National Osteoporosis Society comments on NICE ACD re alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

General comment

The National Osteoporosis Society (NOS) thanks NICE for the opportunity to comment on the ACD for the primary prevention of osteoporotic fragility fractures. In compiling a response we have liaised with our membership; those men and women living with and at risk of osteoporotic fragility fractures, as well as our staff and clinical advisors. We would like to make the following general comment before addressing issues in relation to the three specific headings requested.

By far the most prevailing concern of all consulted by the NOS is the unacceptable decision of the committee to deny preventative treatment to any woman under the age of 70 years because it is not deemed to be cost effective to identify her. Whilst the Society understands the need to make recommendations based on cost-effectiveness arguments to treat the population as a whole, these recommendations, which will have to be used to treat 'individual' women in a clinical setting, inappropriately relegate osteoporosis as a condition of old age. As such, they are counterintuitive to preventative health medicine, government policy, and if not amended will seriously impair good clinical practice for the management of osteoporosis.

Osteoporosis is a serious disease that can result in painful and debilitating fractures. It should be considered in the same way as other disease areas about which we are told that prevention is key; high blood pressure and raised cholesterol are treated to prevent heart attack and stroke, so osteoporosis should be treated in all those individuals at a high enough absolute risk of fracture to prevent first fractures occurring.

> *'The thing that most shocked me about the primary prevention document is that there is no mention at all of women under the age of 70! How can this be described as 'prevention' when they are not proposing to do anything –regardless of clinical risk or T score- until that stage?'*

The following quotes from our membership highlight clinical scenarios in women where investigation and treatment are warranted. Under the current NICE recommendations these women would not be provided with anti fracture medication and as a result, left at an unacceptable risk of fracture.

> *'I am 62 years old and suffer very badly with rheumatoid arthritis. My doctor said that because I am very thin and have been a heavy smoker for many years I am at risk of breaking bones all over my body. I had a scan which showed I had that disease osteoporosis. My doctor has put me on a drug which I will probably have to take for the rest of my life. I don't really like taking medicines but I plan to stick with it as my doctor said I'll be in serious trouble if I don't.'*

> *'I am 57 years old and the scan of my spine showed -3.6. Although I have had no fractures, my mother at 88 years has had painful vertebral collapse. I have been taking bisphosphonates because with family history, (she is similar to me in her build) and such a low scan reading, it is surely sensible to take a preventative medication.'*

> *'My mother has had fractures. I am 66 and a scan has confirmed osteoporosis - I am also a coeliac and very slight in build. I feel I am someone who is at risk because I had eating problems when I was younger and often went without my periods. I am taking Didronel and would be extremely concerned if I was no longer able to take it.'*

	The Society hears from many women like these, younger than 70 years, and with a variety of different risk factor combinations. For these women treatment is deemed to be clinically appropriate as they are at a high absolute risk of fracture. To deny them a drug for several years until they reach the age of 70 based on arguments about cost, despite the fact that there are effective treatments available, is not morally acceptable. These women will be left extremely vulnerable to fracture and all the associated costs, both personal in terms of reduced quality of life and also to the NHS and Social Services in relation to fracture management in the long term. ***The Society urges NICE to reconsider its cost-effectiveness thresholds to ensure that these women do not miss out on appropriate investigation and treatment.***
Summaries of clinical and cost effectiveness	**Threshold of £20K per QALY is unacceptable** The NOS finds it unacceptable that the committee has chosen to adopt a £20k cost per QALY threshold for primary prevention when the secondary prevention TA uses a £30K threshold and the Society is unhappy with the rationale provided for this decision (section 4.3.9). By adopting a lower value of £20K as the maximum amount that it is acceptable to pay for an additional QALY for primary prevention, NICE is downplaying the significance of preventing osteoporotic fractures and penalising those women who have not yet fractured but who are at a comparable level of absolute risk to those who have already broken a bone. ***The NOS urges the committee to reconsider adopting a £30K threshold so that the management of both primary and secondary osteoporotic fractures is treated consistently.***
	Compliance The NOS notes that the committee considered that compliance to medication is generally low and that sensitivity analysis revealed that cost effectiveness was influenced by the level of compliance. The Society would like to highlight emerging evidence on this topic which demonstrates that compliance to bisphosphonate therapy in clinical practice is as good as 60-80%, with the weekly formulations faring better than the daily regimens[1,2]. In addition, research has demonstrated that merely seeing a nurse 3-monthly after starting medication enhances compliance. ***The NOS asks the committee to give due consideration to this work and to make useful recommendations for health care professionals to promote good compliance with medication.***
All relevant evidence taken into account	**Incomplete list of risk factors** The NOS is concerned that the recommendations will not be useful in clinical practice as they focus on a very limited number of risk factors for osteoporotic fracture and as such could result in some women missing out on assessment and intervention (section 1.3).

