National Institute for Health and Clinical Excellence

Osteoporosis
Guideline Consultation Comments Table
09.02.12 – 08.03.12

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
1	Crohn's in Childhood Research Association	3.00				Below you will find two general comments in response to the Osteoporosis Guideline consultation. We appreciate that at this stage we have not completed the special reply form but in view of the nature of our comments we are not sure in which section they should be included ? - We realise that peadiatrics (under 18s) are not within the scope of this important developing guideline and are concerned they will be forgotten given the increasing numbers with chronic conditions, including inflammatory bowel disease(IBD) and where the use of "steroids" and low BMI is a real risk. - While we can understand that you may consider the numbers small for those affected it can be "a life sentence" and so within the new Guidelines there should at least be a reminder to physicians about the risk in specific peadiatric populations. Given the undulating nature of some chronic conditions like IBD where "steroids" are used there is additionally a need for physicians to take account of the accumulating effect especially where children have been prescribed courses of treatment before 18 years of age and then are re-prescribed from time to time as	Thank you for your comment. We understand your concerns, however, paediatric populations was outside the scope of this guideline.

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						the years pass. This is often overlooked. We thank you for offering us the opportunity to comment.	
2	National Osteoporosis Society	5.00	General	-	-	The National Osteoporosis Society welcomes the development of a short clinical guideline on 'Osteoporosis: assessing the risk of fragility fracture'. Introducing assessment of 10 year fracture probability for determining intervention thresholds, with integration of BMD and clinical risk factors, is a major step forward for patient management.	Thank you for your comment.
3	National Osteoporosis Society	5.01	General	-	-	We hope that this will provide a foundation for NICE to produce comprehensive guidance for the management of all patients with osteoporosis and/or at risk of fragility fractures.	Thank you for your comment.
4	NETSCC, HTA Ref 1	6.00	Full			**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** The authors seem to have fulfilled what they planned to do.	Thank you for your comment.
5	NETSCC, HTA Ref 1	6.01	Full			**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** The authors seem to have identified the key epidemiological studies in the area.	Thank you for your comment.
6	NETSCC, HTA Ref 1	6.02	Full			**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise** The economic evaluation is somewhat simplistic.	Thank you for your comment. The economic analysis did not consider future costs and effects related to treatment because such economic work requires complex analysis which was not

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						Whilst a full economic evaluation tracking through patients who are screended, get treatment and modeling fracture effects, future costs QALYs gained etc is a big undertaking, I think extending the economic work to include likely pharmaceutical costs of treatment would be useful. I think we have two scenarios, we could prescribe treatment on the basis of predicted FRAX (no BMD) or QFracture risk or prescribe treatment including referral with BMD. If you assume the 'standard' treatment is alendronate, then what additional savings are possible by including avoiding prescribing to lower risk people. The SCOOP investigators will have data on how many FRAX patients have a BMD measurement and then go on to have treatment.	possible given the short guideline time frame. A cost effectiveness analysis would have to consider the number of patients referred for treatment after risk assessment, the number of fractures prevented with treatment, the age of patients, and the time frame for which cost savings would apply. We have contacted the SCOOP investigators, however the trial is currently in a five year follow-up phase and publication is not expected until 2014 or 2015.
7	NETSCC, HTA Ref 1	6.03	Full			**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Although this may be out of scope it feels that without some kind of discussion, at least, of the treatment options once at risk patients have been identified then it feels somewhat incomplete. Perhaps linking up to previous NICE reviews on treatment options may improve the report.	Thank you for your comment. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools for fragility fracture only. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
8	NETSCC, HTA Ref 1	6.04	Full			**3.2 Are any important limitations of the evidence clearly described and discussed?** As noted above I do wonder whether some comment on treatment options would be helpful.	Thank you for your comment. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools for fragility fracture only. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is

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							preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
9	NETSCC, HTA Ref 1	6.05	Full			**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence** Yes the report is well structured and easy to read	Thank you for your comment.
10	NETSCC, HTA Ref 1	6.06	Full			**4.2 Please comment on whether the research recommendations, if included, are clear and justified** I'm a bit surprised that in the research recommendations there is not a summary of ongoing research, especially a reference to the MRC's SCOOP study, which is testing the FRAX plus BMD strategy, in primary in a RCT. There probably are other ongoing studies that are relevant. Consequently, it would be helpful to identify ongoing major studies, such as SCOOP with an estimated date of when they will be reported.	Thank you for your comment. The SCOOP study (website link and published study protocol) has been added to the list of ongoing studies.
11	NETSCC, HTA Ref 1	6.07	Full			**Section five – additional comments** I think it may be worthwhile to contact Lee Shepstone (University of Norwich), who is the Chief Investigator of the SCOOP study to see if there is any data that could be provided at least to inform the proportions in the economic section of people identified as being at risk by FRAX who need a BMD. This would also indicate to GPs the likely volume of patients who would need treating if they decided to formally screen their patients using FRAX.	Thank you. We have contacted Professor Lee Shepstone following your comment. The trial is currently in a five year follow-up and publication is not expected until 2014 or 2015. However, we have found some data to inform the proportion of people referred for BMD after a FRAX assessment from a recent study by Johansson et al (2012) and we have added this information to the economic considerations and the discussion of the economic analysis.
12	NETSCC,	7.00	Full			**1.1 Are there any important ways in which**	Thank you for your comment.

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	HTA Ref 2					**the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** No	
13	NETSCC, HTA Ref 2	7.01	Full			**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** Good compliance	Thank you for your comment.
14	NETSCC, HTA Ref 2	7.02	Full			**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** No comments made	Thank you for your comment.
15	NETSCC, HTA Ref 2	7.11	Full			**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** Yes	Thank you for your comment.
16	NETSCC, HTA Ref 2	7.13	Full			**Section five – additional comments** Good consideration of the evidence and clear guideline production in general	Thank you for your comment.
17	Society and College of Radiographers	8.02		General		Recommendations regarding steroid use. Does reference to Addison's disease need to be highlighted? Treatment with steroids brings their physiological levels to a normal level due a deficiency of cortisol (steroid hormone) thus these patients may not develop osteoporosis due to steroid therapy.	Thank you for your comment. Patients with Addison's disease are treated with a combination of mineralocorticoids and glucocorticoids and can usually be identified by this combination. The GDG did not consider that specific reference was required to this group.
18	Society and College of Radiographers	8.03		General		It is disappointing that there is no inclusion or any reference to case finding by vertebral fracture at all as requested.	Thank you for your comment. The remit for the guideline was risk assessment and not case finding. The GDG agree that a vertebral fracture should prompt assessment of fragility fracture risk but considered that diagnosis of vertebral fracture was a separate topic. We have added to

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							the text of the guideline that loss of height and kyphosis should prompt healthcare professionals to consider vertebral fracture.
19	Society and College of Radiographers	8.04		General		The guidelines seem to be focused on limiting BMD (as if that was the reason for the cost). Our interpretation of the guidelines, is "if they qualify for an intervention based on an algorithm without BMD, do a BMD to see if we might be able to lower that risk and NOT intervene." No possibility for reclassification in the other direction if they are close, but below, the intervention threshold without BMD.	Thank you for your comment. The wording of the recommendation is 'in the region of an intervention threshold' which we intend to mean either above or below the threshold level. The limited evidence on reclassification is that people are reclassified both above and below the threshold level. People therefore can be reclassified from above to below the threshold or from below to above the threshold. Further detail on this can be found in section 4.4 of the Full guideline
20	Society and College of Radiographers	8.05		General		We are surprised that there is no consideration of the added prognostic value of BMD in the assessment of fracture risk with FRAX? When there are many, many studies already addressing that exact question.	Thank you for your comment. We have included the available evidence on the predictive value of FRAX with and without BMD in this guideline. Most studies reported area under the curve (with some data on sensitivity and specificity) and we did not find significant differences between them. The preferable way of evaluating the added prognostic value of risk factor(s) to a model is reclassification studies, such as net reclassification improvement and this data is limited.
21	Spinal Injuries Association	9.00	Full	General		The Spinal Injuries Association (SIA) welcomes the opportunity to comment on the NICE 'Osteoporosis fragility fracture risk: guideline consultation'.	Thank you for your comment.
22	Spinal Injuries Associati	9.07	Full	General		SIA is very disappointed that there is no consideration of spinal cord injury in the document, despite the very high incident of	Thank you for your comment. The GDG acknowledge there is a variety of causes of secondary osteoporosis, and they could not all be

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	on					fragility fractures in this group. If the reason is a lack of research of sufficient quality to be considered by NICE, SIA believes that this lack of research should be noted, and recommendations for appropriate research be made.	considered singularly in the guideline. The GDG discussed spinal cord injury as a risk factor for fragility fracture, and agreed this is not a risk factor per se, but it is the immobility that derives from spinal cord injury that increases the risk of fragility fracture. Immobility was already listed in the causes of secondary osteoporosis and we have expanded this to include 'immobility due to neurological injury or disease' to the list of causes of secondary osteoporosis.
23	Bone Research Society, the	10.00		General		We welcome this draft SCG from NICE and believe that it will have a major impact on awareness of, and access to, appropriate fracture risk assessments in primary and secondary care.	Thank you for your comment.
24	Bone Research Society, the	10.01		General		A major deficit in the Guideline is that there is no consideration of the evidence for reversibility of risk identified by the assessment algorithms which is a critical component in the choice of risk factors [Kanis 2008a, 2012a]	Thank you for your comment. We acknowledge the importance of reversibility of risk when exploring treatment options with a patient. The GDG do not agree that reversibility of risk is the main factor to consider when assessing risk as e.g. age and gender are most important risk factors and are not reversible. Reversibility of risk may be correlated to response to treatment, and treatment is outside the remit of the guideline.
25	Bone Research Society, the	10.02		General		Simplicity is key and the introduction of a number of age thresholds may cause unnecessary confusion.	Thank you for your comment. The GDG reviewed the recommendations in light of your comment but consider that age stratification is appropriate given the important influence of age on risk.
26	Bone Research Society, the	10.37				**References** Borgström F, Strom O, Coelho J et al (2010a) The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis.	Thank you for this list of references.

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						McCloskey EV **Kanis JA** (2012a) High fracture probability with FRAX® usually indicates densitometric osteoporosis: Implications for clinical practice. Osteoporosis International 23: 391-397. Leslie WD, Morin S, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA (2012b) Manitoba Bone Density Program. Fracture risk assessment without bone density measurement in routine clinical practice. Osteoporos Int. 23: 75-85. Papaioannou A, Morin S, Cheung AM et al (2010) 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 182: 1864-73 Ström O, Borgström F, Kleman M, McCloskey E, Odén A, Johansson H, Kanis JA (2010) FRAX® and its applications in health economics - Cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example. Bone. 2010 47::430-7.	
27	Department of Health	11.00				I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
28	British Society for Rheumatology	12.00		General		We welcome this draft SCG from NICE and believe that it will have a major impact on awareness of, and access to, appropriate fracture risk assessments in primary and secondary care.	Thank you for your comment.
29	British	12.0		Gener		A major deficit in the Guideline is that there is	Thank you for your comment. We acknowledge

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	Society for Rheumatology	1		al		no consideration of the evidence for reversibility of risk identified by the assessment algorithms which is a critical component in the choice of risk factors [Kanis 2008a, 2012a]	the importance of reversibility of risk when exploring treatment options with a patient. The GDG do not agree that reversibility of risk is the main factor to consider when assessing risk as e.g. age and gender are most important risk factors and are not reversible. Reversibility of risk may be correlated to response to treatment, and treatment is outside the remit of the guideline.
30	British Society for Rheumatology	12.02		General		Simplicity is key and the introduction of a number of age thresholds may cause unnecessary confusion.	Thank you for your comment. The GDG reviewed the recommendations in light of your comment but consider that age stratification is appropriate given the important influence of age on risk.
31	British Society for Rheumatology	12.41	Full	General		The guideline document seems to be about taking a risk factor calculator (such as FRAX) and surrounding its use by various restrictions and protocols. This is not the way forward for risk calculation. Any additional algorithms need to be INTERGAL to the calculator so that GPs and others do not have to remember extra rules. Qfracture should not be considered any further. NICE should support the development of FRAX as a stand alone calculator with nationally agreed (signed up to by NICE) intervention thresholds.	Thank you for your comment. The recommendations in the guideline are intended to guide healthcare professionals in optimum use and interpretation of risk assessment. They are intended to guide generalists who use the calculators using expert knowledge of the guideline development group following the review of evidence. We agree that ideally all factors important for risk assessment and any adjustments to risk factors should be integral to a calculator. The addition of factors to a calculator require that the developers of the calculator analyse the effect of the additional factors and validate the new algorithm. When developing NICE guidance we can only make reference to the risk tool as it is currently validated. It is unlikely however that any model will account for all circumstances. We acknowledge your suggestion that Qfracture

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							should not be considered further and that NICE should support the development of FRAX. NICE guideline methods require consultation with stakeholders and the appraisal of existing literature. Stakeholders at scoping stage of this guideline requested inclusion of Qfracture for assessment and appraisal of literature for the guideline indicated that it is appropriately developed and validated. NICE does not support the development of specific tools. .
32	British Society for Rheumatology	12.42				**References** Borgström F, Strom O, Coelho J et al (2010a) The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis. Osteoporosis International 21: 339-350 Borgström F, Ström O, Coelho J et al (2010b) The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX. Osteoporosis International 21: 495-505. Borgström F, Ström O, Kleman M et al (2011) Cost-effectiveness of bazedoxifene incorporating the FRAX® algorithm in a European perspective. Osteoporosis International 22: 955-65. de Lusignan S, Valentin T, Chan T et al (2004) Problems with primary care data quality: osteoporosis as an exemplar. Inform Prim Care 12:147–156 Hippisley-Cox J, Coupland C (2009) Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ.	Thank you for this list of references.

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						using bazedoxifene in a Swedish setting as an example. Bone. 2010 47::430-7.	
33	UK Clinical Pharmacy Association	15.00				We have no comments to make on the draft guidelines.	Thank you for your comment.
34	British Thoracic Society	16.08	Full			We note that CF is mentioned in the footnotes as a secondary cause of osteoporosis more than once. We suggest that it would be useful to include a reference to the guidelines for CF Low Bone Mineral Density.	Thank you for your comment. We have added reference to the CF guidelines on Low Mineral Density to the Full guideline but consider that the care of people with cystic fibrosis is a specialist topic.
35	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.08	Full	General		No data on effective interventions has been included in this guideline. This would be both important and useful in determining the utility of all risk assessments.	Thank you for your comment. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools for fragility fracture only. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
36	Julia Hippisley-Cox, Carol Coupland	18.09				The authors of this review are also the authors of the QFracture.	Thank you for your comment and clarification.

