NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161)

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Background information	Healthcare Improvement Scotland	Although the adverse associations of osteoporosis are discussed there is little information on the benefits of bisphonates. For example when given after hip fracture both oral and iv bisphosphonates can reduce mortality. Beaupre LA1, Morrish DW, Hanley DA, Maksymowych WP, Bell NR, Juby AG, Majumdar SR. Oral bisphosphonates are associated with reduced mortality after hip fracture. Osteoporos Int. 2011 Mar;22(3):983-91.	Comment noted. The background section of the scope intends to provide a brief overview of the condition and treatment pathway. No changes required to the scope.
	Healthcare Improvement Scotland	No issues	Noted
	Healthcare Improvement Scotland	I welcome the QOF advice that leads GPs to look out for osteoporosis in patients with rheumatoid arthritis, but wonder if there is a case for extending such an approach to patients with other inflammatory arthropathies (eg, psoriatic arthritis or ankylosing spondylitis). I suspect support for case finding is critical in the assessment of how useful any appraisal is going to be. "other causes of secondary osteoporosis" – from my recollection NICE has published a lengthy list of causes of secondary osteoporosis – in practice I'm not sure how well these are remembered	Comments noted.
	Merck Sharp &	In the section "The review proposal" there is a discussion on aligning NICE technology appraisal guidance on treatment	Comment noted. The proposed MTA will be based on risk assessment as

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	Dohme Ltd	with the NICE clinical guideline on risk assessment. In addition the population states "identified by applying the recommendations in NICE clinical guideline 146". We would like clarification on whether there is an intention that this proposed MTA will make a recommendation on which risk score, FRAX or QFracture, should be used.	outlined by the clinical guideline. Any differences between the uses of QFracture or FRAX can be considered as part of the appraisal process, if considered relevant to decision making by the Appraisal Committee. No changes to the scope required.
	National Osteoporosis Society	In addition to the points made, CG 146 specifically states the need to consider DXA in all patients with breast and prostate cancer (1.8)	Comment noted. Appendix A of the scope includes the full recommendations listed in CG 146. No changes required to the scope.
	Primary Care Rheumatology Society	Long awaited and essential to update the guidance so that it is practical and realistic for GPs to follow in primary care	Comment noted.
	ScHARR-TAG	No comment on this section	Noted.
The technology/ intervention	Healthcare Improvement Scotland	No issues	Noted.
	Healthcare Improvement Scotland	See BNF	Comment noted.
	National Osteoporosis Society	This MTA includes all bisphosphonates currently licenced for the treatment of osteoporosis, including generic treatments. We believe that inclusion of generics is not standard practice in MTAs and have concerns about the bearings of very low cost generic drugs on the overall analysis of cost effectiveness. The availability of cost-effective generic options is positive for patients as appropriate treatment should be possible with	Comments noted. Generic treatments are not excluded from consideration through the NICE technology appraisal process. The NICE Guide to Methods of Technology Appraisal (2013) states that comparator technologies may include branded and non-proprietary

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		some choice of the options. However, the challenge for NICE will be to incorporate what is clinically appropriate in their analysis as well as what is cost-effective.	(generic) drugs and biosimilar products (see section 2.25). It states further that the public list prices for technologies should be used in the reference-case analysis. The Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts through its Electronic Marketing Information Tool (eMIT) (see section 5.5.2). No changes to the scope required.
		We would welcome clarity also about how guidance will be given on the use of treatments for osteoporosis that are not bisphosphonates.	It was agreed following a stakeholder workshop that an MTA of bisphosphonates for preventing osteoporotic fragility fractures should be scheduled into the work programme as a priority, and that an MTA of non-bisphosphonates treatments should be scheduled to start as the bisphosphonates MTA published its final appraisal determination. The scope has been updated to clarify this.
		Guidance on the duration of therapy would also be welcome.	The scope has been updated to specify that if evidence allows the impact of treatment duration on costs and outcomes will be considered