	'My 88 year old mother suffers severely from osteoporosis but has never fractured a hip. Her fractures have been in the wrist, ankles and vertebra. It seems important not to restrict risk factors solely to hip fracture and vaguely to other medical conditions' The Society notes that the committee considered adopting the WHO approach but then chose to adopt a more simplified approach, dismissing both smoking and alcohol. The NOS does not accept the committee's rationale that '*their effects on fracture risk were relatively small and such behavioural risk factors are difficult to confirm reliably*' (section 4.3.7). Both of these risk factors have been shown to be predictive of fracture[3,4]. Furthermore, current smoking behaviour is straightforward to assess in a clinical situation. The NOS is concerned that by neglecting such factors the TA recommendations will be at odds with the approach of the clinical guideline that incorporates risk identification based on an assessment of absolute risk of fracture. This would result in much confusion for both patients and physicians and would hinder implementation of the guidance and the development of osteoporosis services. ***The Society asks the committee to re-consider the inclusion of both of these risk factors and also to provide 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.***
Provisional recommendations	**Intake of calcium and vitamin D** The NOS is pleased that the ACD recommends that clinicians ensure that women are calcium and vitamin D replete but believes that the recommendations imply 'testing' without providing an explanation about how to do this. ***The Society asks NICE to provide further guidance to clinicians on how to ensure that their patients have adequate levels of calcium and vitamin D.***
	Positioning of etidronate The Society would question the committee's decision to recommend etidronate as equivalent to alendronate and risedronate (section 1.1). The RCT evidence for the prevention of hip fractures is clearly stronger for alendronate and risedronate. It is our experience that patients prefer the weekly formulations of the newer bisphosphonates, rather than the complicated daily regimen associated with etidronate. Similarly, we would also question the positioning of strontium ranelate behind etidronate when it also has greater hip fracture efficacy and appears to be as cost-effective (section 1.4). ***The Society asks NICE to consider recommending etidronate as an alternative to alendronate, risedronate and strontium ranelate, when they are not well tolerated.***
	Positioning of raloxifene We are particularly disappointed to see that raloxifene is no longer recommended for primary prevention of fragility fractures in post

	menopausal women (section 1.5). Raloxifene is a licensed treatment that is effective in preventing vertebral fractures and we know from our membership that it is viewed as an important option for some women, not only for bone health but also because of the protective effect it offers against breast cancer. Whilst we acknowledge that women will now be able to take strontium ranelate if they are unable to tolerate the bisphosphonates, we would ask NICE to maintain raloxifene as an option to allow both clinicians and patients a 'choice' of effective alternatives. ***The Society asks that raloxifene is positioned similarly to etidronate; as an alternative treatment option, when alendronate, risedronate and strontium ranelate are not well tolerated.***
	Definition of intolerance to bisphosphonates The current wording would mean that GPs have to request an endoscopy to confirm symptoms to satisfy the criteria for changing to a different treatment. This is at odds with recommended best practice, particularly as it is recognised that there is a poor correlation between symptoms of dyspepsia and endoscopy findings. ***The NOS believes that the definition of intolerance (section 1.6) will not be useful in clinical practice and would ask that it is amended to reflect symptomatic side effects i.e. upper gastrointestinal disturbances.***
	Link to other relevant NICE guidance To ensure clarity for both clinicians and patients, the NOS would like to see greater reference in the document to TA87 re secondary prevention. In section 4.3.16 the committee states that if a woman sustains a fracture within the first few months of bisphosphonate therapy, continuation with bisphosphonate treatment is likely 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. ***The NOS believes that it would be useful for both clinicians and patients if links were made between both TAs and the forthcoming clinical guideline so that the guidance is consistent and streamlined.***
	In conclusion, the NOS does <u>not</u> consider the provisional recommendations to constitute a suitable base for the preparation of guidance to the NHS. We urge the appraisal committee to re-examine the recommendations to ensure that adequate treatment choices are available for all postmenopausal women deemed to be at high absolute risk of sustaining a fracture.

Refs
1. Prowse et al (2005) Persistence with oral bisphosphonate therapy is high amongst patients followed in a DGH osteoporosis clinic: Rheumatology 44, suppl 1, i35
2. Doherty et al (2005) Compliance and effect on bone protective treatment in elderly remales: 5 year follow-up study: Rheumatology 44, suppl 1, i34
3. Kanis et al. (2005) Smoking and fracture risk: a meta-analysis: Osteoporosis Int 16 (2): 155-162.
4. Kanis et al. (2005) Alcohol intake as a risk factor for fracture: Osteoporosis Int 16 (7): 737-742

