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

Responses to summarised comments from consultees, commentators and the public on the 2005 Appraisal Consultation Document (ACD)

Grouped Comments – General

Comment	Made by	Notes
Cost per QALY Gained (CQG) threshold should be consistent for primary and secondary		
CQG threshold should be consistent for primary and secondary prevention, NICE is penalising women who have not yet fractured but who are at a comparable level of absolute risk to those who have already broken a bone.	Web comments, Clinical Experts, National Osteoporosis Society, Bone Research Society.	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 (see secondary prevention FAD 2007 section 4.3.1). Furthermore, 'The Guide to the Methods of Technology Appraisals' states that *"Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, the innovative nature of the technology,*

		the particular features of the condition and population receiving the technology, where appropriate, the wider societal costs and benefits." The Committee has concluded that with the specific nature of secondary prevention, a threshold of £30,000 is appropriate but the Committee felt that primary prevention should remain at a threshold of £20,000.
Some drugs with a higher CQG have been approved in the past.	Royal College of General Practitioners.	When making its decisions the Appraisal Committee considers not only the ICERs but also the uncertainties associated with the evidence and the ICERs, and *the particular features of the condition and population receiving the technology*.
Queries the rationale behind selecting £20 000/QALY as the maximum acceptable ICER. The guidance as it stands does not appear to provide any justification to support this.	Web comment.	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 (see secondary prevention FAD 2007 section 4.3.1). Furthermore, the maximum acceptable ICER for primary prevention is £20,000 and £30,000 for secondary prevention. 'The Guide to the Methods of Technology Appraisals' states that *"Above a most plausible ICER of*

		£20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, the innovative nature of the technology, the particular features of the condition and population receiving the technology, where appropriate, the wider societal costs and benefits." The Committee did not consider the additional factors supporting the technologies for primary prevention to be sufficiently strong.
Risk factors		
Not all relevant risk factors have been included (comparison with TA87 or RCP)	Allinace for Better Bone Health, Society & College of Radiographers, Web comments, Clinical Expert.	The 2006 ACDs and the 2007 FADs have been updated to include alcohol as a risk factor and the list of medical conditions that can be associated with low BMD.
Request a more comprehensive list of medical conditions other than rheumatoid arthritis that are known to have a significant effect on fracture risk e.g. early menopause, hyperthyroidism, chronic inflammatory bowel disease etc.	National Osteoporosis Society, Royal College of General Practitioners, Clinical Expert, Web comments.	The 2006 ACDs and the 2007 FADs have been updated to include alcohol as a risk factor and the list of medical conditions that can be associated with low BMD..
Current smoking and alcohol intake > 2 units/day should be included as risk factors. It would be useful if this guidance listed the other conditions that had	Clinical Experts, Royal College of	The 2006 ACDs and the 2007 FADs have been updated to include

been agreed with the Clinical Guideline Development Committee. The reasons given for excluding these risk factors are that their effect on fracture risk is small and they are difficult to confirm reliably. The size of the effect on fracture risk has been considered within the economic analysis and the presence of these risk factors is not insignificant.	Nursing, Bone Research Society, Society for Endocrinology, ScHARR.	alcohol intake of 4 or more units per day as a risk factor for fracture. Current smoking has still been excluded by the Committee as they were not persuaded by the evidence on the effect of smoking on fracture risk in women. The effect was shown not to be statistically significant.
Conditions affecting calcium absorption such as Crohns and liver disease not mentioned	Web comment.	Treatment options for women who have conditions affecting calcium absorption may be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Parental hip fracture not relevant for >70s. As guidance is mainly for >70s, it should not be in as a risk factor	Clinical Expert.	The Committee took into account all evidence available on parental hip fracture, and did not consider it appropriate to remove this factor in the fracture risk estimation in the elderly.
The adverse events have not been explicitly included in the model as it was assumed that patients who experienced side effects, which were significant enough to impact on their quality of life, would either switch to an alternative therapy or become non-compliant. The sensitivity analysis on the number of patients switching therapies showed that this did not have a large impact on the overall cost effectiveness of the identification strategy.	ScHARR.	The 2006 ACDs and the 2007 FADs are based on modelling that includes adverse events.
Definition of low BMI needs to be consistent across all NICE guidance.	Guideline Development Group.	The primary and secondary prevention 2006 ACD and 2007 FAD have been updated to define low BMI as 22kg/m^2.