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	ScHARR-TAG	No comment on this section	Noted.
Population	Healthcare Improvement Scotland	Those with osteoporosis risk factor (s) low BMI, early menopause, family Hx and personal history of fragility fracture, those with chronic diseases such as RA and previous steroid use.	Comment noted. The population included in the scope is 'adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146'. The MTA will therefore consider absolute fracture risk (as recommended by Clinical Guideline 146) which takes into account BMI, menopause, family history, previous fragility fractures, presence of rheumatoid arthritis and steroid use. The populations listed are therefore included in the population of the scope. No changes are required.
	Healthcare Improvement Scotland	No issues	Noted.
	Healthcare Improvement Scotland	Sub-groups, such as those with corticosteroid induced osteoporosis/those at risk of steroid induced osteoporosis, may have different mechanisms involved. Those with renal bone disease and osteoporosis form a separate group both because of the complexity of the pathophysiology and because of the limited evidence of benefit from the technologies	Comment noted. The scope has been updated to state that if evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes should be considered.
	Merck Sharp & Dohme Ltd	MSD would like some clarity in the description of the population:	Comments noted. The population in the scope has been updated to

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		What is the age and sex of adults included in the MTA? What is meant by “increased absolute risk”?	state: ‘adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146’. The age and sex of the population will therefore be determined by that stated in NICE clinical guideline 146.
	National Osteoporosis Society	The target population is described as "adults" – the scope should be explicit as to whether or not premenopausal women and younger men will be included. Consideration should be given to setting a minimum age. Young adults will often require consultations with secondary care specialists to ensure appropriate care is given. These nuanced, complex decisions cannot be appropriately reflected in an overarching guidance. Clarification is needed around adults at ‘increased absolute risk’ – this is not defined in CG146 and a definition of this group will be required. The risk estimates given by FRAX and QFracture are different and there is the potential for this to lead to confusion. We would welcome clarity on how these tools can be used to inform clinical decision making in practice. Recommending a preferred option may be a practical solution. Clarification is needed about whether other groups are included in the scope, e.g. patients receiving glucocorticoids or cancer treatments that result in bone loss. Although glucocorticoid-induced osteoporosis is mentioned in the scope several times, it is not absolutely clear that the MTA intends to	Comments noted. The population in the scope has been updated to state: ‘adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146’. The age and sex of the population will therefore be determined by that stated in NICE clinical guideline 146. Any differences between the uses of QFracture or FRAX can be considered as part of the appraisal process, if considered relevant to decision making by the Appraisal Committee. No changes to the scope required. The MTA will consider the population defined in NICE Clinical Guideline 146, which includes the presence of risk factors such as current or frequent use of gluococorticoids. No

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		cover it - this should be clarified.	changes to the scope required.
	ScHARR-TAG	Clinical guideline 146 describes how absolute risk of osteoporotic fracture should be assessed. It doesn't describe a threshold above which individuals should be considered to be 'at increased absolute risk'. Therefore the population described in the draft scope doesn't have a well-defined boundary. If the intended population is those for whom CG146 recommends risk assessment (as specified in recommendations 1.1 and 1.2) then it would be better to state this explicitly.	Comments noted. The population in the scope has been updated to state: 'adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146'.
		With regards to subgroups, any patient characteristic which increases the risk of fracture (e.g those specified in CG 146) or modifies the impact of fracture on life-time costs and QALYs could be used to define a subgroup in which the cost-effectiveness is expected to differ from the population as a whole. For example, age is a predictor of both hip fracture risk and the likelihood of requiring nursing home care following hip fracture and therefore the cost-effectiveness of treatment is expected to vary by age even when holding the absolute risk of fracture constant. Other factors which predict fracture risk may also have differing effects on cost-effectiveness due to their varying ability to predict hip and non-hip fracture and the differing consequences of these outcomes. Gender, prior fragility fracture, BMD and systemic corticosteroid usage may also be considered as subgroup defining factors as these have been used to define trial populations and the licensed indications for bisphosphonates.	The scope has been updated to state that, if evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes should be considered.
Comparators	Healthcare Improvement	Sub groups of vertebral, non vertebral and hip fractures to be considered for each bisphosphonate	Comment noted. The appraisal will consider prevention of fracture and