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37	Cambridge University Hospitals NHS Foundation Trust	19.05		General		The most important omissions are the web links to FRAX and Qfracture.	Thank you for your comment. Web links to FRAX and QFracture are included in the footnotes to the recommendation.
38	Cambridge University Hospitals NHS Foundation Trust	19.06		General		On the algorithm 2.3, please make the following sentence bold "**Following BMD measurement, recalculate absolute risk using FRAX with BMD**". Consider changing it to ".**Following BMD measurement, recalculate absolute risk by entering the femoral neck BMD value into FRAX.**", since only the actual BMD value for the femoral neck provides the correct risk in men. Consider adding the following sentence "Then follow the relevant national treatment guidance"	Thank you for your comment. The sentences the GDG made bold are the key messages of the guideline, that are: - the importance of calculating absolute risk (versus relative risk); - the first step of the risk assessment does not include BMD measure. Making more sentences bold would dilute the key messages. Treatment is outside the remit of this short guideline, therefore recommendations about treatment cannot be made.
39	Sheffield Teaching Hospitals NHS Foundation Trust	20.00		General		We welcome this draft SCG from NICE and believe that it will have a major impact on awareness of, and access to, appropriate fracture risk assessments in primary and secondary care.	Thank you for your comment.
40	Sheffield Teaching Hospitals NHS Foundation Trust	20.01		General		A major deficit in the Guideline is that there is no consideration of the evidence for reversibility of risk identified by the assessment algorithms which is a critical component in the choice of risk factors [Kanis 2008a, 2012a]	Thank you for your comment. We acknowledge the importance of reversibility of risk when exploring treatment options with a patient. The GDG do not agree that reversibility of risk is the main factor to consider when assessing risk as e.g. age and gender are most important risk factors and are not reversible. Reversibility of risk may be correlated to response to treatment,

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							and treatment is outside the remit of the guideline.
41	Sheffield Teaching Hospitals NHS Foundation Trust	20.02		General		Simplicity is key and the introduction of a number of age thresholds may cause unnecessary confusion.	Thank you for your comment. The GDG reviewed the recommendations in light of your comment but consider that age stratification is appropriate given the important influence of age on risk.
42	Sheffield Teaching Hospitals NHS Foundation Trust	20.37				**References** Borgström F, Strom O, Coelho J et al (2010a) The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis. Osteoporosis International 21: 339-350 Borgström F, Ström O, Coelho J et al (2010b) The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX. Osteoporosis International 21: 495-505. Borgström F, Ström O, Kleman M et al (2011) Cost-effectiveness of bazedoxifene incorporating the FRAX® algorithm in a European perspective. Osteoporosis International 22: 955-65. de Lusignan S, Valentin T, Chan T et al (2004) Problems with primary care data quality: osteoporosis as an exemplar. Inform Prim Care 12:147–156 Hippisley-Cox J, Coupland C (2009) Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ. 339:1291-1295	Thank you for this list of references.

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						Ivergård M, Ström O, Borgström F, Burge RT, Tosteson ANA, Kanis JA (2010) Identifying cost-effective treatment with raloxifene in postmenopausal women using risk algorithms for fractures and invasive breast cancer. Bone 47, 966-974 Jiang G, Eastell R, Barrington NA, Ferrar L (2004) Comparison of methods for the visual identification of prevalent vertebral fracture in osteoporosis. Osteoporos Int 2004;15:887–96. Johansson H, Kanis JA, Oden A, Johnell O, McCloskey E (2009) BMD, clinical risk factors and their combination for hip fracture prevention. Osteoporos Int. 20: 1675-1682. Johansson H, Kanis JA, Oden A, Johnell O, Compston J, McCloskey EV (2011) A comparison of case finding strategies in the UK for the management of hip fractures. Osteoporos Int. . Jan 11. [Epub ahead of print] PubMed PMID: 22234810 Jönsson B, Ström O, Eisman JA et al (2011) Cost-effectiveness of denosumab for the treatment of postmenopausal osteoporosis. Osteoporosis International 22: 967-821. PMID: 20936401 Kanis JA, Johnell O, Oden A et al (2000) Long-term risk of osteoporotic fractures in Malmo. Osteoporisis International 11; 669-674. Kanis JA, Borgstrom F, De Laet Cet al (2005) Assessment of fracture risk. Osteoporosis International; 16: 581-589. Kanis JA, Oden A, Johnell Oet al (2007) The	

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						use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int. 18: 1033-1046 Kanis JA on behalf of the World Health Organization Scientific Group (2008a) Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK. Kanis JA, Adams J, Borgstrom F et al (2008b) The cost-effectiveness of alendronate in the management of osteoporosis. Bone 42: 4-15. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, Khaltaev N (2008c) A reference standard for the description of osteoporosis. Bone, 42:467-475. Kanis JA, Johansson H, Oden A, McCloskey EV (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX®.Bone 2009;44:49–54. Kanis JA, Johansson H, Oden A, McCloskey EV (2010a) A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX. Bone. 47: 729-35. Kanis JA, Hans D, Cooper C et al and the Task Force of the FRAX Initiative (2011a) Interpretation and use of FRAX in clinical practice. Osteoporosis International 22: 395-411.	

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						Kanis JA, Johansson H, Oden A, McCloskey EV (2011b) Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporosis International 22:809–816 Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD (2012a) FRAX® with and without BMD. Calcified Tissue International 90: 1-13. Kanis JA, Oden A, Johansson H, McCloskey E (2012b) Pitfalls in the external validation of FRAX. Osteoporosis International 23: 423-31 Leslie WD, Majumdar SR, Lix L, Johansson H, McCloskey EV **Kanis JA** (2012a) High fracture probability with FRAX® usually indicates densitometric osteoporosis: Implications for clinical practice. Osteoporosis International 23: 391-397. Leslie WD, Morin S, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA (2012b) Manitoba Bone Density Program. Fracture risk assessment without bone density measurement in routine clinical practice. Osteoporos Int. 23: 75-85. Papaioannou A, Morin S, Cheung AM et al (2010) 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 182: 1864-73 Ström O, Borgström F, Kleman M, McCloskey E, Odén A, Johansson H, Kanis JA (2010) FRAX® and its applications in health economics - Cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example. Bone. 2010 47::430-7.	

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43	RCGP	22.00	NICE	General		Osteoporosis (with fragility fractures) is an important condition to manage in primary care and the use of prediction risk scores opens up the discussion with patients about not only their risk but also lifestyle and medical interventions that could help reduce the risk of future fragility tests. It would be helpful for the NICE guidelines to explicitly state the limitations of these risk prediction tools (i.e. sensitivity , positive predictive value etc). Integrating the use of the tools with GP systems would be helpful and should be considered by IT providers and it is hoped that guidelines such as these would facilitate that possibility.	Thank you for your comment. A full discussion of the limitations of risk prediction tools is included in the Full guideline, chapter 4. We agree that integration of tools with GP systems would be helpful and that IT providers could consider this. This issue has been discussed with the NICE Implementation team.
44	British Pain Society	25.07	x	all	all	An important contribution of vitamin D deficiency to osteoporosis in white UK population has not been mentioned in the guidance at all. This important risk factor needs to be completely assessed for its contribution (See Hypoonen and Power, American Journal of Clinical Nutrition, Vol. 85, No. 3, 860-868, March 2007 for a very large cohort study) to determine whether the recommended tools integrate the risk of this important factor in determining treatment.	Thank you for your comment. The GDG acknowledge the importance of vitamin D deficiency but do not consider it is a trigger for risk assessment. Vitamin D deficiency is associated with osteomalacia which causes demineralisation of bone and its management is different from osteoporosis.
45	UCB Pharma Ltd	26.15	Full	General		Osteoporotic fragility fractures are a major public health problem in the UK. Understanding the aetiology of fragility fractures is important for creating broad and successful interventions to decrease the risk of fractures and improve the delivery of care. Such fragility fractures result in serious morbidity, disability, quality of life and mortality consequences.	Thank you for your comment. We agree with your observations and have acknowledged all your points in the introduction (chapter 1) of this guideline.
46	UCB	26.1	Full	Gener		Osteoporosis is amenable to treatment but	Thank you for your comment. We agree with your

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	Pharma Ltd	6		al		despite being recognized as a considerable public health problem, it is estimated that only a minority of patients are actively managed with respect to preventive strategies (even effective lifestyle measures) and treatment.	observation. Prevention and treatment are outside the remit of this short guideline, however, this guideline will increase awareness about osteoporosis and risk of fragility fracture. As more people will be assessed for risk of fragility fracture, more people will be appropriately managed and treated.
47	UCB Pharma Ltd	26.17	Full	General		To date, there is no national screening programme to identify patients with osteoporosis at increased risk of fracture in the UK. Rather, patients are identified opportunistically using a case finding strategy (using well documented risk factors and prior history of fragility fracture). The latter (opportunistic screening) is a suboptimal approach in identifying all patients at increased risk of fragility fracture who would benefit from effective lifestyle measures and approved medications.	Thank you for your comment. The GDG considered this an important topic and have made a research recommendation to assess the cost effectiveness of this approach as research recommendation 1.
48	UCB Pharma Ltd	26.18	Full	General		The poor prioritization and uptake of preventative care in osteoporosis needs to be highlighted. Diagnosis without appropriate lifestyle and therapeutic intervention has little merit. Incentivized screening at the primary care level and referral for specialist treatment (where appropriate) are the main drivers of change in this respect, which will require a specific policy directive at the national level in the UK.	Thank you for your comment. We acknowledge that this guideline is covering only part of a potential patient pathway. The remit for the guideline was confined to risk assessment of fragility fracture.
49	RCP	27.00				Please take this email as confirmation that the RCP has had sight of and wishes to endorse the separate submissions of the BSR and the BTS	Thank you for your comment.

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50	Amgen and GSK	28.00				 Comments Pro Forma - Amgen & GSK.pdf *(Have asked stakeholder to send in correct format and will add to the table when they do – AG)*	See 50 B-F below
50 B	Amgen and GSK					In addition to the high cost to the healthcare economy, it should also be noted that fractures represent a significant burden to the social care economy.	Thank you for your comment. This is noted in the introduction to the Full guideline.
50 C	Amgen and GSK					We suggest consideration of inclusion of measurement of height loss as an early screening tool for osteoporosis, as this is an indicator of vertebral fracture. All GP surgeries have a staediometer, which would facilitate easy implementation of this measure.	Thank you for your comment. We acknowledge the importance of height loss as a possible indicator of vertebral fracture. The GDG considered that the correct course of action if height loss is reported is to consider whether a vertebral fracture has occurred. Height loss can be age related and is not always an indication of vertebral fracture. We have added narrative about height loss in the evidence to recommendations for recommendation 2.
50 D	Amgen and GSK					NICE have recently published the osteoporosis QOF indicators. The algorithm within the short clinical guidelines should facilitate compliance with the QOF indicators and therefore the requirements should be consistent with those in QOF.	Thank you for your comment. Guidelines are developed according to the NICE Guidelines manual. QOF indicators will be reviewed and updated in line with new evidence. We have been in contact with the QOF developers to ensure they are aware of this guidance.
50 E	Amgen and GSK					The recently published osteoporosis QOF indicators could form a basis for case finding patients at risk. This will require accurate coding of fractures, or recommendations on the most appropriate fracture codes for GPs to use in	Thank you for your comment.

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						their systems.	
50 F	Amgen and GSK					Whilst there may be a question regarding the prognostic value of BMD in the assessment of fracture risk with FRAX, it should be noted that BMD thresholds are used in existing NICE guidance TA160, TA161 and TA204 as part of the criteria for initiation of therapies recommended by NICE, and as such the role of BMD measurement should not be underestimated.	Thank you for your comment. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
51	Costing, Audit and Education & Learning	29.00	NICE	General		It isn't completely clear who this guideline is aimed at. It will be difficult to implement if we can't establish who should use it. For example, presumably the guideline is relevant to older people's mental health services but I suspect that without this being explicit mental health trusts will assume that it's not relevant to them.	Thank you for your comment. This guideline is for all healthcare professionals and other staff who care for people at risk of fragility fracture. It is likely that most people will have risk assessment conducted by primary care. It offers best practice advice on the assessment of fragility fracture risk in adults.
52	Technical Adviser (HE)	32.04	full	General		While I recognise that subsequent treatment is outside the remit of the guideline, it is often considered in the economics if there are any recommendations that could result in additional costs downstream. Looking at the recommendations it appears that there would be no significant effect on downstream costs. And potentially lead to more focussed use of interventions and cost savings. This would be useful to mention as part of the economic assessment.	Thank you for your comment. We agree and we have added details about the potential of future cost savings associated with the appropriate use of risk assessment tools in relevant sections of the guideline.
53	ProStrakan Group	14.00	Full	37-41		Given the published time to treatment effect in many bone health interventions would it not be better to bring this risk assessment forward to 60+ so that there is time for effective treatment before significant deterioration of bone health sets in, which increases risk – a preventative strategy rather than a treatment approach.	Thank you for your comment. The GDG considered that the effect of pharmacological treatments on bone density is quite rapid and there are concerns about prescribing such drugs for long periods of time. They agreed therefore that assessment around the time of risk was appropriate.

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54	Julia Hippisley-Cox, Carol Coupland	18.05	Full	31-32		Fig 1-4 appear to display numbers of fractures rather than the incidence rate. It would be preferable to display the incidence rates as the denominators vary substantially by age and the graphs don't show how steeply the incidence rises by age.	Thank you for your comment. The GDG was interested in epidemiological data to establish at what age the fragility fracture rate starts increasing. The GDG's aim was to establish a cut-off age below which assessment of fragility fracture in people without risk factors is unlikely to generate a high score, therefore it is not necessary to carry out a risk assessment. The GDG considered that the graphical representation of number of fractures by age is a good indicator to obtain this information. For more clarity, we have changed the label to the Y-axis to read: 'number of incident cases'.
55	Julia Hippisley-Cox, Carol Coupland	18.07	Full	60-61	Last line	QFracture is also available for the iphone/ipad. http://itunes.apple.com/gb/app/qfracture/id503556749?mt=8 Can you add a reference to it here alongside the corresponding sentence for FRAX	Thank you for your comment, this has now been added to the guideline.
56	Bone Research Society, the	10.21	Full	44-45	Table 19-20	The tables omit the validation studies published by the WHO group [Kanis 2008a, 2007]. AUCs are reported for FRAX risk scores and adjusted for age and time since baseline (see comment to page 43, line 18).	Thank you for your comment, we have reviewed the references and the GDG believe these should not be included in the clinical review. In the Kanis 2007 paper it is not clear the data refers to the FRAX tool (which was released in 2008). The results report the gradient of risk and AUC for prediction of hip and other osteoporotic fractures on the basis of risk factors alone and risk factors plus BMD. The risk factors listed do not include secondary osteoporosis, which is included in FRAX. In addition, the ROC curves are adjusted for age, therefore not comparable with the other results reported in the guideline. The WHO Technical Report (Kanis 2008a): 'Assessment of osteoporosis at the primary

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							health-care level' was also published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf It reports the gradient of risk per SD change in risk score for clinical risk factors, BMD and combination of the two, all adjusted for age. Both studies are listed in Appendix C (paragraph C.5): Excluded studies.
57	British Society for Rheumatology	12.25	Full	44-45	Table 19-20	The tables omit the validation studies published by the WHO group [Kanis 2008a, 2007]. AUCs are reported for FRAX risk scores and adjusted for age and time since baseline (see comment to page 43, line 18).	Thank you for your comment, we have reviewed the references and the GDG believe these should not be included in the clinical review. In the Kanis 2007 paper it is not clear the data refers to the FRAX tool (which was released in 2008). The results report the gradient of risk and AUC for prediction of hip and other osteoporotic fractures on the basis of risk factors alone and risk factors plus BMD. The risk factors listed do not include secondary osteoporosis, which is included in FRAX. In addition, the ROC curves are adjusted for age, therefore not comparable with the other results reported in the guideline. The WHO Technical Report (Kanis 2008a): 'Assessment of osteoporosis at the primary health-care level' was also published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf It reports the gradient of risk per SD change in risk score for clinical risk factors, BMD and combination of the two, all adjusted for age. Both studies are listed in Appendix C (paragraph C.5): Excluded studies.
58	Sheffield Teaching	20.21	Full	44-45	Table 19-20	The tables omit the validation studies published by the WHO group [Kanis 2008a, 2007]. AUCs	Thank you for your comment, we have reviewed these references.

