution. The management of osteoporosis needs review of treatment for those who fail alendronate (How is that defined, similarly to TA 87)or cannot the drug. This needs to be published as a whole with clinical guidelines. Younger women with multiple risk factors need advice and reassurance that we will do what we can to reduce the risk of them fracturing like their relatives	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			risk'.
	2	?Other risk factors e.g. smoking, liver disease, treated bone diseases, patients on drugs at risk e.g. aromatase inhibitors	The inclusion of clinical risk factors was based on the evidence available to the Committee.
	4	We need options for those in whom alendronate unwise or intolerant. Advice for those younger with multiple risk factors	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years. Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
NHS Professional 13	–	Run the Bone Densitometry Service in Bradford Previously worked for MRC Mineral Metabolism Unit and worked on Monte Carlo modelling	Comment noted.
	1	1.3 Why were premenopausal amenorrhoea, kyphosis, height loss and radiological osteopenia not included also treatments such as aromatase inhibitors which cause bone loss 1.4 In this part of the world women go to their GP's if they have these conditions and ask for a scan or the GP's search their databases for early menopause it is not always just a serendipitous finding	The inclusion of clinical risk factors was based on the evidence available to the Committee. The list of clinical risk factors has been discussed with the Guideline Development Group.
	2	2.11 Why were premenopausal amenorrhoea, kyphosis, height loss and radiological osteopenia not included also treatments such as aromatase inhibitors which cause bone loss	see above
	4	4.1.2 , 4.26 4.29 The model is fundamentally flawed by using short time horizons. Risk of fracture is related to bone mineral density and to age. The same bone density measured when a person is young will give a much lower risk of fracture at that time probably due to the lower risk of falling and maybe the greater elasticity of the collagen matrix when young but a greater lifetime risk of fracture. Stopping the bone loss for a	The Committee agreed that the 10 year time horizon was appropriate considering the uncertainties around health effects over a longer period (see FAD section

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		number of years by treatment should lessen the lifetime risk. It is the lifetime risk of fracture which should be modelled for individuals of a population based on epidemiological data of means and variation. Then the effects of treatment for a number of years for different ages should be factored in to see how the lifetime risk is reduced by treatment and at what age it is best or most cost effective to give the treatment. Dr A Horsman and M N Birchill presented such a model in Osteoporosis - Physiological basis Assessment and Treatment Ed De Leuca Elsevier 1990 4.2.8 the efficacy of the drugs should be related to reduction in BMD and lifetime fracture risk Discounting should not be used in a cost benefit model see Sheldon 1997	4.3.7). Discounting in economic models has been an agreed factor in cost effectiveness modelling for decision making.
	6	6.1 this evidence should be used in the modelling straight away 6.3 It should be recommended that those patients about to be put on to strontium ranelate should have a bone density measurement just before and treatment and just after cessation of treatment or their bone status may never be known again	Comment noted.
NHS Professional 14	1	1.3 Body Mass Index of less than 22 - normal range for women is 18 to 23. It would be better to state lower normal to below normal.	Comment noted.
NHS Professional 15	1	We recognise that this guidance concerns the initiation of therapy for primary prevention. However, in the absence of any consideration of second line therapy, we suggest that the guidance makes explicit reference to the need to refer to the forthcoming guideline (Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk) for patients who withdraw from initial treatment, for whom the recommended treatment is unsuitable or for whom there is evidence of inadequate response to this treatment. Publication of this forthcoming guidance is urgent. Until then, patients should not be denied second line treatments. A major omission of the ACD is postmenopausal women under the age of 70. Many women with very low BMD in this age group will have a high 5 year absolute risk of future fracture. Give the current cost of generic alendronate, a cost effective model for this group would seem plausible and needs to be evaluated. This group has already been identified as at risk by the ACD in sections 2.5 and 2.7.	In section 1 of both FADs the preambles for primary and secondary prevention of osteoporosis contain an explicit reference to refer to the forthcoming clinical guideline on osteoporosis. The Committee did not consider it appropriate to endorse guideline recommendations which are not yet finalised.
	4	The majority of studies used calcium and /or vitamin D as placebo. Strontium, Alendronate, Risedronate and Ibandronate with doses ranging between calcium 500-1000mg + vit D 400-800IU daily. This section needs amending and defining appropriately. Relative risk reductions were pooled across studies, although there are baseline differences across study groups with respect to mean age, baseline BMD and baseline prevalent fractures. This affects absolute fracture risk reduction between studies, therefore the assumptions made are incorrect. It is also assumed that risk reduction remains constant at all ages, which is incorrect. One of the major limitations of	The pooling of relative risk reductions across studies and the assumption on constant risk reduction at all ages were the result of consultation with the Guideline development group. This has been recognised by the