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	Scotland		therefore the type of fracture is not yet known. The risk of different fracture types, and the associated costs and health related quality of life impact can be considered as part of the appraisal process if considered relevant by the Appraisal Committee.
	Healthcare Improvement Scotland	Denosumab (TA204) is a valid comparator for women with severe osteoporosis who are unsuitable for oral bisphosphonates. It should be compared to treatment with annual zoledronate.	Comment noted. It was agreed following a stakeholder workshop that an MTA of bisphosphonates for preventing osteoporotic fragility fractures should be scheduled into the work programme as a priority, and that an MTA of non-bisphosphonates treatments should be scheduled to start as the bisphosphonates MTA published its final appraisal determination. The scope has been updated to clarify this. NICE Technology Appraisal guidance 204 recommends denosumab for people who cannot take alendronate, risedronate or etidronate. A comparison between denosumab and the bisphosphonates will be considered as part of the non-bisphosphonates MTA. To include any or all non-

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			bisphosphonates as comparators would increase the size of this appraisal and would delay guidance development, without the benefit of providing recommendations for those non-bisphosphonates. Because stakeholders emphasised the urgency for updated guidance on bisphosphonates, only these drugs will be included in this appraisal.
	Healthcare Improvement Scotland	Strontium ranelate, teriparatide or denosumab – why are these not included in the remit?	Comment noted. It was agreed following a stakeholder workshop that an MTA of bisphosphonates for preventing osteoporotic fragility fractures should be scheduled into the work programme as a priority, and that an MTA of non-bisphosphonates treatments should be scheduled to start as the bisphosphonates MTA published its final appraisal determination. Strontium ranelate, teriparatide and denosumab will be considered as part of the non-bisphosphonates MTA, which will include comparison with bisphosphonate treatments. The scope has been updated to clarify this.
		Is there a role for assessing calcium and vitamin D (together or possibly alone)	Based on comments from consultation, it was agreed that calcium and vitamin D did not need to be considered as comparators but

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			could be considered as part of 'no active treatment' and bisphosphonates, as a supplement.
		Adherence is a major issue both with bisphosphonates & Calcium & Vit D tablets. Is there data on measures to help? How do oral therapy to iv therapy compare?	The scope has been updated to state that if evidence allows, the impact of treatment duration and adherence on costs and outcomes will be considered.
	National Osteoporosis Society	The scope states that no active treatment will be used for a comparator. However, for some of the glucocorticoid induced osteoporosis studies an active comparator was used (risedronate versus zoledronic acid, alendronate versus teriparatide).	Comments noted. The Appraisal Committee will consider the evidence available in its decision making.
		Denosumab may be considered as a comparator for Zolendronate.	It was agreed following a stakeholder workshop that an MTA of bisphosphonates for preventing osteoporotic fragility fractures should be scheduled into the work programme as a priority, and that an MTA of non-bisphosphonates treatments should be scheduled to start as the bisphosphonates MTA published its final appraisal determination. Denosumab will be considered as part of the non-bisphosphonates MTA, which will include comparison with bisphosphonate treatments. The scope has been updated to clarify