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	Hospitals NHS Foundation Trust					are reported for FRAX risk scores and adjusted for age and time since baseline (see comment to page 43, line 18).	In the Kanis 2007 paper it is not clear the data refers to the FRAX tool (which was released in 2008). The results report the gradient of risk and AUC for prediction of hip and other osteoporotic fractures on the basis of risk factors alone and risk factors plus BMD. The risk factors listed do not include secondary osteoporosis, which is included in FRAX. In addition, the ROC curves are adjusted for age, therefore not comparable with the other results reported in the guideline. To our knowledge, the WHO Technical Report: 'Assessment of osteoporosis at the primary health-care level' was also published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf It reports the gradient of risk per SD change in risk score for clinical risk factors, BMD and combination of the two, all adjusted for age.
59	Scottish Intercollegiate Guidelines Network	4.06		63-64	1	Recommendations 7 and 8 do not address people with serious vertebral osteoporosis who have a low fracture risk on FRAX (which does not include kyphosis or height loss). Those should be added to risk factors in recommendation 2.	Thank you for your comment. This was discussed at length by the GDG, and they believe the recommendations are applicable to people with vertebral osteoporosis. Kyphosis or height loss are not risk factors for fragility fractures per se, but are possible signs of vertebral fracture. Once the vertebral fracture has been correctly diagnosed (by X-ray), then it is possible to apply FRAX to assess fragility fracture risk, as vertebral fracture is considered part of 'prior fracture' item in FRAX. This has now been added to the evidence to recommendations section for recommendation 2.
60	British Medical	17.03	Full	11-12	3	Are there going to be local directives on these recommendations? If so, these may vary and	Thank you for your comment. This is an implementation issue which is outside the remit

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	Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee					future data assessing the value of the screening programme will be corrupted.	of this guideline. We would hope that any local directives would support implementation of the guideline but NICE are not directly involved in formation of local directives.
61	Editor	31.07	NICE	1.10		A further query that arose when discussing the UNG was whether the wording of this rec made it seem stronger than intended by the placement of the word 'only', so ruling out the possibility of reassessment in other circumstances rather than just suggesting when it should be considered. Should the stress perhaps be on the time between assessments? Perhaps: 1.10 Consider recalculating fracture risk: • if the original calculated risk was close to the intervention threshold for a proposed treatment and only after at least 2 years **or** • when there has been a change in the person's risk factors. Please check that this rec conveys the intended meaning and that the emphasis is correct.	Thank you for your comment, the recommendation has been amended to reflect your suggestion.
62	Editor	31.08	NICE	1.10		We say 'close to the intervention threshold' in this recommendation, but does this mean just below or does it also include just above as in rec 1.8 where it uses the term 'in the region of'.	Thank you for your comment. We have changed this to say 'in the region' of an intervention threshold.

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						Can this be clearer and/or the same term used?	
63	Editor	31.09	NICE	1.11		Should this say 'Take into account that FRAX and QFracture' rather than 'Take into account that risk assessment tools'? Is it based on the evidence for these specific risk assessment tools? It would also be more consistent with the wording of 1.12, which names the specific tools.	Thank you, the recommendation has been changed to reflect your suggestion.
64	Editor	31.01	NICE	1.3		Just a minor query for consistency and clarity: should the example of 'current or regular oral glucocorticoid use' mirror the wording in 1.2 'current use or frequent past use of glucocorticoids' or is a difference in meaning intended?	Thank you for your comment. We have altered both the recommendations to say 'current or frequent recent use of oral or systemic glucocorticoids'.
65	Editor	31.04	NICE	1.5		A very minor query, but should the age range here be between 40 and 85 years, i.e. up to 85 years?	Thank you for your comment. We have amended the recommendation to say 'within their allowed age range' and have specified the current age ranges for the two tools in the footnotes.
66	Editor	31.05	NICE	1.5		The full version explains that FRAX can be used with or without BMD. I wonder if it might help people unfamiliar with FRAX to include something similar in the footnote for this recommendation, e.g. FRAX, the WHO fracture risk assessment tool, is available from www.shef.ac.uk/FRAX. It can be used either with or without BMD results, as specified.	Thank you for your comment. The footnote has been amended to reflect your suggestion.
67	Editor	31.06	NICE	1.6		Is the wording of this recommendation clear enough? I wasn't sure if it meant use clinical judgement alone to assess a person's risk (that is, don't use an assessment tool) or to use clinical judgement to interpret fracture risk calculated by an assessment tool or either. Could this be clearer? E.g. '1.6 Use clinical judgement when assessing fracture risk in people of 85 years and over, either to assess risk or to interpret fracture risk	Thank you for your comment, the recommendation has now been reworded.

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						calculated by an assessment tool…' This came up at the editorial meeting when discussing the UNG.	
68	Costing, Audit and Education & Learning	29.02	NICE	1.8		The examples are helpful	Thank you for your comment.
69	Society and College of Radiographers	8.00		~~2.1~~ 12	9	What about patients with spinal injury under the age of 40 years? They are at significant risk of developing osteoporosis and so it may be appropriate to request a BMD assessment.	Thank you for your comment. Spinal injury is a cause of secondary osteoporosis (immobility due to neurological injury or disease). The GDG discussed this at length and did not consider that this group were at sufficiently high risk to recommend that all should be considered for BMD measurement.
70	Society and College of Radiographers	8.01		2.1	11	What about height loss and curvature of the spine? These can be indications of underlying undiagnosed vertebral fractures.	Thank you for your comment. This was discussed at length by the GDG, and they agreed that height loss and curvature of the spine are not triggers for risk assessment, but they require investigations first (for example X-ray) to find out the cause. Once the vertebral fracture has been correctly diagnosed, then it is possible to apply FRAX to assess fragility fracture risk, as vertebral fracture is considered part of 'prior fracture' item in FRAX. This has now been added to the evidence to recommendations section for recommendation 2.
71	Editor	31.00	NICE	3		In the second para of the introduction the wording of the first sentence still doesn't read quite right. Suggest changing to: Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low energy') trauma. This also applies to the intro in the full version.	Thank you for your comment, this has now been changed.

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72	British Orthopaedic Association - Patient Liaison group	13.00	NICE	3	14	It is our understanding that patients suffering with epilepsy may also suffer other co-morbidities, such as scoliosis. These patients may well be managed by orthopaedic surgeons. We feel that epileptic patients should be specified here & at all other sites where the gudelines refer to 'other'conditions.	Thank you for your comment. The list of risk factors in the NICE introduction is illustrative rather than inclusive. Only the most common risk factors are listed here, we do not mention any causes of secondary osteoporosis.
73	Editor	31.02		1.3 and 1.9		In 1.3 we give the following examples for major risk factors 'current or regular oral glucocorticoid use, untreated premature menopause or previous fragility fracture' In 1.9 the examples of major risk factor are 'history of multiple fragility fractures, major osteoporotic fracture or high-dose oral glucocorticoid use' is this difference because the most important major risk factors are different depending on age? Is this clear enough?	Thank you for your comment. We have changed the wording of these recommendations to use a consistent term to describe steroid use.
74	Editor	31.03	NICE	1.4 and 1.9		We use the term 'major osteoporotic fracture' in these recommendations, but don't explain what that means anywhere. I wonder if this could be explained somewhere in the NICE version? Either in recommendation 1.4: 1.4 Calculate absolute risk when assessing risk of fracture, for example the percentage predicted risk of major osteoporotic fracture (spine, hip or wrist fracture) over 10 years. Or in the introduction, in the same way as we explain fragility fracture, for example it could be added to the first sentence of p.4: Fragility fractures occur most commonly in the spine (vertebrae), hip (proximal femur), and wrist (distal radius). These are known as major osteoporotic fractures…	Thank you for your comment, there is a definition of major osteoporotic fracture in the glossary of the full guideline. We have added this information to the introduction to the NICE version.

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						With the wording depending on the definition used.	
75	William Leslie	1.00	Full	5		Table of contents reference number for Leslie 2010 (42) is incorrect (reference number should be 43).	Thank you for your comment. This has been amended.
76	Costing, Audit and Education & Learning	29.01	NICE	6		Rec 1.3 – is the list of major risk factors a comprehensive list or a partial list? 'For example' suggests that it is a partial list. A comprehensive list would be more helpful to avoid people focusing on the factors in the list and not considering other factors.	Thank you for your comment. The list does cover the main risk factors the GDG considered important but it is not intended to be inclusive of all risk factors.
77	British Orthopaedic Association - Patient Liaison group	13.01	NICE	6	5	As Patient Representative Group we are concerned that any document that does not specify the target audience may fail to deliver its potential as there is always a risk of "Its not my responsibiity" attitude. Therefore we suggest you include mention of those who should be implementing these guidelines e.g.: GPs, Orthopaedic Units, Care of the Elderly Teams, Physicians treating conditions with bone degenerative consequences (e.g.epilepsy) and Falls Prevention Teams	Thank you for your comment. This guideline is for all healthcare professionals and other staff who care for people at risk of fragility fracture. It offers best practice advice on the assessment of fragility fracture risk in adults. Specific mention of those who should be implementing this guideline is an implementation issue which is outside the remit of this guideline. Your concerns will be forwarded to the NICE implementation team.
78	British Orthopaedic Association - Patient Liaison group	13.02	NICE	6	19 Rec3	Mention those receiving bone-toxic treatments for epilepsy	Thank you for your comment. The GDG reviewed the risk factors listed in this recommendation but did not consider that epilepsy drugs should be added. The GDG acknowledge that epilepsy drugs can effect bone density and these drugs are already included as factors not included in risk scores that may effect risk. The GDG did not consider that these were major risk factor in younger people.
79	British Orthopaedic Associati	13.03	FULL	7	1	As a Patient Group representing people who need orthopaedic intervention we are curious to know why no Orthopaedic Surgeon is included in the panel? We would hope this can be	Thank you for your suggestion. When convening the guideline development group the developers have followed the principles outlined in the NICE Guidelines Manual. The developers are mindful

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	on - Patient Liaison group					rectified during the analysis of the consultation.	of the need for ensuring that a broad range of experience and knowledge is represented on the group. The appropriate membership was discussed at the public stakeholder meeting. The remit for the guideline was the assessment of fracture risk. We agree that some people might require orthopaedic intervention, however, intervention and management of fracture are outside the remit of this short guideline.
80	Cambridge University Hospitals NHS Foundation Trust	19.00	Guideline document	~~4~~ **9** para 3	~~4~~ **28**	"difficult" seems the wrong word here, "uncertain" or better still "imprecise" would be preferable. Prediction is always in medicine a matter of probabilities and predicting fractures is now no more difficult than many other prognostic tasks in medicine. This choice of word seems to offer an unwelcome excuse for GP inaction (since they shy away from anything that is difficult unless their hand is held by a specialist).	Thank you, this has been amended to reflect your suggestion.
81	Cambridge University Hospitals NHS Foundation Trust	19.01		6 para 1.2		Other secondary causes of osteoporosis" is not English, even if it is jargon commonly bandied around in the NOS, because it is the osteoporosis not the cause that is secondary. It should read "Other causes of secondary osteoporosis". The same lack of literacy appears in the heading to Para 4.3	Thank you for your comment, this has now been corrected throughout the guideline.
82	Cambridge University Hospitals NHS Foundation Trust	19.02		6 para 1.3		There are some exceptions eg sub-mariners who are made acidotic by excess CO2 and a family history of OI (those who are considering a family but may not have fractured themselves).	Thank you. We acknowledge there are some exceptions but the GDG considered that this is too much detail for inclusion in this guideline

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83	Costing, Audit and Education & Learning	29.03	NICE	8		Rec 1.9 – is the list of major risk factors a comprehensive list or a partial list? 'For example' suggests that it is a partial list. A comprehensive list would be more helpful to avoid people focusing on the factors in the list and not considering other factors.	Thank you for your comment. The list does cover the main risk factors the GDG considered important but it is not intended to be inclusive of all risk factors
84	Johnson & Johnson	2.00	Full, NICE Version	8	1.11	• We support NICE's guidance that that "risk assessment tools may underestimate fracture risk in the following situations: history of multiple fractures and in particular previous vertebral fracture(s)", as it is reported that patients with vertebral compression fractures (VCFs) are confined to bed nine times more often than those without VCFs, increasing their risk of further VCFs which can further complicate recovery[1]. 1) *Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med. 1998 May 15;128(10):793-800.*	Thank you for your comment. We acknowledge the importance of correctly identifying vertebral fractures. The additional paper you provided looked at the association of new vertebral fractures with back pain and back-related functional limitation, therefore the data in this paper are not relevant to the reviews undertaken for the guideline and could not be included.
85	British Pain Society	24.00	x	9	16-18	Note that fractures may cause severe pain and disability is buried in other information and should be more prominent	Thank you for your comment. The remit for the guideline is assessment of fragility fracture risk. We acknowledge the pain and disability potentially caused by fractures but do not think it requires further mention in this guideline.
86	Johnson & Johnson	2.01	Full, NICE Version	9	4	• We would welcome further investigation into the impact fracture treatment has on future risk of fracture such as how data could inform the use of devices. An	Thank you for your comment and additional references. Management of fracture and treatment are outside the remit of this short clinical guideline.