If DXA scanning is undertaken, it appears that there are only two risk factors being included-parental history of hip fracture and medical conditions associated with bone loss. In these instances, the Committee should advise on how three risk factors are to be identified.	Bone Research Society.	The 2006 ACDs and the 2007 FADs have been updated to include alcohol as a risk factor..
Definition of bisphosphonate intolerance		
Section 1.6 implies endoscopy to confirm intolerance. This is too restrictive. Increased gastroscopy costs, morbidity and ultimately mortality should be included in the cost effectiveness modelling.	Clinical Experts, Guideline Development Group, Royal College of General Practitioners, Royal College of Nursing, Servier, Web comments.	The 2006 ACDs and the 2007 FADs have been revised.. Endoscopy is no longer implied to confirm intolerance. Recommendations for women who are intolerant to initial treatment will be developed in the NICE clinical guideline
Definition of unsatisfactory response inappropriate		
There is substantial evidence that strontium ranelate causes BMD measurements to be amplified unless a corrective adjustment is made to the DXA scan.	National Osteoporosis Society, Clinical Experts, Society for Endocrinology.	The 2006 ACDs and the 2007 FADs have been updated to remove the requirement for a decline in baseline BMD.
Definition will not be workable in practice for those women who will be eligible for treatment without the need for a DXA scan, as there will be no record of 'pre-treatment baseline' BMD levels.	National Osteoporosis Society, Clincial Experts, Web comment.	The 2006 ACDs and the 2007 FADs have been updated to remove the requirement for a decline in baseline BMD.
Expand definition of unsatisfactory response	Royal College of Pathologists.	The term unsatisfactory response has been removed from the 2007 FAD.
'Hierarchy' of treatment		

Hierarchical categorisation of interventions is inappropriate in the absence of direct comparator studies	Guideline Development Group.	The 2007 FADs provide recommendations only for the initiation of therapy for primary and secondary prevention of osteoporosis. Treatment options for women who are contra-indicated to alendronate, intolerant to or have withdrawn from initial therapy will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Alendronate should be differentiated		
Alendronate should be differentiated from other bisphosphonates based on superior clinical and cost effectiveness.	Merck, Sharpe and Dohme.	The 2007 FADs recommend alendronate (at the lowest acquisition cost) for the initiation of therapy for primary and secondary prevention of osteoporosis following the evidence on clinical and cost effectiveness.
Etidronate		
Etidronate is not more effective than strontium. Positioning of strontium ranelate behind etidronate does not make sense. Raloxifene should be positioned similarly to etidronate; as an alternative treatment option, when alendronate, risedronate and strontium ranelate are not well tolerated (hip fracture efficacy data more robust than for etidronate)	Clinical Experts, Web comments, National Osteoporosis Society, Royal College of General Practitioners, Royal College of Pathologists, Society for	For risedronate, strontium ranelate, raloxifene and etidronate it has not been demonstrated that they are a cost effective option for the initiation of therapy for primary or secondary prevention of osteoporotic fractures. Treatment options for women who are contra-indicated to alendronate, intolerant to or have withdrawn from initial therapy will be defined in the

	Endocrinology.	clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
An estimate of the generic efficacy of the bisphosphonate class must use a meta-analysis of the data and not the data from one drug using trial evidence that is itself less than robust. Indeed etidronate has no evidence for the prevention of hip fracture and no license for this.	Servier.	This has been revised based on subsequent meta-analysis and remodelling of the data for the 2006 ACDs and the 2007 FADs.
Medication errors with etidronate are common (GPs not aware of its calcium component and lack of Vitamin D)	Web comment.	Comment noted.
Raloxifene		
Breast cancer benefit should be included ; holistic approach to patient welfare; younger women	Clinical Experts, Eli Lilly, Guideline Development Group, Royal College of Pathologists, Society for Endocrinology, Web comments.	The Committee considered that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost effective option for the initiation of therapy for the prevention of osteoporotic fragility fractures, see FAD section 4.3.21. .
As a minimum, raloxifene should also be applied to primary prevention joint second-line with strontium (on balance, with 'a bit' of BC benefit included)	Eli Lilly, Web comment.	Raloxifene has not been recommended as a treatment option for the initiation of therapy for primary and secondary prevention of osteoporosis
Guidance should state that women already being treated with raloxifene do not need to stop treatment unless clinically indicated	Eli Lilly.	NICE guidance is prospective. This is conveyed in section 1.6 and 1.3 of the primary and secondary 2007 FADs respectively.
Clinical data for strontium is not as robust as for the bisphosphonates. Raloxifene, in contrast, has been available for many years and has an established efficacy and safety record in clinical practice globally.	Eli Lilly.	Comment noted.