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			this. To include any or all non-bisphosphonates as comparators would increase the size of this appraisal and would delay guidance development, without the benefit of providing recommendations for those non-bisphosphonates. Because stakeholders emphasised the urgency for updated guidance on bisphosphonates, only these drugs will be included in this appraisal.
	ScHARR-TAG	Raloxifene, strontium ranelate, teriparatide and denosumab could all be considered to be competing interventions in some of the patients in whom bisphosphonate could be recommended. It would therefore be best practice, from a health economic methodology perspective, to conduct an incremental cost-effective analysis including these comparators. We would ask that NICE make the rationale for excluding these non-bisphosphonate comparators clearer in the final scope. One rationale for excluding them as comparators is that existing NICE guidance restricts their use to patients who cannot take bisphosphonates and therefore they are not competing interventions in the same population. Taking this approach would effectively assume that the Committee's previous conclusions on the optimal sequencing of interventions would not be altered by any change in the evidence base or list prices since TA160, TA161 and TA204 were completed. We would expect, based on our previous work in this area and from examining current list prices, that this assumption would hold true. This assumption could be re-examined when the update for non-bisphosphonate	Comments noted. It was agreed following a stakeholder workshop that an MTA of bisphosphonates for preventing osteoporotic fragility fractures should be scheduled into the work programme as a priority, and that an MTA of non-bisphosphonates treatments should be scheduled to start as the bisphosphonates MTA published its final appraisal determination. Strontium ranelate, raloxifene, teriparatide and denosumab will be considered as part of the non-bisphosphonates MTA, which will include comparison with bisphosphonate treatments. The scope has been updated to clarify this. To include any or all non-bisphosphonates as comparators

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		osteoporosis interventions is conducted following completion of this appraisal. Splitting the decision problem into two separate MTAs in this manner also has the advantage of making the process more manageable.	would increase the size of this appraisal and would delay guidance development, without the benefit of providing recommendations for those non-bisphosphonates. Because stakeholders emphasised the urgency for updated guidance on bisphosphonates, only these drugs will be included in this appraisal.
Outcomes	Healthcare Improvement Scotland	Yes	Noted.
	Healthcare Improvement Scotland	If possible the outcomes should relate to those fractures associated with the greatest morbidity and mortality i.e. hip and vertebral fractures. For some of the rarer but potentially important side-effects such as atypical femoral fractures and osteonecrosis of the jaw the use of an easily understood comparator index such as number needed to treat/number needed to harm would be useful.	Comments noted. The type of fracture should be captured within 'osteoporotic fragility fracture'. The risk of different fracture types and the associated costs and health impact can be considered as part of the appraisal process, if considered relevant by the Appraisal Committee. No changes required to the scope. Atypical femoral fractures and osteonecrosis of the jaw should be captured within adverse effects of treatment. No changes required to the scope.
	Healthcare Improvement Scotland	If health economics is being rigorously applied, I think they will – but there is a major difference between a Colles fracture of the wrist & a hip fracture. Should hospital admission/ need for surgery be included?	Comment noted. The type of fracture should be captured within 'osteoporotic fragility fracture'. The risk of different fracture types, and the associated costs and health

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			impact, can be considered as part of the appraisal process, if considered relevant by the Appraisal Committee. No changes required to the scope.
	Merck Sharp & Dohme Ltd	MSD believe discontinuation should be added to the outcomes. Under the outcome adverse effects of treatment, gastrointestinal side effects should be included.	Comments noted. The scope has been updated to state that if evidence allows, the impact of treatment duration and adherence on costs and outcomes will be considered. Gastrointestinal side effects should be captured within adverse effects of treatment. No changes required to the scope.
	National Osteoporosis Society	An appropriate range of outcomes has been identified in the scope however it would be useful to provide detail on what constitutes 'treatment adherence'; how it is measured and what thresholds will be used to define adherence?	Comment noted. The scope has been updated to state that if evidence allows, the impact of treatment duration and adherence on costs and outcomes will be considered. How to measure adherence and apply thresholds can be considered as part of the appraisal process, if the Appraisal Committee consider it relevant to the decision making.
	ScHARR-TAG	Yes	Noted.
Economic analysis	Healthcare Improvement	2, 3, 5 10 years where data available Economic benefits for age bands to be considered 40-50, 50-	Comments noted. The scope has been updated to state that if