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						example being large femoral heads (>32mm) which have been developed to increase the jumping distance required for hip dislocation. One of the recognised complications of hip arthroplasty is postoperative hip dislocation and large femoral heads have been shown to reduce dislocation[2,3]. • This could be especially key in a population prone to revisions given there is an association between osteoporosis, increasing age and fragility fracture and the statistically significant association with risk of osteoporotic fracture found for those with a history of falls[4,5]. 2) *Berry DJ, Von Knoch M, Schleck CD, et al. Effect of femoral head diameter and operative approach on risk of dislocation after primary total hip arthroplasty. J Bone Joint Surg 2005; 878:2456* 3) *Dowd J, Kindsfater K, Barrett W, Southworth C, Dalury D. Large Femoral Heads can Help Reduce the Risk of Dislocation in Total Hip Arthroplasry. J Arthroplasty 2008;1:231* 4) *Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of Q Fracture Scores. BMJ. 2009; 339: b4229.* 5) *Porthouse J, Birks YF, Torgerson D, Cockayne S, Puffer S, Watt I. Risk factors for fracture in a UK population: a*	

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						prospective cohort study. QJM: An International Journal of Medicine, Volume 97, Issue 9,Pp. 569-574	
87	Spinal Injuries Association	9.01	Full	9	9	Despite the almost universal occurrence of osteoporosis and accompanying fragility fractures in the condition there is no mention of spinal cord injury, either directly or as part of the enforced sedentary/wheelchair using group of conditions. Whilst the numbers involved may be small relative to elderly women, the years of life spent at risk of fragility fractures is high and the consequences and costs severe; such as increased disability and increased risk of pressure sores, spasms, contractures, loss of education and employment. Unfortunately such fractures are often treated in district general hospitals where there is little knowledge of the specialised care needs of spinal cord injured people, which often results in inappropriate treatment and further medical complications. Why has the important subgroup of spinal cord injury been ignored?	Thank you for your comment. The GDG acknowledge there is a variety of causes of secondary osteoporosis, and they could not all be considered singularly in the guideline. The GDG discussed spinal cord injury as a risk factor for fragility fracture, and agreed this is not a risk factor per se, but it is the immobility that derives from spinal cord injury that increases the risk of fragility fracture. Immobility was already included in the list of causes of secondary osteoporosis and we have now added the example of 'immobility due for example to neurological injury or disease' to the list of causes of secondary osteoporosis.
88	British Orthopaedic Association - Patient Liaison group	13.04	FULL	9	10	Our perception is that some bone-toxic treatments for epilepsy lead to early rik of osteoporosis & fracturing. We are concerned that there is very scant reference to this, especialy as it can affect <50 yr olds. Therefore we suggest you include reference to bone-toxic anti-epileptic drugs, or even the disease not only here but also in some way at the other points listed below...	Thank you for your comment. The GDG reviewed the risk factors listed in this recommendation but did not consider that epilepsy drugs should be added. The GDG acknowledge that some epilepsy drugs can effect bone density and these drugs are already included as factors not included in risk scores that may effect risk in recommendation 13 and related link to evidence (see section 4.7 of the full guideline). This recommendation applies to the ages-ranges covered by the tools,

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							including people less than 50 years. The GDG disagreed that all people using anti-epileptic drugs should have risk assessment .People with epilepsy represent a heterogeneous group – not all antiepileptic drugs are considered to have an effect on bone and of those that do e.g. sodium valproate the effect can be on calcium metabolism and risk of osteomalacia rather than osteoporosis. The BNF reports osteoporosis as being a 'very rare' side effect with carbamazepine.
89	NETSCC, HTA Ref 2	7.03	Full	9	11	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Suggest including that actual bone density varies across ethnic groups	Thank you for your comment. A specific review on BMD across ethnic groups was not carried out. During the scoping phase of the guideline, ethnic minorities were not considered to be a priority issue for the guideline, therefore the review protocols were developed without specific mention of ethnic groups. The stakeholders at the scoping workshop and the GDG indicated that there was not specific evidence available about ethnic groups in UK population and international evidence would not be relevant as ethnic groups can differ significantly in different countries. As stated in the equality impact assessment form, when making recommendations the GDG did consider different ethnic groups but did not consider they could usefully make a distinction between ethnic groups . The GDG made a research recommendation about performance of FRAX, QFracture and BMD for different ethnic origin in the UK population.
90	UCB Pharma Ltd	26.00	Full	9	22	In addition to direct medical costs from fragility fractures in the UK, consider adding indirect medical costs which reflect the costs of productivity loss as a result of osteoporosis.	Thank you for your comment. We have added this to the introduction.

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						Indirect medical costs not only consist of the productivity loss of the patient, but also of the productivity loss of family or friends who take time off work to care for the patient. This productivity loss may take the form of time lost from work ('absenteeism') or reduced productivity at work ('presenteeism').	
91	British Orthopaedic Association - Patient Liaison group	13.05	FULL	10	1	As a Group represetning patients requiring Orthopaedic intervention we feel this brief section is not specific enough: we feel it is necessary to specify the key healthcare professionals who have the oportunity to identify those at risk as well as those who have already suffered at least one fracture. This group should include Orthopaedic Teams, Orhto-Gerontologist and Geriatric teams, Physicians & Nurses treating Diabetes & Epilepsy and Falls Prevention teams as well as Primary Care H/C Professionals.	Thank you for your comment. This section was not meant to be inclusive. The GDG believe that "staff who care for people at risk of fragility fracture" includes all the groups you mention. Orthopaedic intervention is outside the remit of this guideline.
92	Johnson & Johnson	2.02	Full, NICE Version	10	4.1	• We support the targeting of risk assessment in general and advocate the use of primary care data sets to support subsequent prevention strategy and treatment. • There also needs to be sufficient linkage to primary care incentives such as an associated QOF indicator to ensure compliance to any risk assessment strategies that are identified.	Thank you for your comment. The guideline is recommending a targeting of risk assessment and we have included a research recommendation to assess the systematic use of primary care data sets to identify people who would benefit from fracture risk assessment . We have informedthe QOF team at NICE regarding the development of this guidance
93	British Orthopaedic Association - Patient	13.13	NICE	10	10	The use of the GP's patient data bank to identify at-risk patients is solid – however it would be a more potent comment if there is a table of risk-factors inserted here.	Thank you for your comment. This is a summary of a research recommendation. Further detail about the research recommendation is included in appendix B.

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	Liaison group						
94	British Orthopaedic Association - Patient Liaison group	13.14	FULL	10	14	Keeping the patient at the centre is ideal: however surely a campaign to highlight the risk & get patients to flag their own concerns (may be a poster campaign in surgeries or a round-robin letter from the CCG) would under-pin this initiative	Thank you for your comment. We agree that that keeping the patient at the centre is ideal, but this is outside the scope of this guideline.
95	PPIP	33.02	Full	11	24-25	As discussed at the editorial meeting, please could this clarify that it means using the clinical judgement when using tools to assess fractutre risk in people aged 85 and over?	Thank you for your comment, the recommendation has been reworded.
96	PPIP	33.00	Full	11	4	Rec 1: Please could this recommendation clarify that his recommendation is about those 'in the absence of any specific risk factors'. Could it also clarify whether this is meant to be a global approach to *all* men and women over the specified ages, whenever they present to the NHS?	Thank you for your comment. Your comment was discussed by the GDG. The group disagreed with your suggestion and agreed to keep the recommendation as it was. With this recommendation the GDG wanted to highlight that age is the primary risk factor to trigger a risk assessment, therefore adding "in the absence of any specific risk factors" would dilute this key message; other specific risk factors are considered throughout the guideline.
97	National Osteoporosis Society	5.02	Full	11	6	Recommendation 2 states "Consider assessment of fracture risk in women under 65 years and men under 75 years if they have any of the following risk factors". Family history of hip fracture is listed as one of the risk factors, however it is noted on p40 that "..patients who report clear history of family vertebral or other osteoporotic fracture should	Thank you for your comment. The GDG consider there is not enough evidence to add history of family vertebral or other osteoporotic fracture to the recommendation. As explained in the Quality of evidence box for this recommendation, family history of any fractures and family history of hip fractures are both associated with increased fracture risk, but the effect of family history of hip fracture is stronger.

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						also have opportunistic risk assessment performed." We would like to see this reflected in the list of risk factors.	
98	NETSCC, HTA Ref 2	7.04	Full	11	10	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Suggest include susceptible to falls – poor sight, neuro-muscular condition	Thank you for your comment. This area was debated extensively by the guideline development group and the views you put forward were discussed. The GDG agreed to keep the recommendation unchanged as the risk factor you listed are risk factors for falls rather than fragility fracture, and the GDG believe these are covered in 'history of falls'.
99	PPIP	33.01	Full	11	10	'history of falls' – please could this clarify if there is a type of fall (for instance frequency, circumstance) which would come into play here? It would seem that virtually everyone has a 'history of falls'.	Thank you for your comment. As explained in the Quality of evidence box, definitions of history of falls were heterogeneous across studies, for example a fall in the past 12 months, a fall in the past 6 months or 90 days, a fall in the past 1 month, greater than two falls in the last year of follow up. The GDG were therefore not able to agree one definition for it, but in general it is implied a recent fall.
100	National Osteoporosis Society	5.11	Full	11	12	Recommendation 2 states "…other secondary causes of osteoporosis". However the term is incorrect. It is either 'secondary osteoporosis', or 'causes of osteoporosis', as the causes are not secondary. This needs to be addressed throughout the document.	Thank you for your comment, this has now been corrected throughout the guideline.
101	British Orthopaedic Association - Patient	13.06	FULL	11 Rec 2	12	This mentions footnote 'a' and in this footnote we feel that specific reference should be made to either epilepsy or the bone-toxic treatment there of which leads to osteoporosis	Thank you for your comment. The GDG included major risk factors that they considered should trigger risk assessment and did not consider that epilepsies or treatments for epilepsy should be added.

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	Liaison group						
102	British Pain Society	25.00	x	11	12	Other causes are buried in footnotes- not clear. Should specifically mention women with TAH-BSO or oopherectomy in text as an important cause of osteoporosis. Also vitamin D deficiency is not mentioned as an n important cause of fragility fractures. Could prevent GPs correctly identifying fracture risk until fracture has already occurred, with attendant pain, disability and healthcare utilisation. Also, no dose threshold for "hi-dose" steroids given.	Thank you for your comment. Women with premature untreated menopause are included and the GDG considered this was adequate to cover women who had surgical menopause. Vitamin D deficiency is a cause of osteomalacia and treatment differs from that of osteoporosis. A discussion on glucocorticoid doses is reported in the evidence to recommendations table for this recommendation, 'other considerations' box (section 3.7).
103	Bone Research Society, the	10.03	Full	11	14	Light smoking is associated with a significant increase in fracture risk, especially at the hip. The threshold of 10/day is unwarranted	Thank you for your comment. We have now amended the recommendation to 'smoking', without any threshold.
104	British Society for Rheumatology	12.04	Full	11	14	Light smoking is associated with a significant increase in fracture risk, especially at the hip. The threshold of 10/day is unwarranted	Thank you for your comment. We have now amended the recommendation to 'smoking', without any threshold.
105	Sheffield Teaching Hospitals NHS Foundation Trust	20.03	Full	11	14	Light smoking is associated with a significant increase in fracture risk, especially at the hip. The threshold of 10/day is unwarranted	Thank you for your comment. We have now amended the recommendation to 'smoking', without any threshold.
106	NETSCC, HTA Ref 2	7.05	Full	11	15	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the**	Thank you for your comment. A systematic review on caffeine was not carried out therefore the GDG is unable to add it to the list of risk

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						evidence? b) Complete? i.e. are all the important aspects of the evidence reflected Has caffeine intake, 3+ cups coffee per day, been evaluated as a risk factor – there is some evidence supporting this?	factors. The aim of the guideline was not to identify all factors that might be associated with a relative risk of fragility fracture but to identify the main factors that would prompt health care practitioners to consider assessment of absolute risk. When setting up the protocol, the GDG decided that the following risk factors were likely to be the most important: BMI, glucocorticoid use, family history of fracture, previous fracture, smoking, alcohol, and history of falls. Therefore a review was carried out for these risk factors only (see review protocols in appendix C, section C.3).
107	NETSCC, HTA Ref 2	7.06	Full	11	15	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Lack of Vitamin D through lack of sunlight, particularly for some cultural groups is also a risk factor worth consideration, with supporting evidence	Thank you for your comment. The GDG acknowledge the importance of vitamin D deficiency, however, this is not a trigger for risk assessment, it is not a risk factor for osteoporotic fractures, and its management is different from osteoporosis.
108	Bone Research Society, the	10.04	Full	11	15	The rationale for setting a threshold >4 units when one of the risk tools has a threshold >3 units seems illogical.	Thank you for your comment. We have amended this recommendation following consultation and now recommend that risk assessment is considered for people between 50 and 65 for women and 50 and 75 for men if they drink amounts of alcohol which exceed the recommendations i.e. > 21 units a week for men and >14 units a week for women. The recommendation is based on the evidence that risk of fracture increases with alcohol intake and the level in the recommendation is in keeping with general advice about alcohol intake. It is not related to how the available tools treat an alcohol

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							history.
109	British Society for Rheumatology	12.05	Full	11	15	The rationale for setting a threshold >4 units when one of the risk tools has a threshold >3 units seems illogical.	Thank you for your comment. We have amended this recommendation following consultation and now recommend that risk assessment is considered for people between 50 and 65 for women and 50 and 75 for men is they drink hazardous amounts of alcohol i.e. > 21 units a week for men and >14 units a week for women. The recommendation is based on the evidence that risk of fracture increases with alcohol intake and the level in the recommendation is in keeping with general advice about alcohol intake. It is not related to how the available tools treat an alcohol history.
110	Sheffield Teaching Hospitals NHS Foundation Trust	20.04	Full	11	15	The rationale for setting a threshold >4 units when one of the risk tools has a threshold >3 units seems illogical.	Thank you for your comment. We have amended this recommendation following consultation and now recommend that risk assessment is considered for people between 50 and 65 for women and 50 and 75 for men is they drink hazardous amounts of alcohol i.e. > 21 units a week for men and >14 units a week for women. The recommendation is based on the evidence that risk of fracture increases with alcohol intake and the level in the recommendation is in keeping with general advice about alcohol intake. It is not related to how the available tools treat an alcohol history.
111	British Orthopaedic Association - Patient Liaison group	13.07	FULL	11	16	recommendation 3 misses the opportunity to safe-guard Epilepsy by not specifying it here	Thank you for your comment. The GDG discussed your suggestion but did not consider it appropriate to include epilepsy here as a major risk factor.