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		the unpublished fracture-risk algorithm currently in development under the auspices of the WHO, is that it does not include major falls risk factors. Most non-vertebral fragility fractures occur after a fall. Anti-resorptive agents do not augment falls risk factors. Falls prevention is therefore an important component of a clinical strategy to prevent fractures. For older people, this guidance should be read and applied in the context of an integrated approach to falls and fractures as indicated in NICE Guidance CG	Committee. Comment noted.
	8	We would recommend a 2 yearly review	Technology appraisal guidance will be reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
Private Sector Professional 1	1	Age restriction and awaiting first fracture before treating with bisphosphonates is madness. NOF(USA) recommends all below -2.0 SDs to have treatment. Why is UK so backward. Morbidity and mortality from Fractures is huge.	The Appraisal Committee bases its decision on clinical and cost effectiveness as per section 6.1.2 of the 'Guide to the methods of technology appraisal'. The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis in the NHS.
	2	NOF(USA) recommends treating below -2.0 SDs. Why risk lives? The cost savings in fracture prevention would justify earlier treatment. DEXA Scans are cheaper than chest x-rays cf. the Tb surveys of old. All with risk factors at any age should be scanned. All over 60 to be scanned.	see above
	3	Costs of drugs fall with usage.	Comment noted.
	4	There is clear and adequate evidence for the efficacy of Alendronate in younger osteoporotics. Why delay till the patient is in distress? Warped thinking - or is it the money? ""Don't wear a seatbelt till after your first accident"".	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis in the NHS.
	8	WHAT NO ORTHOPAEDIC SURGEONS on the appraisal committee? Just economists. statisticians. Any body there treating patients???? Too many professors!	The Appraisal Committee comprises of a range of professions including consultants, GPs, nurse advisors, pharmacists, lay members, pharmaceutical industry representatives, medical statisticians, health economists and NHS management. The Appraisal Committees are standing committees and hear evidence from clinical specialists within the respective field for each appraisal.
Private Sector Professional 2	1	Drug treatment should be available for all post-menopausal women who are at a high risk of breaking a bone, regardless of age, even if they have not broken a bone. The risk of future fracture increases 4-5 fold after the first fracture; and increases 70 fold after two or more fractures. Current NICE recommendations allow the stable door to be shut, but only after the horse has bolted.	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis in the NHS.
	2	Quite apart from t score, treatment should be considered when z score is < -1 SD	The Appraisal Committee made recommendations based on the evidence presented, and this evidence was presented by T-score.
Other 1	1	I do not agree that primary prevention of osteoporotic fractures should be restricted to women over 70, especially as NICE identifies a number of medical conditions as risk factors for osteoporotic fractures yet denies women under 70 with these conditions or other identified risk factors preventative treatment	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	2	You identify the high risk of fracture in women over 50 but there are a significant number of younger women with osteoporosis who are also at high risk such as anorexia	see above