Strontium ranelate		
Committee should demonstrate on what grounds they believe the hip fracture data for strontium ranelate is “less robust” than for bisphosphonates.	Bone Research Society.	Please refer to section 4.3.3 of the 2007 primary prevention FAD and section 4.3.4 of the 2007 secondary prevention FAD.
Strontium ranelate has robust and valid evidence for the prevention of fractures to the hip. The ACDs misrepresent the efficacy of strontium ranelate in hip fracture. We request that NICE endorses the measure of efficacy of a 36% reduction in fracture risk endorsed by the EMEA and the JEIM peer review process.	Servier	The Committee did not accept the estimate of efficacy for strontium ranelate in preventing hip fracture from the post-hoc subgroup analysis, but accepted the statistically non-significant RR of 0.85 for hip fracture to acknowledge an effect on this important type of fracture (see 2007 FAD section 4.3.19 (secondary prevention) and 2007 FAD section 4.3.23) (primary prevention).
The data on Strontium would appear to depend on an age effect and this should be taken in to account when making the graded recommendation within the current guideline.	Royal College of Pathologists.	Strontium ranelate has not been recommended as a treatment option for the initiation of therapy for primary and secondary prevention of osteoporosis.
Strontium ranelate has the only evidence available demonstrate the prevention of non-vertebral fractures in patients over 80 years. An examination of the evidence for strontium ranelate in the elderly demonstrates that this is the only drug with a substantial and convincing case for use in this patient population	Servier	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 guidance for the women 80 years or older and thereby age-stratify the recommendations even further
Modelling Assumptions		
Inconsistency with Kanis et al 2005 model; 10 year absolute risks should be used	Guideline Development Group,	Recommendations based on absolute risk of fracture are not currently possible as an absolute

	Web comment.	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 at the moment.
The confidence intervals of all estimates of relative risk completely overlap. The cost effectiveness ratios for strontium ranelate and bisphosphonates completely overlap.	Servier	Comment noted. The modelling structure required the use of midpoint efficacy estimates.
Proportion of patients entering nursing homes after hip fracture may be seriously underestimated	Guideline Development Group.	The 2006 ACDs and the 2007 FADs are based on revised modelling with updated data on nursing home entry.
5 year fall time: A two-year period after therapy discontinuation, during which the therapy effect remains the same, would be a more accurate reflection.	Merck, Sharpe and Dohme.	Comment noted.
We wanted to question whether the use of a 10 year time horizon in the Assessment Group's model is appropriate. This horizon is based on an assumption of 5 years treatment plus 5 years linear decline to no treatment effect.	Web comment.	See FAD section 4.3.7. (primary prevention) and 4.3.8(secondary prevention)
Calcium and Vitamin D		
Guidance on what are adequate levels of calcium and vitamin D, and how to assess.	National Osteoporosis Society, Royal College of General Practitioners, Royal College of Pathologists, Royal College of Physicians, Bone Research	The use and guidance on levels of calcium and vitamin D will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.