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112	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.00	Full	11	16	The most significant increase in all fractures at all sites happens in both sexes over 75 years. Routine screening of this age group should perhaps be established first before lower age groups are targeted.	Thank you for your comment. We agree that this group is most at risk but consideration of routine screening is outside the scope of a guideline
113	British Society for Rheumatology	12.03	Full	11	**4 and 16** Rec 11 and 12 ?	It should be unnecessary to put in these restrictions unless there is good evidence that the risk calculator is giving the wrong answer in these populations	Thank you for your comment. Risk assessment tools are developed on patient populations but will inevitably be used for individuals. The GDG considered from evidence reviews and their experience of risk assessment tools that resultant risk from risk assessment tools may need adjustment in some cases. The GDG intention is to make the healthcare professional mindful to use clinical judgement in particular situations. The reasons for this are fully explained in the 'Recommendations and link to evidence' section of the full guideline document.
114	Bone Research Society, the	10.05	Full	11	21	Specific advice is required about which tool to use in the presence of a prior fragility fracture– patients with documented prior fractures were excluded from the derivation and validation studies of QFracture.	Thank you for your comment. The two tools take into consideration different risk factors, however (as explained in the 'Recommendations and link to evidence' section of the full guideline document) there is no strong evidence to suggest that one tool performs better than the other in

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							people with a specific risk factor; for example, even if QFracture contains data for history of falls, there is no evidence it actually works better than FRAX in predicting risk of fracture in people who fall.
115	British Society for Rheumatology	12.06	Full	11	21	Qfracture is not something that has been discussed much in Osteoporosis circles and the introduction of this as an option to FRAX is likely to lead to confusion. FRAX has always been "work in progress" so supporting further development of this internationally acclaimed tool seems the best way forward.	Thank you for your comment. The developers and the GDG reviewed the evidence for both FRAX and QFracture, and the performances of the two tools were similar (please see Chapter 4 of the full guideline), therefore the GDG felt appropriate to recommend the use of either the two tools.
116	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.01	Full	11	21	Using these screening tools will impact on GP consultation time. A fair percentage of patients in this cohort will not be mobile enough to come into surgery and will need to be visited in nursing or residential home.	Thank you for your comment. We are not suggesting screening. The GDG took into account GP consultation time in the economic evaluation. Both FRAX and QFracture are also available on iPhone/iPad, so can be used during visits in nursing or residential home.
117	Sheffield Teaching Hospitals NHS Foundation Trust	20.05	Full	11	21	Specific advice is required about which tool to use in the presence of a prior fragility fracture– patients with documented prior fractures were excluded from the derivation and validation studies of QFracture.	Thank you for your comment. The two tools take into consideration different risk factors, however (as explained in the 'Recommendations and link to evidence' section of the full guideline document) there is no strong evidence to suggest that one tool performs better than the other in people with a specific risk factor; for example,

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							even if QFracture contains data for history of falls, there is no evidence it actually works better than FRAX in predicting risk of fracture in people who fall.
118	National Osteoporosis Society	5.03	Full	11	24	Recommendation 6 states "Use clinical judgement when assessing fracture risk in people of 85 years and over, because predicted 10-year fracture risk may underestimate their short-term fracture risk." However it is unclear in the guideline what this means in practice and how fracture risk is determined. It assumes a prior knowledge of fracture risk assessment which will not be suitable for a generalist audience.	Thank you for your comment, this recommendation has been reworded.
119	Bone Research Society, the	10.06	Full	11	24 Rec 6	The rationale for this may be true for QFracture but not for FRAX. FRAX reports the probability of fracture i.e. integrates the death and fracture hazard [Kanis 2008a, 2012a]. After about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability [Kanis 2000]. The use of too many age-thresholds adds to confusion and is at odds with 2.1.1. It also implies that we should not use clinical judgement at younger ages?	Thank you for your comment. The developers acknowledge the fact that after about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability, and this is included in FRAX. However, as explained in section 4.7 'Recommendations and link to evidence' of the full guideline, the GDG concern is that the short-term risk of fracture in this age group might actually be higher than the 10-year risk predicted by the tool, which in fact is equal to the risk of death. The GDG believe that a shorter time frame for risk assessment in this age group may be more appropriate depending on co-morbidities of the patient. Clinical judgment is required at all ages but the GDG wished to highlight systematic issues with the use of risk tools.
120	British Society for Rheumat	12.07	Full	11	24	The rationale for this may be true for QFracture but not for FRAX. FRAX reports the probability of fracture i.e. integrates the death and fracture hazard [Kanis 2008a, 2012a]. After about the	Thank you for your comment. The developers acknowledge the fact that after about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability and this is included

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	ology					age of 80 years, the 10 year probability is equal to the remaining lifetime probability [Kanis 2000]. The use of too many age-thresholds adds to confusion and is at odds with 2.1.1. It also implies that we should not use clinical judgement at younger ages?	in FRAX. However, as explained in section 4.7 'Recommendations and link to evidence' of the full guideline, the GDG concern is that the short-term risk of fracture in this age group might actually be higher than the 10-year risk predicted by the tool, which in fact is equal to the risk of death. The GDG believe that a shorter time frame for risk assessment in this age group may be more appropriate depending on co-morbidities of the patient. Clinical judgment is required at all ages but the GDG wished to highlight systematic issues with the use of risk tools.
121	Julia Hippisley-Cox, Carol Coupland	18.00	Full	11	24	QFracture (2009) web calculator allows calculation of risk over a variable time period (1-10 years) - a short period (eg 5 year risk) might be more suitable for elderly patients. We have updated QFracture (2012) to include patients aged 30-100 so that it is possible to assess risk in those aged over 85 years.	Thank you for your comment. The developers are aware that QFracture allows calculation of risk over a variable time period, however, only the data to calculate the 10-year risk are validated, and the GDG did not wish to recommend the use of a non-validated tool.
122	Sheffield Teaching Hospitals NHS Foundation Trust	20.06	Full	11	24	The rationale for this may be true for QFracture but not for FRAX. FRAX reports the probability of fracture i.e. integrates the death and fracture hazard [Kanis 2008a, 2012a]. After about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability [Kanis 2000]. The use of too many age-thresholds adds to confusion and is at odds with 2.1.1. It also implies that we should not use clinical judgement at younger ages?	Thank you for your comment. The developers acknowledge the fact that after about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability and this is included in FRAX. However, as explained in section 4.7 'Recommendations and link to evidence' of the full guideline, the GDG concern is that the short-term risk of fracture in this age group might actually be higher than the 10-year risk predicted by the tool, which in fact is equal to the risk of death. The GDG believe that a shorter time frame for risk assessment in this age group may be more appropriate depending on co-morbidities of the patient. Clinical judgment is required at all ages but the GDG wished to highlight systematic issues with the use of risk tools.

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123	British Society for Rheumatology	12.08	Full	11	26 Rec 7	There is little evidence to support this statement. For those of us who have ready access to bone densitometry we are likely to continue to incorporate BMD In to FRAX	Thank you but the evidence and clinical consensus do not support your view. The GDG would like to recommend a change in practice and not refer patients for BMD if not necessary. The GDG are confident that FRAX (without a BMD value) and QFracture give an accurate estimate of the absolute risk of fragility fracture, therefore if a person is well above the intervention threshold, they can be treated without further BMD measurement. This is also supported by the evidence on reclassification, that shows that the addition of BMD to FRAX reclassifies people (from low to high risk) mainly if their risk was in the region of an intervention threshold.
124	British Thoracic Society	16.00	Full	12		High dose inhaled steroids are only mentioned under Section 2 (Consider assessment of fracture risk in women under 65 years and men under 75 years if they have any of the following risk factors)....where it states ".....The IPD analysis included oral glucocorticoid use only and follow up search did not find more up to date analyses that included inhaled glucocorticoids....". This is a major issue for patients with more severe asthma and clinicians are frequently asked about this. There is some literature to support an effect on bone density and high dose inhaled steroids and there is significant systemic bioavailability at higher doses but we agree the data is not as good as oral steroids. The Guidance should include a clear statement on high dose inhaled steroids even if this reflects a lack of data / knowledge - this	Thank you for your comment. We have altered the wording of the recommendations to say that it is relevant for oral and systemic glucocorticoids. The GDG discussed including a recommendation not to assess people on high dose inhaled steroids and did not think this was appropriate to do this without more extensive review of this literature.

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						should state that high dose inhaled steroids are not included in the risk factors for any of the recommended tools, the evidence is not clear on the threshold or effect size and thus high dose inhaled steroids should NOT routinely (or perhaps should at a certain dose???) be considered a risk factor for osteoporosis.	
125	Cambridge University Hospitals NHS Foundation Trust	19.03		12		This suggestion will only work in the context of a formal Trial since many patients escape treatment despite the demonstrated need for it, based on FRAX, BMD etc.	Thank you for your comment.
126	Cambridge University Hospitals NHS Foundation Trust	19.04		12		Care home residents also frequently are kept indoors so become vitamin D deficient through lack of sunlight. In the study of Italian centenarians, all were pretty grossly vitamin D deficient, I was told by the investigators	Thank you for your comment. The GDG agree with your observation and made a research recommendation on FRAX and QFracture in adults living in long-term care (see appendix B, section B.1.5).
127	National Osteoporosis Society	5.04	Full	12	1	Recommendation 8 states "Following risk assessment with FRAX (without a BMD value) or QFracture, consider measuring BMD: in people whose fracture risk is in the region of an intervention threshold for a proposed treatment…." Within section 4.7 (p65) this is expanded and states "People well above the threshold can be treated without measurement of BMD." However the National Osteoporosis Society	Thank you but the evidence and clinical consensus did not support your view. The GDG are confident that FRAX (without a BMD value) and QFracture give an accurate estimate of the absolute risk of fragility fracture, therefore if a person is well above the intervention threshold, they can be treated without further BMD measurement. This is also supported by the evidence on reclassification, that shows that the addition of BMD to FRAX reclassifies people (from low to high risk) mainly if their risk was in

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						considers BMD measurement as an important component of the decision to treat and would encourage this recommendation to reflect this.	the region of an intervention threshold.
128	National Osteoporosis Society	5.05	Full	12	1	Recommendation 8 states "Following BMD measurement in these situations, recalculate absolute risk using FRAX with the BMD value." However it is unclear if using BMD assessment following QFracture how fracture risk can be recalculated as it is not a variable in QFracture. We would welcome some clarity on this issue.	Thank you for your comment. The developers recognize the fact that QFracture does not allow the inclusion of BMD, therefore if BMD measure was done after initial assessment with QFracture, the healthcare professional should then switch to the FRAX tool to recalculate risk assessment including BMD. The developers believe this is clearly explained by: "*using FRAX with the BMD value*"
129	NETSCC, HTA Ref 2	7.07	Full	12	2	**3.2 Are any important limitations of the evidence clearly described and discussed?** Suggest clarifying that BMD should be measured with DXA, rather than any alternative such as QCT, as a gold standard set by WHO	Thank you for your comment, the developers have added 'with DXA' to the recommendation.
130	NETSCC, HTA Ref 2	7.08	Full	12	2	**3.2 Are any important limitations of the evidence clearly described and discussed?** Is there a place in the guideline to stress that only 2 sites need to be measured i.e. hip and spine or one of those plus wrist as there can be cases of excess measurement occurring?	Thank you for your comment, the preferred sites of measurement are explained in the introduction to Chapter 4. We discussed this with the GDG who advised not to include site in the recommendations themselves. They considered that this is a good practice point and that there is already general agreement about this.
131	British Thoracic Society	16.02	Full	12	5 Rec 8	States here 'high –dose ' oral glucocorticoids – elsewhere in the document and in the algorithm the term 'oral glucorticoid' is used. No definition of dose.	Thank you for your comment, high-dose glucocorticoid use has now been defined in the recommendation.
132	Bone Research Society, the	10.07	Full	12	9 Rec 9	What is meant by high dose glucocorticoid use?	Thank you for your comment, high-dose glucocorticoid use has now been defined in the recommendation.
133	British Society	12.09	Full	12	9	What is meant by high dose glucocorticoid use?	Thank you for your comment, high-dose glucocorticoid use has now been defined in the

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	for Rheumatology						recommendation.
134	Sheffield Teaching Hospitals NHS Foundation Trust	20.07	Full	12	9	What is meant by high dose glucocorticoid use?	Thank you for your comment, high-dose glucocorticoid use has now been defined in the recommendation.
135	NETSCC, HTA Ref 2	7.09	Full	12	10	**3.2 Are any important limitations of the evidence clearly described and discussed?** Those with a sedentary lifestyle, immobility or disability are also at increased risk, could this be incorporated into the guidelines?	Thank you for your comment. Immobility is already included in the list of causes of secondary osteoporosis (footnote to recommendations 2 and 11). The GDG did not consider it possible to accurately define sedentary life style or disability in a way that would be useful for a recommendation.
136	National Osteoporosis Society	5.06	Full	12	12	Recommendation 10 addresses recalculating fracture risk, but it is not clear whether the intention is to re-measure BMD as part of a reassessment. We would welcome clarification on the issue of reassessing BMD.	Thank you for your comment. If BMD was part of the original assessment, then BMD should be re-measured. If BMD was not part of the original assessment, then the decision of measuring BMD will be based on the result of the risk assessment. This has now been clarified in the 'Other considerations' box for this recommendation.
137	Bone Research Society, the	10.08	Full	12	12	The statement is dogmatic and confusing and implies that some patients should never have their fracture risk re-assessed. A change in risk factors (e.g. a higher dose of glucocorticoids) should stimulate a reassessment. Age is also an important determinant. We would suggest something along the lines of the following wording: Consider recalculating fracture risk: when there has been a change in risk factors	Thank you for your suggestions. Following discussion the GDG agreed that they did not wish to change this wording as it was felt that the current wording is clear. A change in risk factors is already included in the recommendation. The GDG did not think annual assessment were necessary in older people who had a prior assessment.

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						or after an interval determined by clinical judgement. Earlier reassessments (e.g annually) should target older patients or those lying close to intervention thresholds.	
138	British Society for Rheumatology	12.10	Full	12	12	The statement is dogmatic and confusing. We would suggest something along the lines of the following wording: Consider recalculating fracture risk: when there has been a change in risk factors or after an interval determined by clinical judgement. Earlier reassessments (e.g annually) should target older patients or those lying close to intervention thresholds.	Thank you for your suggestions. Following discussion the GDG agreed that they did not wish to change this wording as it was felt that the current wording is clear. A change in risk factors is already included in the recommendation. The GDG did not think annual assessment were necessary in older people who had a prior assessment.
139	Sheffield Teaching Hospitals NHS Foundation Trust	20.08	Full	12	12	The statement is dogmatic and confusing. We would suggest something along the lines of the following wording: Consider recalculating fracture risk: when there has been a change in risk factors or after an interval determined by clinical judgement. Earlier reassessments (e.g annually) should target older patients or those lying close to intervention thresholds.	Thank you for your suggestions. Following discussion the GDG agreed that they did not wish to change this wording as it was felt that the current wording is clear. A change in risk factors is already included in the recommendation. The GDG did not think annual assessment were necessary in older people who had a prior assessment.
140	PPIP	33.03	Full	12	15	How will the 'change in the person's risk factors' come to light? There is nothing in the recommendations about providing information to individuals, for instance after they have had a risk assessment, about its results and what to do in future, should relevant circumstances change. This might be a helpful addition to the guideline, which at the moment is lacking in any indication of the kind of discussion that might	Thank you for your comment. The guideline refers to the Patient Experience guideline which covers communication and shared decision making, with specific reference to risk communication. Change in the person's risk factors has to be evaluated on an individual level. We are unable to recommend any systematic method of reviewing risk factors. We have included a