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	Scotland	60, 60-70, 70-80, 80-90, 90-100	evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes should be considered. Age is taken into account when determining fracture risk and therefore will be considered in this context.
	Healthcare Improvement Scotland	No issues	Noted.
	Healthcare Improvement Scotland	none	Noted.
	National Osteoporosis Society	We agree that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between technologies being compared. We will be interested to see what time horizons emerge from the analysis.	Comment noted.
	ScHARR-TAG	We have some comments related to the linking of absolute fracture to interventions thresholds which are provided below under 'any additional comments'.	Comment noted.
Equality	Healthcare Improvement Scotland	Can data from studies of Caucasians be extrapolated to Asians or Africans? Is subgroup data available so that these extrapolations can be made?	Comment noted. The Appraisal Committee will consider all relevant available evidence in its decision making. Any evidence on differences in effectiveness of the interventions according to race will be taken into

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			account if considered relevant to the decision making. No changes to the scope required.
	Healthcare Improvement Scotland	The oral bisphosphonates have a strict regime for how to take the medication. This leads to the risk of under-treating certain groups of patients such as those with a cognitive impairment or learning difficulties. Many of these patients have both osteoporosis and a significant falls risk. Options may include parenteral treatment (zoledronate, ibandronate or denosumab) or for some patients more careful supervision of how they take their medication.	Comment noted.
	Healthcare Improvement Scotland	none known	Noted.
	National Osteoporosis Society	Previous guidance has only pertained to the treatment of postmenopausal women. Clarification of the term 'adults' used in the draft scope, and broadening the target population to include men and premenopausal women would be welcome and avoid inequitable access to treatment.	Comments noted. The population in the scope has been updated to state: 'adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146'. The population is defined by the guideline, which includes men, and therefore reflects the license extensions of many of the treatments.
		Some groups will have difficulty adhering to the complex instructions for taking oral bisphosphonates and their benefit from these treatments may be compromised. E.g. people with dementia, learning disabilities; those unable to remain upright for the specified time period; and patients in whom oral bisphosphonates might be contraindicated such as those with	The scope has been updated to state that if evidence allows, the impact of treatment duration and adherence on costs and outcomes will be considered. Potential equality issues relating to groups protected by the equality legislation, such as

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		oesophageal stricture.	people who have a disability, will be considered as part of the appraisal process.
	ScHARR-TAG	No comments on this section.	Noted.
Other considerations	Healthcare Improvement Scotland	It will be important to give guidance on duration of therapy with oral bisphosphonates.	Comments noted. The scope has been updated to state that if evidence allows, the impact of treatment duration and adherence on costs and outcomes will be considered.
	Healthcare Improvement Scotland	See above & below	Noted.
Questions for consultation	Healthcare Improvement Scotland	So that more people benefit from bisphosphonates public and GP awareness of the morbidity and mortality of osteoporosis needs to be increased Benefits of bisphosphonates in reducing morbidity and mortality need greater emphasis Reduction in need for funded and unfunded carer support for affected individuals with OP that fracture The cost of osteoporotic fractures in the UK: projections for 2000–2020 2001, Vol. 4, No. 1-4 , Pages 51-62 Russel T Burge PhD12 , Dan Worley BSc1 , Antony Johansen MA MRCP3 , Samir Bhattacharyya PhD1 and Uday Bose MSc4 Read More: http://informahealthcare.com/doi/abs/10.3111/200104051062	Comments noted.
	Healthcare	Bisphosphonates are an established treated for osteoporosis.	Comment noted. This appraisal will