	Society	
Generic alendronate		
Alendronate is now available generically	Royal College of General Practitioners, Royal Collge of Nursing, Royal College of Pathologists, Bone Research Society, Web comments.	The 2006 ACDs and the 2007 FADs are based on revised modelling which include up to date price changes in generic alendronate.
Lumbar BMD		
Explanation as to why lumbar bone mineral density has not been used; trabecular bone more useful than the proximal femur, for monitoring response to treatment Will lumbar DXA be stopped or ignored?	Royal College of General Practitioners, Web comments, Clinical Expert.	The 2007 FADs refer to using the axial [hip and/ or spine] for BMD measurements.
Complex administration for strontium		
Strontium also has complex modes of administration and that should be mentioned	Alliance for Better Bone Health.	The method of administration for strontium ranelate is detailed in section 3.11 of the 2007 FADs for primary and secondary prevention of osteoporosis.
Emphasis on adverse effects		
SPC for strontium ranelate lists nausea and diarrhoea as being common adverse reactions.	Novartis.	The 2007 FAD sections 3.12 for primary and secondary prevention of osteoporosis refer to the Summary of Product Characteristics which gives full details of side effects.
Gastrointestinal side effects - suggest that the evidence summary is not appropriate.	Clinical Expert.	A systematic review of adverse effects and persistence was

		commissioned after consultation on the 2005 ACD.
The increased VTE risk for strontium ranelate from pooling of two large published studies (unpublished data)	Clinical Expert.	The increased risk of VTE when using strontium ranelate is referred to in the Summary of Product Characteristics.
Important to provide guidelines on the assessment of kidney function in the target population, given the high prevalence of CKD amongst the elderly. The recommendations made in the ACDs are inconsistent, in that contraindications in the presence of renal impairment are specifically mentioned for Raloxifene, Strontium ralenate, and Teriparatide, but not for any of the bisphosphonates.	Royal College of Physicians.	The Summary for Product Characteristics for each product should be referred to when prescribing a treatment.
There is a significant and growing body of evidence that undermines the clinical and cost effectiveness of bisphosphonate as a result of the side effects of these drugs. Account should be made of this evidence and, where necessary, alternative first line agents recommended.	Servier.	The 2006 ACDs and the 2007 FADs are based on modelling that includes adverse events. Treatment options for women who are contra-indicated to alendronate, intolerant to or have withdrawn from initial therapy will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
9.3% of patients on bisphosphonates are prescribed PPIs who would otherwise not require them.	Servier.	Comment noted.
We would like to suggest that this statement is qualified that these side effects are common with oral bisphosphonates	Web comments.	This has been amended in section 3.5 of the 2007 FADs for primary and secondary prevention of osteoporosis.
Adherence		

Clarify how adherence could be improved	Alliance for Better Bone Health, Web comments.	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'.
WHO data		
'unpublished WHO data needs to be made available for scrutiny and discussed by the medical community before replacing it with current practice'.	Clinical Expert	As stated in the 'Guide to Technology Appraisal Process', to ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Committee's decision should be publicly available. 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.
Treatment without DXA confirmation of osteoporosis		
It has been demonstrated that bisphosphonates are less effective if T-scores are in the normal or osteopenic range. Many experts are unhappy about treating patients in the absence of more abnormal DXA results.	Royal College of General Practitioners.	Treatment options for women who have osteopenia will be defined in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals

		at high risk'.
A recent audit from the Fracture Clinic at Newcastle General Hospital suggests that a third of women above the age of 75 years with an apparent low trauma fracture (excluding hip fracture) do not have osteoporosis on bone densitometry. Section 4.3.10 states that in cases of uncertainty, a DXA can be performed to confirm osteoporosis. It would be more appropriate to advocate BMD measurement in all older women with an osteoporotic fracture, unless the clinician is confident that the fracture followed only minimal trauma.	Clinical Expert.	DXA scans for women over the age of 75 years for secondary prevention (and for those age 75 with two risk factors in primary prevention) are at the discretion of the .physician.
Capacity for DXA		
Large numbers of women over the age of 75 years with one or more risk factors for fracture will be referred for BMD measurements. These guidelines would change the opportunity to treat promptly. We have concerns that long waiting times for a DXA scan would extend time of treatment commencing to unacceptable levels.	Clinical Expert, Royal College of Nursing.	Women older than 75 years old for secondary prevention or 75 years old or older with two or more clinical risk factors for primary prevention or may not require a DXA scan required if the responsible clinician considers it to be clinically inappropriate or unfeasible. The provision of DXA services is outside the remit of Technology Appraisals.
Miscellaneous		
Clinicians should be permitted to use clinical judgement as well as absolute thresholds.	Royal College of Nursing, Web comments.	The Committee needs to make recommendations based on clinical and cost effectiveness.
We need an explanation as to what is meant by fully adherent.	Royal College of General Practitioners.	The term fully adherent has been removed from the 2007 FAD documents.
Using the proposed criteria very few people would be eligible for treatment and that as a consequence there will be an increase in the number of osteoporotic fractures. It would be interesting to see an analysis modelled on current case	Royal College of Nursing.	The economic modelling takes into account all costs and health effects including avoided and not avoided