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						occur with the person being assessed, about their risk now or in the future.	research recommendation about the identification of people at risk which if effective would also indicate who should be reassessed.
141	British Society for Rheumatology	12.11	Full	12	16	It is helpful to point out areas in which FRAX (at present) is not able to adjust to the magnitude of a risk factor (rather than considering it as a binary variable).	Thank you for your comment. This is explained in the 'recommendations and link to evidence' section for this recommendation.
142	Bone Research Society, the	10.09	Full	12	19	This is more complex than it appears. It is true that clinical vertebral fractures (a minority of all vertebral fractures) confer a higher fracture risk. However subclinical vertebral fractures, particularly grade 1 fractures have little or no predictive value [Jiang 2004, Kanis, 2009, 2010a]. The hazard of the two combined are probably reflected in the output of the model.	Thank you for your comment. This was debated extensively by the group, and the GDG believe this recommendation to be accurate. We considered the additional references you suggested; the two Kanis papers, 2009 and 2010a were excluded as they address clinical effectiveness of the drugs (which is outside the remit of this guideline); Jiang 2004 provides information on diagnosis of vertebral fractures, but does not directly address vertebral fractures as risk factors for fragility fracture.
143	British Society for Rheumatology	12.12	Full	12	19	This is more complex than it appears. It is true that clinical vertebral fractures (a minority of all vertebral fractures) confer a higher fracture risk. However subclinical vertebral fractures, particularly grade 1 fractures have little or no predictive value [Jiang 2004, Kanis, 2009, 2010a]. The hazard of the two combined are probably reflected in the output of the model.	Thank you for your comment. This was debated extensively by the group, and the GDG believe this recommendation to be accurate. We considered the additional references you suggested; the two Kanis papers, 2009 and 2010a were excluded as they address clinical effectiveness of the drugs (which is outside the remit of this guideline); Jiang 2004 provides information on diagnosis of vertebral fractures, but does not directly addresses vertebral fractures as risk factors for fragility fracture.
144	Sheffield Teaching Hospitals NHS	20.09	Full	12	19	This is more complex than it appears. It is true that clinical vertebral fractures (a minority of all vertebral fractures) confer a higher fracture risk. However subclinical vertebral fractures,	Thank you for your comment. This was debated extensively by the group, and the GDG believe this recommendation to be accurate. We considered the additional references you

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	Foundation Trust					particularly grade 1 fractures have little or no predictive value [Jiang 2004, Kanis, 2009, 2010a]. The hazard of the two combined are probably reflected in the output of the model.	suggested; the two Kanis papers, 2009 and 2010a were excluded as they address clinical effectiveness of the drugs (which is outside the remit of this guideline); Jiang 2004 provides information on diagnosis of vertebral fractures, but does not directly addresses vertebral fractures as risk factors for fragility fracture.
145	UCB Pharma Ltd	26.01	Full	12	19	Not all vertebral fractures come to clinical attention. The majority of vertebral fractures are silent, only being diagnosed radiographically. Thus a clinical history alone may underestimate the vertebral fracture risk. However, height loss or thoracic kyphosis can serve as triggers to investigate (vertebral fractures) radiographically.	Thank you for your comment. This was discussed at length by the GDG, and they agreed that kyphosis or height loss are not risk factors for fragility fractures per se, but are possible signs of vertebral fracture. Once the vertebral fracture has been correctly diagnosed (by X-ray), then it is possible to apply FRAX to assess fragility fracture risk, as vertebral fracture is considered part of 'prior fracture' item in FRAX. This has now been added to the evidence to recommendations section for recommendation 2.
146	Bone Research Society, the	10.10	Full	12	22	The correct expression is "causes of secondary osteoporosis" and should be used throughout the document.	Thank you for your comment; this has now been corrected throughout the guideline.
147	British Society for Rheumatology	12.13	Full	12	22	The correct expression is "causes of secondary osteoporosis" and should be used throughout the document.	Thank you for your comment, this has now been corrected throughout the guideline.
148	Sheffield Teaching Hospitals NHS Foundation Trust	20.10	Full	12	22	The correct expression is "causes of secondary osteoporosis" and should be used throughout the document.	Thank you for your comment, this has now been corrected throughout the guideline.

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149	Bone Research Society, the	10.11	Full	12	23	To our knowledge, there is no published evidence that obesity confers a risk that is independent of QFracture or FRAX. Rather, a limited publication base suggests that there appears to be a small increase in risk in obese subjects over and above that provided by BMD.	Thank you for your comment. Obesity has now been removed from the recommendation.
150	British Society for Rheumatology	12.14	Full	12	23	To our knowledge, there is no published evidence that obesity confers a risk that is independent of QFracture or FRAX. Rather, a limited publication base suggests that there appears to be a small increase in risk in obese subjects over and above that provided by BMD.	Thank you for your comment. Obesity has now been removed from the recommendation.
151	Sheffield Teaching Hospitals NHS Foundation Trust	20.11	Full	12	23	To our knowledge, there is no published evidence that obesity confers a risk that is independent of QFracture or FRAX. Rather, a limited publication base suggests that there appears to be a small increase in risk in obese subjects over and above that provided by BMD.	Thank you for your comment. Obesity has now been removed from the recommendation.
152	Julia Hippisley-Cox, Carol Coupland	18.01	Full	12	24	The updated QFracture algorithm now includes - Living in a residential care home - Conditions which might affect immobility (eg dementia and Parkinson's) - Drugs which might impair bone metabolism (such as anti-epileptic drugs). - Other factors (which are listed in later parts of this response against the relevant section of the guideline). - The revised web calculator is available at www.qfracture.org/2012 - The accompanying paper - which describes the detail of the updated algorithm and its validation - has been submitted to the BMJ but is also available	Thank you for this information. Unfortunately we were unable to use this evidence as it was not in the public domain during the development of this guideline. All included evidence should be in the public domain to ensure transparency of the development process.

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						to the NICE committee on request. -	
153	NETSCC, HTA Ref 2	7.10	Full	12	25	**3.2 Are any important limitations of the evidence clearly described and discussed?** Living in a care home per se does not seem to be sensible as a risk factor, rather it is the possible immobility or susceptibility to falls through frailty that should be highlighted here as the risk	Thank you for your suggestions. We agree with your point that living in a residential home is likely to be a marker for several issues such as susceptibility to falls, poor sight, reduced cognition and poor nutrition. The GDG considered it difficult to define all of these felt it and preferable to alert healthcare professionals to this population group. They have agreed not to change this wording as it was felt that the current wording is clear
154	British Society for Rheumatology	12.15	Full	12	28e	The guideline has not addressed the issue of intervention thresholds which is really the most important question for a guideline committee to address. It is not acceptable to refer to 'local protocols or other National advice'. One of the main problems faced by clinicians in the osteoporosis field is that we have multiple (and often conflicting) guidance on intervention thresholds. TAGs 160, 161, 204 and the RCP corticosteroid guidance have a bewildering array of thresholds base on age, risk factors and BMD. How do these fit in with the proposed guideline? Presumably these TAGs will be updated with 10 year risk thresholds	Thank you for your comment. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools for fragility fracture only. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
155	Julia Hippisley-Cox, Carol Coupland	18.02	Full	13	2-10	1. **Recommendations 1.** We agree with the first research recommendation (ie to determine clinical and cost-effectiveness of using GP practice lists to identify high risk patients) and would be willing to contribute to such a project 2. **Recommendation 3**: We have added additional causes of osteoporosis to QFracture (2012) in response to this as	Thank you for this information. Unfortunately we were unable to use this evidence as it was not in the public domain during the development of this guideline. All included evidence should be in the public domain to ensure transparency of the development process.

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						mentioned above. 3. **Recommendation 5**: QFracture (2012) now includes a variable for residence in a care home which increases risk especially for men 4. **Recommendation 6:** The QResearch database holds a substantial volume of data on self-assigned ethnicity which has been utilitised in other risk prediction equation. QFracture (2012) now includes ethnicity (White/not recorded, Indian, Pakistani, Bangladeshi, Other Asian, Black African, Black Caribbean, Chinese, Other including mixed). The addition of this and the other new variables) has significantly improved the discrimination of QFracture.	
156	Spinal Injuries Association	9.02	Full	13	1	Given that spinal cord injuries are most commonly acquired in early adulthood and that the years spent in an at risk state are far longer than most other causes of fragility fractures, why are there no research recommendations with regard to long-term or repeated use of bone density increasing drugs?	Thank you for your comment. The GDG made two research recommendations that are useful for this subgroup: one for people taking drugs for increasing bone density (2. What is the utility of FRAX and QFracture in adults receiving bone protective therapy?) and the other for people with causes of secondary osteoporosis (3 What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults with causes of secondary osteoporosis?). Please see appendix B for further information.
157	Spinal Injuries Association	9.03	Full	13	2	As spinal cord injury and other conditions which lead to "immobility" are not included in the scope, how can GP practice lists be of any use in identifying members of this group that might benefit from therapy?	Thank you for your comment. This research recommendation was designed for screening at a population level (identifying people with major risk factors), not at an individual level. The GDG made a separate research recommendation for people with causes of secondary osteoporosis,

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							which includes immobility due to neurological injury or disease (3 What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults with causes of secondary osteoporosis?). Please see appendix B for further information.
158	Servier Laboratories Ltd	21.01	Full	13	4	Servier fully welcomes the inclusion of FRAX into this guideline document as it offers significant benefit to the patient. We would like to draw the authors' attention to the available published evidence in support of the predictive validity of FRAX in individuals taking anti-osteoporotic treatment. In a recent retrospective study by Leslie et al (2012)[1] of 35,764 women aged over 50 years with baseline BMD testing (1996-2007), FRAX probabilities were calculated. A pharmacy database was used to identify osteoporosis medication use. Fracture outcomes to 10 years were also calculated for each patient from a health database. Concordance plots for major osteoporotic and hip fracture incidence showed good agreement between treated and untreated subgroups. This work suggested that FRAX can be used to predict fracture probability in women currently or previously treated for osteoporosis. This is particularly useful for those needing continued treatment or treatment withdrawal. In summary, whilst the inclusion of FRAX is very welcomed, we feel that evidence in support of the predictive validity of FRAX in patients taking osteoporotic treatments is also worthy of inclusion. References: 1. Leslie WD, Lix LM, Kanis MD et al. *Journal of Bone and Mineral Research*	Thank you for your comment and additional reference, this study has now been included in the clinical review on risk assessment tools (see sections 4.2.1 and 4.3.2). Reference to this study has also been added to the research recommendation 2 (see appendix B, section B.1.2), however, the GDG do not believe that this study alone is sufficient to fully answer this research recommendation. Further data is needed in UK population (preferably a prospective cohort study), and also for the QFracture risk assessment tool.

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						Accepted for publication 24 February 2012. DOI: 10.1002/jbmr.1582	
159	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.04	Full	13	5	It would be difficult to use both FRAX and QFracture screening tools for patients with low muscle strength.	Thank you for your comment. We agree with your observation and the research recommendation you are referring to will address risk assessment in people with causes of secondary osteoporosis, including low muscle strength due for example to rheumatoid arthritis or spinal cord injury.
160	NETSCC, HTA Ref 2	7.12	Full	13	7	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** Is this a valid question as BMD needed to follow up treatment for effect and patient compliance with treatment?	Thank you for your comment. This research recommendation is aimed to establish whether the performance of FRAX is improved by the addition of BMD value. BMD measurement for effectiveness and compliance with treatment would be a different question, outside the remit of this short guideline.
161	Bone Research Society, the	10.12	Full	14	Algorithm	Should accommodate <40y olds "before starting treatments that may adversely affect bone density (for example, high-dose glucocorticoid use or treatment for breast or prostate cancer)."	Thank you for your comment, this has now been amended in the algorithm.
162	British Society for Rheumat	12.16	Full	14	Algorithm	Should accommodate <40y olds "before starting treatments that may adversely affect bone density (for example, high-dose glucocorticoid use or treatment for breast or prostate cancer)."	Thank you for your comment, this has now been amended in the algorithm.

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	ology						
163	British Thoracic Society	16.01	Full	14	Algorithm	A trial run of patients through the Algorithm 2.3 on Page 14 has found that it is difficult to follow.	Thank you for your comment. We have altered the recommendations and amended the algorithm to make the pathway clearer following stakeholder feedback..
164	British Thoracic Society	16.03	Full	14	Algorithm	Oral glucocorticoid –see above	Thank you for your comment.
165	Sheffield Teaching Hospitals NHS Foundation Trust	20.12	Full	14	Algorithm	Should accommodate <40y olds "before starting treatments that may adversely affect bone density (for example, high-dose glucocorticoid use or treatment for breast or prostate cancer)."	Thank you for your comment, this has now been amended in the algorithm.
166	National Osteoporosis Society	5.07	Full	14	1	Within the layout of the algorithm the recommendation which states "or before starting treatments that may adversely affect bone density (for example, high-dose glucocorticoids or treatment for breast or prostate cancer)") is positioned towards the bottom of the algorithm. There is potential when referring to the algorithm to miss this statement for the younger (<50) group undergoing treatment.	Thank you for your comment. We have now repeated the same sentence in the <40 group box. People <50 years follow the same pathway as people up to 84 years.
167	British Orthopaedic Association - Patient Liaison group	13.08	FULL	14	1	the algorythm for <50 should we feel specify epileptic patients as they may have a higher risk of problems	Thank you for your comment. The algorithm reflects the recommendations. The aim of the recommendations is to highlight the groups most at risk. The GDG felt that younger people using anti-epileptic drugs should not all have risk assessment .People with epilepsy represent a heterogeneous group – not all antiepileptic drugs are considered to have an effect on bone and of

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							those that do e.g. sodium valproate the effect can be on calcium metabolism and risk of osteomalacia rather than osteoporosis. The BNF reports osteoporosis as being a 'very rare' side effect with carbamazepine.
168	British Pain Society	25.01	x	14	1	Consider altering to "premature or surgical" untreated menopause	Thank you for your suggestion. Following debate, the developers do not wish to change this wording as it was felt the current wording is clear. The GDG believe that the term premature untreated menopause includes menopause as a result of surgical treatment.
169	British Orthopaedic Association - Patient Liaison group	13.09	FULL	15	1	We fell that these 'wavey' little boxes should also make reference to epilepsy	Thank you for your comment. The boxes have now been removed. Epilepsy was not included as the GDG did not consider it an independent major risk factor.
170	Julia Hippisley-Cox, Carol Coupland	18.03	Full	15	3	QFracture (2012) has been updated to include additional variables all of which were significant and had hazard ratios of > 1.2. The additional factors include previous fragility fracture, ethnicity, all classes of antidepressants, COPD, Epilepsy diagnosis/treatment, dementia, parkinsons disease, cancer, SLE, chronic renal disease, Type 1 diabetes, residential care home status. Some variables have been combined with existing ones where appropriate (eg asthma and COPD have similar risks and are now one variable which includes either asthma or COPD). The adjusted hazard ratios for the new	Thank you for this information. Unfortunately we were unable to use this evidence as it was not in the public domain during the development of this guideline. All included evidence should be in the public domain to ensure transparency of the development process.