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	Improvement Scotland	However the most appropriate method in which to use them remains less clear. Particular questions include intervention thresholds e.g. 10 year fracture risk and how long treatment should be continued especially in those <80 years old. The economic analysis should address whole system costs eg McLellan, A.R., Wolowacz, S.E., Zimovetz, E.A., Beard, S.M., Lock, S., McCrink, L., et al. (2011). Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporosis International, 22 (7):2083-2098. This may not be accounted by simply quoting QALYs.	consider the most appropriate clinical and cost effective way to use bisphosphonates.
	Healthcare Improvement Scotland	Isn't the word "sufficiently" needed before "innovative"? If so, Yes! The main current issues are whether iv therapies have something to offer (accepting that many patients who are prescribed oral bisphosphonates won't take them)	Comments noted. The innovative nature of the technologies will be considered as part of the appraisal process.
		Data on need to use Ca +Vit D alongside bisphosphonates is important	Based on comments from consultation, it was agreed that calcium and vitamin D did not need to be considered as comparators but could be considered as part of 'no active treatment' and a supplementary treatments to the bisphosphonates.
		I have v limited expertise in this area – but there is a need to consider that old ladies who may care for their elderly relatives may suffer quite far reaching consequences of their falls	The impact of fracture in terms of costs and outcomes (including quality of life impact) will be considered as part of the appraisal

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		n/a n/a In 2012, NICE Clinical Guideline 146 recommended FRAX or QFracture as the main tools for assessing fracture risk. Since then, have any other tools become established in clinical practice? Are any other tools, or factors, considered similarly important for decision making? If so, what are they? We don't use any others Have all relevant comparators for bisphosphonates and manufacturers been included in the scope? Should calcium and vitamin D supplements be included as comparators? Yes; role of addressing risk factors perhaps along with ca + vit d Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Steroid treated pts	process. Comment noted Based on comments from consultation, it was agreed that calcium and vitamin D did not need to be considered as comparators but could be considered as part of 'no active treatment' and bisphosphonates, as supplements. The population included in the scope has been updated to state: 'adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146'. The MTA will therefore consider absolute fracture risk, (as recommended by Clinical Guideline 146), which takes into account steroid use. In addition, the scope now states 'If evidence allows, subgroups based on patient

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			characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146, and include steroid use) or that affect the impact of fracture on lifetime costs and outcomes should be considered.
	Merck Sharp & Dohme Ltd	Specific questions for consultation Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? It is expected that the sub-group analysis would include the following subgroups: men and women primary and secondary prevention of osteoporotic fragility fracture absolute risk of fracture	Comments noted. The population included in the scope has been updated to state: 'adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146'. The MTA will therefore consider absolute fracture risk (as recommended by Clinical Guideline 146), which takes into account sex and prior fracture. In addition, the scope now states 'If evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146, and include sex and prior fracture) or that affect the impact of fracture on lifetime costs and outcomes should be considered.
		Where do you consider these technologies will fit into the existing NICE osteoporosis pathway? Current NICE guidance recommends alendronate as first-line therapy. For women who cannot take alendronate, then primarily a second bisphosphonate is recommended as second-line treatment. MSD recommend that	Comments noted.

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		bisphosphonates as a class (i.e. those included in this MTA) should be considered as first-line therapy. If someone cannot take a bisphosphonate, then another bisphosphonate should not be considered as second-line therapy.	
	National Osteoporosis Society	We do not feel that calcium and vitamin D need to be used as comparators. These technologies fit into the existing NICE osteoporosis pathway under primary and secondary prevention of fractures.	Comments noted. Based on comments from consultation, it was agreed that calcium and vitamin D did not need to be considered as comparators but could be considered as part of 'no active treatment' and bisphosphonates as supplements. Comment noted
	ScHARR-TAG	No comments on this section.	Noted.
Any additional comments on the draft scope	Healthcare Improvement Scotland	In 2012, NICE Clinical Guideline 146 recommended FRAX or QFracture as the main tools for assessing fracture risk. Since then, have any other tools become established in clinical practice? Are any other tools, or factors, considered similarly important for decision making? No. Limitations of FRAX need to be made more clear. Should calcium and vitamin D supplements be included as comparators? Seasonal variation in Vit D make it a complex comparator.	Comments noted. Based on comments from consultation, it was agreed that calcium and vitamin D did not need to be considered as comparators but could be considered as part of 'no active treatment' and bisphosphonates as supplements.