management and one based on the proposed guidelines and for these to be costed for quality of life issues (not simply related to being admitted to a nursing home) and the real costs of increased factures in those people who do not meet the criteria set.		fractures in in the treatment and control arms of the model.
The model appears at odds with data and preliminary recommendations from WHO	Bone Research Society.	Different organisations may develop different recommendations because of the methods and decision criteria used. Furthermore, the Institute is not aware that the final WHO algorithm has been published.
The guidelines should state that recommendations are not relevant for people with coeliac disease.	Web comment.	Treatment options for women who have Coeliac disease may be defined in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
The statistical model should be more transparent and peer-reviewed	Web comment.	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 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.
When WHO algorithm becomes available we should use absolute risk intervention thresholds	Web comment.	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 at the moment.
Why is there a distinction between primary and secondary prevention	Web comment.	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 (see secondary prevention FAD 2007 section 4.3.1).
Importance of fragility fractures 'lost from ACDs'	Alliance for Better Bone Health.	The Committee was mindful of the importance of fragility fractures in its considerations (see FAD sections 2.5 - 2.10)
Mention in section 1 that another biophosphanate should be prescribed if one is not tolerated	Alliance for Better Bone Health.	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, are intolerant or not responding to from initial treatment.

Grouped Comments – Primary Prevention

Comment	Made by	Notes
Primary - Identification Strategy		
Identification costs will not be uniform for all risk factors. For prior fracture, this is set at 0. The same situation also pertains to women with rheumatoid arthritis or women taking glucocorticoids, who can be cost effectively treated without any identification costs	Guideline Development Group, Clinical Expert, Bone Research Society, Society for Endocrinology, Web comment.	Women under 70 with medical conditions independently associated with bone loss are now included in the recommendations.
Questions the use of so-called "RCP" model, when the assessment report shows substantial increased net benefit when the WHO model is used in preference to the RCP model.	Society for Endocrinology.	The 2006 ACDs and 2007 FADs are based on revised modelling.
Suggested identification approach is wrongly described as being close to the RCP approach	Society for Endocrinology.	The 2006 ACDs and 2007 FADs are based on revised modelling.
The costs of identification considered by the committee are much greater than is actually the case in clinical practice	Clinical Expert.	The Committee was aware of uncertainties in the modelling and has taken this into account (see FAD sections 4.3. 12)
Including cost effectiveness evaluation of identification is beyond the remit	Alliance for Better Bone Health.	The Committee has to take all relevant costs and benefits into account.
Lack of understanding of what the identification strategy is, disagreement about what to factor into screening (only the DXA for the treated women!)	Alliance for Better Bone Health.	The text of the 2006 ACDs and the 2007 FADs has been revised.
T-score thresholds - Discrepancy between ACD and AR		
Side effects and compliance do not provide enough justification for lowering thresholds compared with modelling results (no excess of side-effects in bisphosphonate treated	Alliance for Better Bone Health,	The modelling for the 2006 ACDs and the 2007