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						variables compare well with those published in other suitable studies and those referred to in section 3.3.1 and 3.6.1. The updated regression coefficients for QFracture are included in the paper and the algorithm will be published as freely available open source software when the paper is published. The updated web calculator is at www.qfracture.org/2012 The password will be removed when the paper is published.	
171	Spinal Injuries Association	9.04	Full	16	15	Why is spinal cord injury not included given that it is a far stronger prognostic factor than any of the conditions mentioned?	Thank you for your comment. This area was debated extensively by the group and the views you forward were discussed. The group disagree with your suggestions as immobility is included as cause of secondary osteoporosis.
172	The Children's Trust	21.00	full	16	15	There is a lot of data on the increased risk of fracture in children with severe developmental disorders, including Cerebral Palsy. There is some evidence that children with severe acquired brain injury also have reduced BMD. Hermon G, Liegeois F, Watt H and Mayston M. (2011) *Abstracts. Developmental Medicine &*  Untitled.msg *Child Neurology, 53:*53	Thank you for your comment and this information. The assessment of children is outside the scope of the guideline.
173	Technical	30.0	full	16	17	Is it possible to clarify the steps that were taken	Full details of this review are explained in

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	Advisers	0				in the identification of studies for this review? I think you started by searching for IPD meta-analysis (why choose to do this?) followed by a search specifically for updates? How was the additional information prognostic factors identified (page 17 line 1). For 'history of falls', was a full search carried out just for this or was the information from the other searches?	Appendix C (section C.1.2). A summary of this is also included in the Full guideline, chapter 3 (section 3.1, 3.2 and 3.3) The GDG recognised that IPD meta-analysis was the ideal study design for this type of question due to a number of reasons listed in Appendix C. A search for these IPD meta-analyses of all the prognostic factors was carried out and we identified one IPD-meta-analysis for each of the prognostic factors, except for falls history. A full search was then carried out for this prognostic factor and all the relevant studies were selected and reviewed (as a comprehensive systematic review).
174	Technical Advisers	30.01	full	17	10	How was quality assessed for this question? It isn't clear in the appendix either.	Different quality assessment checklists were used for IPD meta-analysis and systematic review of falls history. Full details about quality assessment for Question 1 are available in appendix C (section C.2.1.1) In appendix D, after each evidence table, there is a quality assessment table. For IPD studies, the quality assessment is explained in the table caption for each study: Methodology checklist* for quality assessment of systematic reviews of prognostic studies (*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden JA, Côté P, Bombardier C.) For prognostic studies (history of falls), we have completed the standard NICE methodology checklist in the guidelines manual.
175	British Thoracic	16.04	Full	18	Tables	Widespread use of relative risk makes this a difficult document for practicing clinicians to	Thank you for your comment. We agree that data like ARR and NNT could be more informative and

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Society					interpret for the individual patient. There should be more ARR and NNT and information given in such a way that would be useful for a patient to know.	clinically relevant, but we are reporting here what the authors reported in their studies.
176	Technical Advisers	30.02	full	18	Table 1	This approach of putting the footnotes in the comments column is good. But I wonder if it could be made clearer? Could symbols in the results column be subscripted? And separate the explanations for the different symbols in the comments column by starting them on separate lines?	Thank you for your comment. We have improved the tables 1-16 following your suggestion.
177	Technical Advisers	30.03	full	28	2	Were any other sources of data on regression coefficients available or considered? A short explanation of Q-fracture and FRAX might be useful here or a cross-referral to the later sections where they are described.	Thank you for your comment, we have added a cross reference to chapter 4. We have explained in this paragraph that at present, regression coefficients for FRAX are not publicly available.
178	British Pain Society	25.02	x	28	13	Tricvclics specifically mentioned as risk factor- no dose threshold; not mentioned in formal pathway or in initial scope (see p 9)	Thank you for your comment. This section is reporting the results from the derivation of QFracture. They are not risk factors that were pre-specified in scope.
179	British Pain Society	25.03	x	28	19	Tricvclics specifically mentioned as risk factor- no dose threshold; not mentioned in formal pathway or in initial scope (see p 9)	Thank you for your comment. This section is reporting the results from the derivation of QFracture. They are not risk factors that were pre-specified in scope.
180	Bone Research Society, the	10.13	Full	28	23	Adjusted hazard ratios for fracture are available for FRAX [Kanis 2005, 2008a]	Thank you for your comment, we have reviewed these references. In the Kanis 2005 paper it is not clear whether the data are linked to the FRAX tool (which was released in 2008). Results from univariate analysis are not available (they are all adjusted for age), and RR for some risk factors (for example Secondary osteoporosis) are not reported. To our knowledge, the WHO Technical Report (Kanis 2008a): 'Assessment of osteoporosis at

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							the primary health-care level' was published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf The 10-year probability data reported in this paper are adjusted for at least age, and univariate analysis are not available. This paper does not state that the hazard ratios reposted are in fact the regression coefficients for FRAX.
181	British Society for Rheumatology	12.17	Full	28	23	Adjusted hazard ratios for fracture are available for FRAX [Kanis 2005, 2008a]	Thank you for your comment, we have reviewed these references. In the Kanis 2005 paper it is not clear whether the data are linked to the FRAX tool (which was released in 2008). Results from univariate analysis are not available (they are all adjusted fir age), and RR for some risk factors (for example Secondary osteoporosis) are not reported. To our knowledge, the WHO Technical Report: 'Assessment of osteoporosis at the primary health-care level' was published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf The 10-year probability data reported in this paper are adjusted for at least age, and univariate analysis are not available.
182	Sheffield Teaching Hospitals NHS Foundation Trust	20.13	Full	28	23	Adjusted hazard ratios for fracture are available for FRAX [Kanis 2005, 2008a]	Thank you for your comment, we have reviewed these references. In the Kanis 2005 paper it is not clear whether the data are linked to the FRAX tool (which was released in 2008). Results from univariate analysis are not available (they are all adjusted fir age), and RR for some risk factors (for example

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							Secondary osteoporosis) are not reported. To our knowledge, the WHO Technical Report: 'Assessment of osteoporosis at the primary health-care level' was published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf The 10-year probability data reported in this paper are adjusted for at least age, and univariate analysis are not available.
183	Spinal Injuries Association	9.05	Full	28	24	Given that table entry "other causes of secondary osteoporosis" (of which spinal cord injury is probably the most important) is the only one amongst 32 not to contain any "regression coefficients" why are there no research recommendations to investigate this lack of information?	Thank you for your comment. The table is reporting the coefficients reported in the derivation study of QFracture. The GDG made the following research recommendations that can be applied to people with spinal cord injury: 3) What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults with causes of secondary osteoporosis? (see appendix B for further details)
184	Julia Hippisley-Cox, Carol Coupland	18.04	Full	28	10,15	QFracture also includes age and BMI which need to be added to the list of risk factors in this section.	Thank you for your comment. The section has been amended to include age and BMI.
185	British Thoracic Society	16.05	Full	31	Figures	Axes – incidence no denominator	Thank you for your comments. We have re-labelled the figures accordingly.
186	Technical Advisers	30.04	full	33	Table 5 and 6	Typo in axes	Thank you, the typo has been corrected.
187	Bone Research Society, the	10.14	Full	35	2	This may be true in one sense, but there are several economic studies that examine the fracture probability at which an intervention becomes cost-effective [Borgstrom 2010a,b, 2011, Ivergaard 2010, Kanis 2008b Jonsson 2011, Strom 2010]	Thank you for bringing these studies to our attention. However, after considering these studies we have concluded that they do not pertain specifically to the targeting of fragility fracture risk assessment tools, which is our review question.

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188	British Society for Rheumatology	12.18	Full	35	2	This may be true in one sense, but there are several economic studies that examine the fracture probability at which an intervention becomes cost-effective [Borgstrom 2010a,b, 2011, Ivergaard 2010, Kanis 2008b Jonsson 2011, Strom 2010]	Thank you for bringing these studies to our attention. However, after considering these studies we have concluded that they do not pertain specifically to the targeting of fragility fracture risk assessment tools, which is our review question.
189	Sheffield Teaching Hospitals NHS Foundation Trust	20.14	Full	35	2	This may be true in one sense, but there are several economic studies that examine the fracture probability at which an intervention becomes cost-effective [Borgstrom 2010a,b, 2011, Ivergaard 2010, Kanis 2008b Jonsson 2011, Strom 2010]	Thank you for bringing these studies to our attention. However, after considering these studies we have concluded that they do not pertain specifically to the targeting of fragility fracture risk assessment tools, which is our review question.
190	British Pain Society	25.04	x	35	18	Family history shown to be an important factor in determining risk for both men and women- not included in P9 formal at-risk groups.	Thank you for your comment. We agree that family history is an important prognostic factor and this was reflected in the guideline, as well as in the recommendations (recommendation 2).
191	Bone Research Society, the	10.15	Full	37		*Quality of evidence:* The statement on vertebral fractures is too soft. There is good evidence that the vast majority of vertebral fractures are missed in GP databases [de Lusignan 2004]. Whereas there is indirect evidence that hip fractures are well recorded [Hippisley-Cox 2009], there is little convincing evidence that all the risk factors are well recorded. This aspect of quality at least deserves review.	Thank you for your comment and additional references. We reviewed the de Lusignan 2004 paper, but did not find any specific mention to vertebral fracture, but only to fragility fracture in general. The GDG acknowledged the limitations of GP databases for recording risk factors, however, the recommendations in this section (Recommendations 1 and 3) focus on age as the primary risk factor for fragility fracture, and the GDG's aim was to estimate a cut-off age below which assessment of fragility fracture in people without risk factors would be unlikely to be necessary, therefore the GDG was interested in epidemiological data only (Hippisley-Cox 2009, Collins 2011, and Singer 1998). The evidence for all the other risk factors is

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							considered in the next section (Recommendation 2), where the quality of evidence for the risk factors is explained in more detail.
192	British Society for Rheumatology	12.19	Full	37		*Quality of evidence:* The statement on vertebral fractures is too soft. There is good evidence that the vast majority of vertebral fractures are missed in GP databases [de Lusignan 2004]. Whereas there is indirect evidence that hip fractures are well recorded [Hippisley-Cox 2009], there is little convincing evidence that all the risk factors are well recorded. This aspect of quality at least deserves review.	Thank you for your comment and additional references. We reviewed the de Lusignan 2004 paper, but did not find any specific mention to vertebral fracture, but only to fragility fracture in general. The GDG acknowledged the limitations of GP databases for recording risk factors, however, the recommendations in this section (Recommendations 1 and 3) focus on age as the primary risk factor for fragility fracture, and the GDG's aim was to estimate a cut-off age below which assessment of fragility fracture in people without risk factors would be unlikely to be necessary, therefore the GDG was interested in epidemiological data only (Hippisley-Cox 2009, Collins 2011, and Singer 1998). The evidence for all the other risk factors is considered in the next section (Recommendation 2), where the quality of evidence for the risk factors is explained in more detail.
193	Sheffield Teaching Hospitals NHS Foundation Trust	20.15	Full	37		*Quality of evidence:* The statement on vertebral fractures is too soft. There is good evidence that the vast majority of vertebral fractures are missed in GP databases [de Lusignan 2004]. Whereas there is indirect evidence that hip fractures are well recorded [Hippisley-Cox 2009], there is little convincing evidence that all the risk factors are well recorded. This aspect of quality at least deserves review.	Thank you for your comment and additional references. We reviewed the de Lusignan 2004 paper, but did not find any specific mention to vertebral fracture, but only to fragility fracture in general. The GDG acknowledged the limitations of GP databases for recording risk factors, however, the recommendations in this section (Recommendations 1 and 3) focus on age as the primary risk factor for fragility fracture, and the GDG's aim was to estimate a cut-off age below which assessment of fragility fracture in people without risk factors would be unlikely to be

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							necessary, therefore the GDG was interested in epidemiological data only (Hippisley-Cox 2009, Collins 2011, and Singer 1998). The evidence for all the other risk factors is considered in the next section (Recommendation 2), where the quality of evidence for the risk factors is explained in more detail.
194	British Orthopaedic Association - Patient Liaison group	13.10	FULL	37 Rec1	1	make ref to epilepsy	Thank you for your comment. The recommendation is that all men ≥ 75 years and all women ≥ 65 years should be considered for fragility fracture assessment. The GDG did not consider that all people who suffer from epilepsy should have risk assessment performed.
195	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.05	Full	37	1	The practicality of increased workload is not covered in detail in this guideline. The impact on all practice staff, including both GPs and nurses, need to be considered in detail, along with the implications for treatment and associated counselling resources.	Thank you for your comment. The guideline is not recommending screening and we have made a research recommendation to consider the effectiveness of a screening approach which would include the issues you mention. The GDG considered that many people are currently being referred inappropriately for DXA scans and better use of risk assessment tools may be time and cost saving.
196	Scottish Intercollegiate	4.00	Full	37	2	The list of risk factors / secondary causes of osteoporosis considered in recommendation 2 does not include:	Thank you for your comment and information on the development of the forthcoming SIGN guideline. The lists of risk factors and causes of

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Guidelines Network					▪ HIV ▪ Anorexia nervosa ▪ Depression (or treatment with antidepressants) ▪ Multiple sclerosis ▪ Use of PPIs ▪ Use of antipsychotic medications ▪ Use of aromatase inhibitors ▪ Use of gonadotrophin releasing hormone inhibitors ▪ Use of long acting progestogen only contraceptives ▪ Use of beta-blockers ▪ Use of loop diuretics. These are being investigated by the SIGN guideline on osteoporosis currently in development.	secondary osteoporosis in this short guideline are not intended to be exhaustive, the focus is on prediction of risk and not whether individual factors were associated with increased relative risk.
197	British Thoracic Society	16.07	Full	37	Recommendation 3	This is clearly a very older adult orientated document. However routine screening for reduced bone mineral density takes place in Cystic Fibrosis children and young adults from 10 years on an alternate year basis which is at odds with this NICE guidance. It would seem sensible to add CF as a major risk factor in the younger population in addition to those they have already listed in the text.	Thank you for your comment. This guideline is for adults (aged 18 years and over) and the assessment of children is outside the remit of the guideline. We have added reference to the CF guidelines on Low Mineral Density to the Full guideline but consider that the care of people with cystic fibrosis is a specialist topic
198	Technical Advisers	30.05	full	37	Section 3.7	'Other considerations'. More discussion on why fracture risk should not be routinely assessed in <50 years old is needed	Thank you for your comment, we have now added more explanation.
199	British Pain Society	25.05	x	38	Footnote g	No mention of tricvclics, or FH as risks here.	Thank you for your comment. The GDG acknowledge there is a variety of causes of secondary osteoporosis, and they could not all be considered singularly in the guideline.
200	Technical	32.0	full	38	Economic	There should be consideration of false	Thank you for your comment. We agree and we