National Osteoporosis Society comments on NICE ACD re alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the <u>secondary prevention</u> of osteoporotic fragility fractures in postmenopausal women	
General comment	The National Osteoporosis Society (NOS) thanks NICE for the opportunity to comment on the ACD for the secondary prevention of osteoporotic fragility fractures. In compiling a response we have liaised with our membership; those men and women living with and at risk of osteoporotic fragility fractures, as well as our staff and clinical advisors. We would like to make the following comments in relation to the three specific headings requested.
Summaries of clinical and cost effectiveness	**Different economic models** The Society welcomes the updated economic modelling that the assessment group has carried out but believes that the committee's decision to utilise the model for some of the assessed therapies and not others is confusing and inconsistent with the approach adopted in the primary prevention TA.
All relevant evidence taken into account	**Incomplete list of risk factors** The NOS is concerned that the recommendations will not be useful in clinical practice as they focus on a very limited number of risk factors for osteoporotic fracture and as such could result in some women missing out on assessment and intervention (section 1.1). Furthermore, there is inconsistency within the document with risk factors listed differently in various sections (1.1; 1.5; 4.3.21). *'My 88 year old mother suffers severely from osteoporosis but has never fractured a hip. Her fractures have been in the wrist, ankles and vertebra. It seems important not to restrict risk factors solely to hip fracture and vaguely to other medical conditions'* The Society notes that the committee considered adopting the WHO approach which includes six major risk factors but then chose to adopt a more simplified approach, dismissing both smoking and alcohol. The NOS does not accept the committee's rationale that '*their effects on fracture risk were relatively small and such behavioural risk factors are difficult to confirm reliably'* (section 4.3.3). Both of these risk factors have been shown to be predictive of fracture[1,2]. Furthermore, current smoking behaviour is straightforward to assess in a clinical situation. The NOS is concerned that by neglecting such factors the TA recommendations will be at odds with the approach of the clinical guideline that incorporates risk identification based on an assessment of absolute risk of fracture. This would result in much confusion for both patients and physicians and would hinder implementation of the guidance and the development of osteoporosis services. *The Society asks the committee to re-consider the inclusion of both of these risk factors and also to provide 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.*

Provisional recommendations	**Intake of calcium and vitamin D** The NOS is pleased that the ACD recommends that clinicians ensure that women are calcium and vitamin D replete but believes that the recommendations imply 'testing' without providing an explanation about how to do this. ***The Society asks NICE to provide further guidance to clinicians on how to ensure that their patients have adequate levels of calcium and vitamin D.***
	Positioning of etidronate The Society would question the committee's decision to recommend etidronate as equivalent to alendronate and risedronate (section 1.1). The RCT evidence for the prevention of hip fractures is clearly stronger for alendronate and risedronate. It is our experience that patients prefer the weekly formulations of the newer bisphosphonates, rather than the complicated daily regimen associated with etidronate. ***The Society would ask that etidronate is positioned similarly to raloxifene; as an alternative to alendronate, risedronate and strontium ranelate, when they are not well tolerated.***
	Inclusion of strontium ranelate The NOS welcomes the inclusion of strontium ranelate as a treatment option but questions the positioning of the drug behind etidronate when it has greater hip fracture efficacy and appears to be as cost-effective (section 1.3).
	Use of teriparatide in younger postmenopausal women The Society is disappointed that the committee has opted to retain the age restriction around the use of teriparatide despite the fact that cost-effective scenarios were identified in this age group. Whilst we acknowledge that these women will now be able to take strontium ranelate if they are unable to tolerate the bisphosphonates we believe that it is important that they also have access to teriparatide. '*It seems my age would not qualify me for teriparatide even though I've had 3 fractures and nothing has helped. I will have to wait until I am older, have broken more bones and am more frail. It seems disgraceful in a western society that one must measure one's pass mark for treatment not by how ill one is but by one's age…do people with very high blood pressure have to be over 65 years and have at least one stroke before they can have the medication that they receive?'* *'I had my first vertebral fracture when I was 60 after an early menopause. I had two further fractures 3 years later and have since had more vertebral fractures making a total of five. Although I am now over 70 and receiving treatment, I do feel that if a bone is broken easily by someone at a young age then drugs should be prescribed to prevent further fractures happening. I certainly would not wish anyone to suffer as I have.'*

	The Society would once again ask NICE to remove the 65 year age restriction to allow both clinicians and patients a 'choice' of effective alternatives.
	Definition of an unsatisfactory response The current definition of an unsatisfactory response i.e. '*a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is also evidence of a decline in BMD below her pre-treatment baseline'* (section 1.6) is inappropriate in relation to strontium ranelate. There is substantial evidence that strontium ranelate causes BMD measurements to be amplified unless a corrective adjustment is made to the DXA scan. As a result it will be impossible for a woman to fail on strontium until it is too late and she has fractured, as BMD will always increase. This has the consequential effect of limiting access to raloxifene which is inappropriate. Furthermore, the 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. ***The NOS asks NICE to rephrase this definition and to make it more workable in clinical practice.***
	Definition of intolerance to bisphosphonates The current wording would mean that GPs have to request an endoscopy to confirm symptoms to satisfy the criteria for changing to a different treatment. This is at odds with recommended best practice, particularly as it is recognised that there is a poor correlation between symptoms of dyspepsia and endoscopy findings. ***The NOS believes that the definition of intolerance (section 1.7) will not be useful in clinical practice and would ask that it is amended to reflect symptomatic side effects i.e. upper gastrointestinal disturbances***
	In conclusion, the NOS does <u>not</u> consider the provisional recommendations to constitute a suitable base for the preparation of guidance to the NHS and urges the appraisal committee to give due consideration to the issues that the Society has raised.

Refs
1. Kanis et al. (2005) Smoking and fracture risk: a meta-analysis: Osteoporosis Int 16 (2): 155-162.
2. Kanis et al. (2005) Alcohol intake as a risk factor for fracture: Osteoporosis Int 16 (7): 737-742