patients in the clinical trials and sensitivity analyses show that compliance only has a significant effect when it is lower than 50%.	Guideline Development Group, Merck, Sharpe and Dohme, Clinical Expert, ScHARR.	FADs has been revised to be more explicit about the uncertainties around compliance and side effects.
The uncertainty in the costs and benefits of implementing the identification strategy is not reduced by restricting the group of women eligible for treatment. As the identification strategy relies on the net benefit of treating women to offset the costs of identifying those women, it is possible that restricting the group of women eligible for treatment will lower the overall net benefit of the strategy. A better way to proceed would be for the Assessment Group to calculate the optimum identification strategy using a lower cost maximum acceptable incremental cost-effectiveness ratio (MAICER).	ScHARR	The 2006 ACDs and the 2007 FADs are based on revised modelling.
This seems to suggest that we diagnose that the patient has established osteoporosis by WHO definition but do not offer treatment until the BMD drops to -3.5 SD or the patient sustains a fracture.	Society & College of Radiographers.	The Committee now recommends that patients aged 70 years and above with one clinical risk factor and a BMD of -2.5 SD can be treated with generic alendronate for primary prevention.
Highlight evidence on this topic which demonstrates that compliance with bisphosphonates may be as good as 60-80%	Merck Sharp & Dohme, National Osteoporosis Society, Clinical Expert, Society for Endocrinology, Web comment.	Subsequent to the 2005 round of consultation, persistence at 5 years has been modelled as 50% which has been estimated from the results of the systematic review.
In all chronic diseases, poor compliance with therapy will have an adverse effect on the cost-effectiveness of treatment. The Committee should offer a balanced view on this area, and only comment on this if it is unique to the primary prevention of osteoporotic fracture.	Bone Research Society.	Issue relating to the management of persistence may be defined in the clinical

		guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
We are not aware of any systematic bias in DXA scanning, nor would we expect that the standard deviations would be large enough to change the identification strategy, as women falsely positioned above or below the cost-effectiveness risk, would be those closest to the threshold and the loss in net benefit would be unlikely to be severe.	ScHARR.	Comment noted.
No treatment for under 70s		
No treatment for <70 year olds not acceptable - importance of prevention.	Clinical Experts, National Osteoporosis Society, Royal College of Nursing, Royal College of Pathologists, Web comments.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years with at least one clinical risk factor and a medical condition suggestive of low BMD.
There will be some women under 70 who will need to be treated, and options for them should be stated. GPs need guidance on how to advise patients under the age of 70.	Eli Lilly, Clinical Expert, Royal College of General Practitioners, Web comments.	Following consultation on the ACD, the Committee has included recommendations for women below the age of 70 years with at least one clinical risk factor and a medical condition suggestive of low BMD.

At £20K per QALY it appears to be cost effective to treat at all ages at a BMD threshold of 4	Clinical Expert	Subsequent remodelling still indicates for some age groups in the absence of risk factors that treatment is not cost effective at £20,000 per QALY.
Wyeth believes that establishing such restrictive entry criteria runs counter to a public health remit whereby preventative strategies are seen to be of equal value to curative strategies.	Web comment	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 (see secondary prevention FAD 2007 section 4.3.1).

Grouped Comments – Secondary Prevention

Comment	Made by	Notes
Teriparatide		
Reconsider teriparatide in <65 year olds (as some women can be treated cost effectively)	Clinical Experts, Eli Lilly, National Osteoporosis Society, Royal College of Pathologists, Society for Endocrinology.	The 2007 FADs provide recommendations for initiation of treatment only, and teriparatide has not been found to be a cost-effective option for the initiation of prevention therapy
4.3.13/16. The committee states that if a woman sustains a fracture within the first few months of bisphosphonate therapy, continuation with bisphosphonate treatment is likely	National Osteoporosis Society,	Treatment options for women who withdraw

to be the most appropriate therapy in many women. However, we would like to point out that if the woman were to sustain a further fracture it would also be appropriate to consider teriparatide, in line with the criteria set out in TA87.	Web comment.	from initial treatment will be defined in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Teriparatide is not recommended for initial therapy for secondary prevention osteoporosis.
Over 75s: If patients fail bisphosphonates and have multiple risk factors, should they also be required to have such a low BMD to qualify for treatment? i.e. will they need a DXA although they did not need one to get bisphosphonates?	Royal College of Nursing, Web comments.	Treatment options for women who are contra-indicated to alendronate, who have withdrawn from, are intolerant or not responding to initial treatment, will be defined in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Teriparatide is licensed as a 20μg daily dose. The guidance should report on side-effects related to this dose rather than a higher dose that is not used in clinical practice.	Bone Research Society.	Teriparatide is not recommended for initial therapy for secondary prevention osteoporosis.
Use of pooled relative risks		
Reanalysis should be conducted using estimates of efficacy derived only from secondary prevention studies as in the initial appraisal.	Guideline Development Group. Clinical Expert.	Based on advise from clinical experts, the assumption was included that efficacy is constant