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		Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Those with previous fracture risk.	The scope has been updated to state 'If evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146, which includes prior fracture) or that affect the impact of fracture on lifetime costs and outcomes should be considered.
	National Osteoporosis Society	The term "osteoporotic fragility fracture", used throughout, should be changed to "fragility fracture", since T-scores are being replaced by fracture probability. Fragility fracture was the term used in the clinical guideline on risk assessment. While not the focus, more detail on how to define and ensure patients are calcium and vitamin D replete as listed in NICE TA160/161 is needed	Comments noted. Fragility fractures may occur because of causes other than osteoporosis, therefore for clarity 'osteoporotic' has been included in the scope. No changes required.
	Healthcare Improvement Scotland, Dr Hunter	There is the issue on how to monitor such therapies after starting them, whether there is any significant concern over jaw necrosis or long bone fractures after yrs of therapy – and therefore how to tail them off	Comment noted, where the evidence allows adverse events and duration of treatment will be taken into consideration.
	SCHARR	The review proposal states that one of the intended outcomes of this MTA is to "develop the framework to link absolute fracture risk with intervention thresholds". We would like to draw your attention to the 2013 NICE Decision Support Unit (DSU) report by Stevenson which concluded that, "it does not appear straightforward to generate an algorithm based on	Comments noted. The NICE Decision Support Unit[1] suggested that there were limitations to generating an algorithm, based only on absolute fracture risk (defined by either FRAX or Q Fracture), to

[1] Stevenson, M. Assessing the feasibility of transforming the recommendations in ta160, ta161 and ta204 into absolute 10-year risk of fracture, NICE Decision Support Unit, May 2013. http://www.nice.org.uk/guidance/ta204/resources/ta204-technologies-for-the-primary-and-secondary-prevention-of-osteoporotic-fractures-appendix-c-decision-support-unit-report2

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		absolute fracture risk (including ratio of hip to major fractures) that could robustly predict a positive recommendation in TA160 or TA161".1 The factors driving this conclusions are already expressed in detail in the DSU report, but to put it briefly, the problem lies in the fact that one unique value for absolute fracture risk can arise in a multitude of ways by using different combinations of risk factors (such as age, BMD, previous fracture, current smoking etc) but each of these will impact differently on the cost-effectiveness of treatment. Therefore selecting a group of patients for treatment based on the fact that they have the same absolute fracture risk may lead to cost-effective treatment for some and cost-ineffective treatment for others in the group resulting in an inefficient allocation of NHS resources. It may be that NICE is willing to accept a certain degree of inefficiency in the allocation of resources in order to achieve a simple set of treatment thresholds which link with the existing recommendations for fracture assessment in CG146. If this is the case then it would be helpful for this to be stated explicitly in the scope as it requires the assessment group to deviate from the approach taken previously in which treatment threshold were defined using multiple factors which determine cost-effectiveness (age, T-Score, number of risk factors) rather than a single absolute risk score. Furthermore, it should be noted that the assessment group anticipates that it may be difficult to populate a model in which subgroups are defined using a common value for absolute risk but where there is heterogeneity in risk factors within those subgroups as this requires detailed epidemiological data on the prevalence of the risk factors used to determine absolute risk including any correlations between risk factors. Stevenson. Assessing the feasibility of transforming the recommendations in TA160, TA161 and TA204 into absolute	robustly predict the cost effectiveness of interventions, and that these limitations could be overcome by using pragmatic and simplifying approaches. This MTA will establish the acceptability of such simplifying approaches.

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		10-year risks of fracture. A report produced by the Decision Support Unit in the context of the review proposal forTA160 /1 and TA204. 2013. Sheffield, NICE Decision Support Unit, The University of Sheffield.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Primary Care Rheumatology Society
The Royal College of Pathologists