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		nervosa, prolonged immobility, rheumatoid arthritis but I appreciate this is not currently within the remit	
	3	The emphasis on Alendronate Sodium seems to be based on cost above everything else, this is important but should not be the sole concern as not everyone can take the "cheap" version [my husband had a problem with one manufacture of a diabetic drug but is fine with other brands and I came across similar problems with other drugs when I was working as a nurse & brands were changed because of cost]	The Appraisal Committee bases its decision on clinical and cost effectiveness as per section 6.1.2 of the 'Guide to the methods of technology appraisal'.
	4	More work for GPs if they have to assess whether patient has adequate Ca & Vit. D intake - the majority of elderly women do not and most of the research was done giving Ca & Vit. d supplement with drug or placebo	Comment noted.
	5	Although these are "Guidelines",5.1 effectively stops clinicians using their clinical judgement & expertise to prescribe a treatment they think will be most effective because it costs more than that in Guidelines.	The Appraisal Committee bases its decision on clinical and cost effectiveness as per section 6.1.2 of the 'Guide to the methods of technology appraisal'.
	6	I agree that more research is needed on length of treatment, long-term effects on bone quality & on strontium ranelate. This should not only be down to pharmaceutical companies to fund but should have DoH input	Comment noted.
	8	Review date may need to be amended given that new drugs are coming on line such as Ibandronate	Ibandronate has not yet been referred for Appraisal. At the time of this appraisal, teriparatide was not licensed for use in women without prior fracture.
Other 2	1	1 These recommendations do not mention people with coeliac diseases 2 The barring of treatment to those under the age of 70 means those patients who are aware they have osteopenia or osteoporosis (possibly through DXA scan arranged privately) will know they are at risk of a major fracture, such as neck of femur. This, in itself, may cause depression (which can be costly) and inhibit any exercise/occupation that might in any way be likely to cause a fracture. Fractures of the neck of femur in particular can cause long-term/life disability (assuming they do not die within a year)! This is acknowledged BUT I do not feel the costs - both in treatment and in quality of life - have been fully considered. The proposals are in direct conflict with the Government's decree that ageism should be no bar to treatment.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years.
	2	One cannot comment on these recommendations adequately without knowing the outcome of the review mentioned in 2.13. All those with osteopenia/osteoporosis should	Comment noted.

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		be treated, but it is obvious that treatment for these groups is essential.	
	4	NICE accepts that certain groups re at higher risk, but to not appear to have costed the effects of non-treatment.	The economic modelling considers all health effects, for example the cost of fractures where no treatment is given, is included in the modelling.
	6	These are reasonable. ["breaks" from treatment are practised in the United States with no apparent adverse effects]	Comment noted.
Other 3	1	Drug treatments should be available for all post-menopausal women who are at high risk of fragility fracture. It is neither logical nor cost-effective to limit treatment to women over 70 years of age	The recommendations in section 1 of the FAD reflect when the treatments within the appraisal are clinically and cost effective for the initiation of treatment for primary prevention of osteoporosis.
	4	GPs should be encouraged to assess fracture risk in post-menopausal women using one of the validated questionnaires available, and refer appropriately for DXA scanning	Comment noted.
Other 4	1	It is not clear when reference is made to women who have experienced premature menopause (Section 1.3) whether treatment should not be commenced until they reach the age of 70.	Recommendations for women with pre-menopausal osteoporosis will be covered by the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	4	The model assumes that persistence with treatment is 50% at five years. This is unrealistic as all of the evidence from observational studies (including those using GPRD) show that in clinical practice less than half are persistent at two years. There is no consideration of the evidence that patients persist longer on a weekly regimen than those on a daily regimen and there are significant differences between the two.	In the absence of firm long-term persistence data the Committee agreed to use a figure of 50% as an optimistic approach in favour of preventative treatment.
	5	Any implementation guidance should encourage GPs to monitor persistence levels of their patients (easily done at a practice level) and regularly encourage the adoption of lifestyle measures known to have a positive benefit on RR (exercise, diet, etc.)	Comment noted.
	6	As there are currently only two studies reporting on the reduction of fracture risk in clinical practice this area should probably have priority on future research.	Comment noted.
	8	It may be appropriate for an earlier review schedule to accommodate evidence from	Technology appraisal guidance

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		ibandronate (monthly regimen)	will be reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.

Comments received from public by email:

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
Patient 1		I just wanted to express my strong feelings about the possible new guidelines. I was prescribed didronel and then fosomax for osteoporosis when I was diagnosed. I now enjoy an excellent quality of life thanks to these drugs. If I had been diagnosed now under the new proposed rules I would have been denied these drugs. Who knows how I would have been feeling now? It seems to me to be a very short-sighted policy to refuse to prescribe these drugs at an earlier stage. I do hope that the relevant committee will have a rethink.	Comments noted.