		across age, T-scores, age and fracture status.
Modelling to be rerun to undertake sensitivity analyses	Guideline Development Group.	The modelling has been revised to undertake sensitivity analyses.
The calculated RR reduction from pooled data is likely to underestimate the efficacy and cost-effectiveness of treatment in osteoporotic women.	Clinical Expert.	The analysis was carried out for combined (second generation) bisphosphonates on the advice of the Guidelines Development Group as it was considered that the second generation bisphosphonates had an overlapping efficacy range and could be considered a clinical class
NICE has previously acknowledged the importance of relative risk to baseline risk and demonstrated this by requesting relative risks that informed the previous secondary prevention appraisal, be drawn only from high-risk secondary prevention patients. The decision by the appraisal committee and the Assessment Group to reject the evidence for strontium ranelate in higher risk patients is perverse in the light of previous policy. The total TROPOS population included patients with a t-score >-2.5 (NHANES). This is an osteopenic population outside the license for the use of the drug and according to the standard procedures for assessment by NICE, cannot justifiably be included in the analysis. The sub-group analysis excluded these patients.	Servier.	Section 4.3.19 of the FAD explains the committee's consideration of the Strontium ranelate data.
Women under 65		
The implication that a women aged 60 with several fragility fractures should not be treated is clinically inappropriate.	Guideline Development Group.	The 2007 FAD recommends alendronate for all post menopausal women with a confirmed T-score of -

		2.5 SD or below for the initiation of therapy for the secondary prevention of osteoporosis.
A woman < 65 who already has a low trauma and documented osteoporosis, will be denied effective treatment, unless the T Score is lower than -3.0, or there is an additional risk factor present. This is particularly the case in women with an incident vertebral fracture, where there is a 20% risk of further fracture in the subsequent year.	Clinical Expert, Royal College of Nursing.	The 2007 FAD recommends alendronate for all post menopausal women with a confirmed T-score of -2.5 SD or below for the initiation of therapy for the secondary prevention of osteoporosis.
A very small percentage of women under the age of 65 years would meet the ACD treatment criteria, given that the average T-Score at age 60-64 is –1.17SD, (page 17 of Strontium Ranelate Assessment Report). The vast majority of women receiving a DXA scan at this age would not be treated. The DXA costs would outweigh the net benefit of those successfully treated, implying that the use of DXA in women with a prior fracture aged 65 years and under is not cost-effective, using the ACD treatment criteria. …. This work was subsequently updated to allow for the lower average BMD seen in women with a prior fracture. (average BMD assumed lower by 0.2SD). This was provided to the NICE technical lead, but too late to inform the Committee. This analysis showed that, when accounting for the lower average BMD of women with a prior fracture, cost-effective identification strategies could be identified for women over the age of 55.	ScHARR.	The 2007 FAD recommends alendronate for all post menopausal women with a confirmed T-score of -2.5 SD or below for the initiation of therapy for the secondary prevention of osteoporosis.
No update of existing recommendations		
The opportunity for improvement of the existing guidance may have been missed.	Clinical Expert.	Because of the extension of the timelines in this appraisal, several opportunities have been used to improve the modelling.and reconsider the recommendations.
To utilise the (new) model for some of the assessed therapies and not others is confusing and inconsistent with the approach adopted in the primary prevention TA.	National Osteoporosis Society.	Subsequent revisions of the model have been

		used for the development of 2006 ACD and the 2007 FAD. The same model has been used for both primary and secondary prevention.
Miscellaneous		
Prior fracture – does it matter how long ago a prior fracture has occurred and if so this should be specified	Web comment.	Evidence on time elapsed since fracture was not available to the Committee. .

Editorial Comments

Comments	**Made by**	**Notes**
Section 1, change 'normal levels of Calcium and/or Vitamin D' to 'and'	Alliance for Better Bone Health.	The 2007 FADs have been amended.
Section 4.3.12 and 4.3.20 from secondary ACD should also be in primary ACD	Alliance for Better Bone Health.	The 2007 FADs have been amended.
'Costs may differ due to locally negotiated procurement discounts' should be removed for teriparatide there are none.	Eli Lilly.	The 2007 FAD has been amended.
Section 4.3.18 of the Primary Prevention ACD and Sections 4.3.17/4.3.18 of the Secondary Prevention ACD should present the same information.	Novartis.	The 2007 FADs have been amended.
Care is required when making recommendation for use of teriparatide in "….medical conditions independently associated with bone loss…." This needs to be in light of the contraindications for use as specified in the data sheet and conditions that might predispose to hypercalcaemia/hypercalciuria.	Royal College of Pathologists.	Teriparatide is not recommended as a treatment option for the initiation of therapy for secondary prevention of osteoporosis.
Clinical risk factors for teriparatide appear to differ from those recommended for bisphosphonates and strontium ranelate. This should be clarified. Use of corticosteroids should not be included as this is not covered by this guidance.	Bone Research Society.	The clinical risk factors referred to in the 2007 secondary prevention

		FAD are consistent across the drugs included in the scope of the appraisals. Treatment options for women who are on long term corticosteroid therapy will be defined in the clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
Strontium ranelate		
In 5.4 The evidence that strontium ranelate interferes with DXA scanning is because strontium has a higher molecular weight than calcium and thus it appears that the patient is putting on around 8 times more bone than they are in reality - not because strontium has properties similar to calcium	Web comment.	Comment noted.
WHO definition of osteopenia/ osteoporosis overlap (both including -2.5)	Web comment.	Comment noted.

Process Comments

No response received to comments on Assessment Report.	Guideline Development Group.	The Institute does not respond to comments on the Assessment report. The Assessment Groups are invited to respond to such comments.
Agreement that risk factors and identification is the role of the GDG and this has been infringed.	Guideline Development Group.	This has been resolved through the responses to comments on the 2006 ACD and including GDG members as advisors on

		the Technology Appraisals Committee meetings.
GDG has the remit to make recommendations for all groups.	Guideline Development Group.	Comment noted.
Risk factor systematic review was ignored.	Guideline Development Group.	This was resolved by subsequent meetings between the GDG and the Appraisal Committee.
NCC/ GDG should be on list of Consultees and Commentators.	Guideline Development Group.	The GDG/ NCC are commentators on Technology Appraisals.
The role of the GDG to develop clinically appropriate guidelines becomes redundant, certainly as far as prevention of osteoporotic fractures in postmenopausal women is concerned.	Clinical Expert.	This has been resolved through the responses to comments on the 2006 ACD and including the GDG members as advisors on the Technology Appraisals Committee meetings.
GDG responses were not discussed	Clinical Expert.	This was resolved by subsequent meetings between the GDG and the Appraisal Committee
Furthermore, in view of the marked discrepancies between the recommendations generated by the guidance and guidelines, it is hard to see how the two sets of recommendations could be reconciled.	Clinical Expert.	This was resolved by subsequent meetings between the GDG and the Appraisal Committee
Appraisal Committee chose to ignore the evidence. Comments submitted by the GDG to the Appraisal Committee on various drafts have been largely ignored and there has never been any formal response to these comments	Clinical Expert.	This was resolved by subsequent meetings between the GDG and the Appraisal Committee
Insistence that guidance recommendations are included in the clinical guideline means	Clinical Expert.	The 2006 ACDs and the

that inclusion of the WHO risk assessment approach would be at odds with the guidance recommendations and would become essentially redundant in terms of its impact within the NICE guideline.		2007 FADs are based on revised modelling based on the WHO algorithm.
Links were made between both Technology Appraisals and the forthcoming clinical guideline so that all NICE guidance is consistent.	National Osteoporosis Society.	Comment noted.
It is inappropriate for the Health Technology Appraisal to be making treatment recommendations before the publication of the guidelines.	Royal College of Nursing.	The Committee did not consider it appropriate to endorse guideline recommendations which are not yet finalized but refers readers to the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
The two models provided by Servier were commissioned from external bodies –NB Consulting and SHE (Stockholm Health Economics).	Servier.	Comment noted.
Should ibandronate be mentioned (as 'not covered').	Web comment.	Ibandronate is not within the scope of the appraisal.
Audit section not realistic	Web comment.	Comment noted.
Review in 2009 too late.	Web comment.	Comment noted.