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	Adviser (HE)	0			considerations	negatives and whether the balance between focussed assessment offset the missed events?	have expanded our explanation and added more considerations to the relevant section.
201	British Orthopaedic Association - Patient Liaison group	13.11	FULL	38	1	ditto	Thank you for your comment. We agree and we have expanded our explanation and added more considerations to the relevant section.
202	Bone Research Society, the	10.16	Full	39		*History of falls*: Validation of self-reports and adjusting for confounders is not relevant to opportunistic case finding [Kanis 2008a, 2012a]. The exercise is not to seek causality or a mechanism. In case-finding, the history is taken as delivered. Accuracy errors will be appropriate for the clinical context. Adjustment for confounders (other than the risk factors used in the algorithm and time since baseline) risks distorting the hazard ratio.	Thank you for your comment. We acknowledge that accuracy errors will be appropriate for the clinical context as information on falls history largely rely on self-reporting. But this was something that we needed to take into consideration when assessing study quality. History of falls is considered as an important prognostic factor in this guideline and this is reflected in recommendation 2.
203	British Society for Rheumatology	12.20	Full	39		*History of falls*: Validation of self-reports and adjusting for confounders is not relevant to opportunistic case finding [Kanis 2008a, 2012a]. The exercise is not to seek causality or a mechanism. In case-finding, the history is taken as delivered. Accuracy errors will be appropriate for the clinical context. Adjustment for confounders (other than the risk factors used in the algorithm and time since baseline) risks distorting the hazard ratio.	Thank you for your comment. We acknowledge that accuracy errors will be appropriate for the clinical context as information on falls history largely rely on self-reporting. But this was something that we needed to take into consideration when assessing study quality. History of falls is considered as an important prognostic factor in this guideline and this is reflected in recommendation 2.
204	Sheffield Teaching Hospitals	20.16	Full	39		*History of falls*: Validation of self-reports and adjusting for confounders is not relevant to opportunistic case finding [Kanis 2008a, 2012a].	Thank you for your comment. We acknowledge that accuracy errors will be appropriate for the clinical context as information on falls history

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	NHS Foundation Trust					The exercise is not to seek causality or a mechanism. In case-finding, the history is taken as delivered. Accuracy errors will be appropriate for the clinical context. Adjustment for confounders (other than the risk factors used in the algorithm and time since baseline) risks distorting the hazard ratio.	largely rely on self-reporting. But this was something that we needed to take into consideration when assessing study quality. History of falls is considered as an important prognostic factor in this guideline and this is reflected in recommendation 2.
205	Bone Research Society, the	10.17	Full	40		*Family history of fracture:* The drawing of attention to fracture history other than that captured by the algorithms (e.g. family vertebral) is important as it highlights the difference between risk factors used in the algorithms and those used for case finding. The distinction could usefully be emphasized earlier. Other examples are kyphosis, poor falls history (for FRAX) etc	Thank you for your comment. We have clarified this point in the evidence to recommendations section for recommendation 2 ('other considerations box'), section 3.7 of the full guideline, and added more detail about examples like kyphosis.
206	British Society for Rheumatology	12.21	Full	40		*Family history of fracture:* The drawing of attention to fracture history other than that captured by the algorithms (e.g. family vertebral) is important as it highlights the difference between risk factors used in the algorithms and those used for case finding. The distinction could usefully be emphasized earlier. Other examples are kyphosis, poor falls history (for FRAX) etc	Thank you for your comment. We have clarified this point in the evidence to recommendations section and added more detail about examples like kyphosis.
207	Sheffield Teaching Hospitals NHS Foundation Trust	20.17	Full	40		*Family history of fracture:* The drawing of attention to fracture history other than that captured by the algorithms (e.g. family vertebral) is important as it highlights the difference between risk factors used in the algorithms and those used for case finding. The distinction could usefully be emphasized earlier. Other examples are kyphosis, poor falls history (for FRAX) etc	Thank you for your comment. We have clarified this point in the evidence to recommendations section and added more detail about examples like kyphosis.
208	Technical	30.0	full	40	Section 3.7	'other considerations'. Is 'the review' referring to	No, it's the IPD review. We have clarified this in

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Advisers	6				the review undertaken by the NCC	the text.
209	ProStrakan Group	14.01	Full	41	1-10	PCT wide audits of GP practices have been systematically undertaken. Assessing highest risk individuals using validated tools is the next logical step. FRAX seems to give more comprehensive guidance on whether to treat especially in borderline cases and the link to NOGG red/amber/green decision guide provides further support for clinical decision making – Qfracture does not seem to provide as much support to GPs, so FRAX is generally favoured.	Thank you for your comment. Treatment and intervention thresholds are outside the remit of this short clinical guideline. The evidence reviewed show that performances of FRAX and QFracture in predicting risk of fragility fracture are similar.
210	British Orthopaedic Association - Patient Liaison group	13.12	FULL	41	1	other consideration – the continuation of the table from P40: here is another instance where it will benefit epileptic patients to be highlighted.	Thank you for your comment. The GDG included major risk factors that they considered should trigger risk assessment and did not consider that epilepsys or treatments for epilepsy should be added.
211	Scottish Intercollegiate Guidelines Network	4.01	Full	41	2	The following article addresses this research recommendation: Maclean FR, Thomson SA, Gallacher SJ. Using WHO-FRAX to describe fracture risk: experience in primary care. Scott Med J. 2011 Dec 16. [Epub ahead of print]	Thank you for highlighting this recent reference to us. We agree that the paper begins to answer the research recommendation. As the paper suggests data is present on GP computers to allow risk calculation to be made. We have retained the research recommendation as a full review of cost effectiveness of this approach is also required. The analysis should include use of routine data to identify men, use integral calculators if possible, and assess how many of these people would be seen opportunistically.
212	UCB Pharma Ltd	26.02	Full	41	4	Identification of individuals at high risk of fragility fracture is important to effectively target healthcare interventions. Prevention efforts	Thank you for your comment. The strategy proposed included considering assessment of all older people and younger people with risk

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						should target all women, especially if they have multiple risk factors.	factors.
213	UCB Pharma Ltd	26.03	Full	41	4	There are limits to what can be achieved by opportunistic screening, which relies on people seeking out healthcare services for another reason, rather than proactively inviting them to attend for interview and clinical assessment. Consider supplementing the opportunistic screening programme with a system targeting specific high-risk of fracture groups. Effective implementation of the latter will most likely require financial incentives at the primary care level. Risk assessment tools such as FRAX and QFracture can help primary care physicians identify these individuals once they commit to screening but do not address the broader topic of opportunism. Primary care centres are typically closer to the patient and thus convenient for opportunistic screening.	Thank you for your comment. We have made a research recommendation on the use of GP computer systems to target risk assessment. (See appendix B for further details).
214	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.06	Full	42	3-4	There does not seem to be a significant difference between the two screening tools. It is disappointing that no agreed intervention threshold has been suggested.	Thank you for your comment. Intervention thresholds are outside the remit of this short clinical guideline.

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215	Technical Advisers	30.07	full	42	3	Why and how did the GDG agree on these particular tools? Are others available and why were they not considered?	These are the tools listed in the scope. There are other tools available, but the stakeholders during the scoping workshop indicated that FRAX and QFracture are the ones the guideline should focus on: http://www.nice.org.uk/nicemedia/live/13281/56271/56271.pdf More information has been added to the introduction in Chapter 4.
216	Bone Research Society, the	10.18	Full	42	19	Internal and external validation of QFracture is confined to GP databases which may be subject to common errors of recording (see example on comment to page 37). Additionally patients with prior fractures have been excluded.	Thank you for your comment. All these factors have been taken into account in the quality assessment of this study.
217	British Society for Rheumatology	12.22	Full	42	19	Internal and external validation of QFracture is confined to GP databases which may be subject to common errors of recording (see example on comment to page 37). Additionally patients with prior fractures have been excluded.	Thank you for your comment. All these factors have been taken into account in the quality assessment of this study.
218	Sheffield Teaching Hospitals NHS Foundation Trust	20.18	Full	42	19	Internal and external validation of QFracture is confined to GP databases which may be subject to common errors of recording (see example on comment to page 37). Additionally patients with prior fractures have been excluded.	Thank you for your comment. All these factors have been taken into account in the quality assessment of this study.
219	National Osteoporosis Society	5.08	Full	42	29	In the section introducing risk assessment tools the role of BMD in FRAX is stated. It should also be made clear that it is not possible to enhance a 10-year fracture risk assessment with BMD in QFracture.	Thank you for your comment. This is reflected in recommendation 8, where we recommend the use of FRAX to recalculate fracture risk after BMD assessment.
220	Bone Research	10.19	Full	42	38	Uses a female reference range only and BMD measured by DXA at the femoral neck [Kanis	Thank you for your comment. We have amended the introduction.

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	Society, the					2008c].	
221	British Society for Rheumatology	12.23	Full	42	38	Uses a female reference range only and BMD measured by DXA at the femoral neck [Kanis 2008c].	Thank you for your comment. We have amended the introduction.
222	Sheffield Teaching Hospitals NHS Foundation Trust	20.19	Full	42	38	Uses a female reference range only and BMD measured by DXA at the femoral neck [Kanis 2008c].	Thank you for your comment. We have amended the introduction.
223	Bone Research Society, the	10.20	Full	43	18	It should be noted that the AUCs of the different studies are not comparable because of different follow up times and age ranges both of which affect AUC [Kanis 2012b]	Thank you for your comment. To our knowledge, comparing AUC between studies is completely valid and in fact an essential component when evaluating the transportability of a prediction model in patients from other settings, different case-mix and different follow-up times compared to the datasets used to derive the model.
224	British Society for Rheumatology	12.24	Full	43	18	It should be noted that the AUCs of the different studies are not comparable because of different follow up times and age ranges both of which affect AUC [Kanis 2012b]	Thank you for your comment. To our knowledge, comparing AUC between studies is completely valid and in fact an essential component when evaluating the transportability of a prediction model in patients from other settings, different case-mix and different follow-up times compared to the datasets used to derive the model
225	Sheffield Teaching Hospitals NHS Foundatio	20.20	Full	43	18	It should be noted that the AUCs of the different studies are not comparable because of different follow up times and age ranges both of which affect AUC [Kanis 2012b]	Thank you for your comment. To our knowledge, comparing AUC between studies is completely valid and in fact an essential component when evaluating the transportability of a prediction model in patients from other settings, different

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	n Trust						case-mix and different follow-up times compared to the datasets used to derive the model
226	Technical Advisers	30.09	full	43	18	A very brief summary of how studies in this review were quality assessed would be useful. And did this differ from the approach in question 1?	Thank you for your comment. Full details about quality assessment for this review question are in appendix C (section C.2.1.2). We have now added a brief explanation and the link to this methodology section (in addition to the link to the quality assessment tables).
227	Bone Research Society, the	10.22	Full	47	Table 25	For comparability, AUCs need adjustment for age and time since baseline (see comment to page 43, line 18).	Thank you for your comment. We recognised the limitations of using AUC as an outcome and this was noted in the quality of evidence section in recommendation 5 (Section 4.7). The GDG recognised that discrimination data based on the AUC alone are not an adequate way of establishing whether one tool performs better than another; the AUC is based on the ranks of the predicted probabilities and compares these ranks in people with and without the disease; but the ROC curve does not use the actual predicted probabilities and therefore it is not very sensitive to differences in probabilities between risk scores. In addition, studies included in the review contained individuals of different age ranges which may affect the AUC. Data on calibration and sensitivity/specificity were used when comparing risk assessment tools where possible.
228	British Society for Rheumatology	12.26	Full	47	Table 25	For comparability, AUCs need adjustment for age and time since baseline (see comment to page 43, line 18).	Thank you for your comment. We recognised the limitations of using AUC as an outcome and this was noted in the quality of evidence section in recommendation 5 (Section 4.7). The GDG recognised that discrimination data based on the AUC alone are not an adequate way of establishing whether one tool performs better than another; the AUC is based on the ranks of the predicted probabilities and compares these

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							ranks in people with and without the disease; but the ROC curve does not use the actual predicted probabilities and therefore it is not very sensitive to differences in probabilities between risk scores. In addition, studies included in the review contained individuals of different age ranges which may affect the AUC. Data on calibration and sensitivity/specificity were used when comparing risk assessment tools where possible.
229	Sheffield Teaching Hospitals NHS Foundation Trust	20.22	Full	47	Table 25	For comparability, AUCs need adjustment for age and time since baseline (see comment to page 43, line 18).	Thank you for your comment. We recognised the limitations of using AUC as an outcome and this was noted in the quality of evidence section in recommendation 5 (Section 4.7). The GDG recognised that discrimination data based on the AUC alone are not an adequate way of establishing whether one tool performs better than another; the AUC is based on the ranks of the predicted probabilities and compares these ranks in people with and without the disease; but the ROC curve does not use the actual predicted probabilities and therefore it is not very sensitive to differences in probabilities between risk scores. In addition, studies included in the review contained individuals of different age ranges which may affect the AUC. Data on calibration and sensitivity/specificity were used when comparing risk assessment tools where possible.
230	British Medical Association (BMA) - Clinical and Prescribing	17.02	Full	11; 37	11; 17-21	History of family fractures is not always available to GPs. If this is going to be a trigger, consideration needs to be given as to how to advertise for this information.	Thank you for your comment. It is not intended that GPs search for these factors, should they come to light during an assessment, they should be considered. It was the experience of the GDG that people do present to healthcare professionals with a family history of fracture.

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	Subcommittee of the General Practitioners Committee						
231	Bone Research Society, the	10.23	Full	49	2	It should be noted that calibration of FRAX to the UK is derived from the epidemiology of fracture (in Edinburgh) and national death statistics. Predicted and observed risks are different units of measurement (incidence vs. probability). Ratios of unity are thus not expected [Kanis 2012b]	Thank you for your comment. We are aware of the reference and we have looked at it. On page 49, calibration data of the Canadian FRAX tool was presented by gender. Figure 9 showed the graphs of predicted risk vs. observed risk, both expressed as proportions (%).
232	British Society for Rheumatology	12.27	Full	49	2	It should be noted that calibration of FRAX to the UK is derived from the epidemiology of fracture (in Edinburgh) and national death statistics. Predicted and observed risks are different units of measurement (incidence vs. probability). Ratios of unity are thus not expected [Kanis 2012b]	Thank you for your comment. We are aware of the reference and we have looked at it. On page 49, calibration data of the Canadian FRAX tool was presented by gender. Figure 9 showed the graphs of predicted risk vs. observed risk, both expressed as proportions (%).
233	Sheffield Teaching Hospitals NHS Foundation Trust	20.23	Full	49	2	It should be noted that calibration of FRAX to the UK is derived from the epidemiology of fracture (in Edinburgh) and national death statistics. Predicted and observed risks are different units of measurement (incidence vs. probability). Ratios of unity are thus not expected [Kanis 2012b]	Thank you for your comment. We are aware of the reference and we have looked at it. On page 49, calibration data of the Canadian FRAX tool was presented by gender. Figure 9 showed the graphs of predicted risk vs. observed risk, both expressed as proportions (%).
234	Bone Research Society, the	10.24	Full	52	12	The hip fracture risks used in the New Zealand FRAX model are national data. Thus lack of concordance might equally be attributed to mis-calibration of FRAX or selection biases of the cohort [Kanis 2012b]	Thank you for your comment. This has been amended in the quality assessment of the study (appendix D).
235	British	12.2	Full	52	12	The hip fracture risks used in the New Zealand	Thank you for your comment. This has been

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Society for Rheumatology	8				FRAX model are national data. Thus lack of concordance might equally be attributed to mis-calibration of FRAX or selection biases of the cohort [Kanis 2012b]	amended in the quality assessment of the study (appendix D).
236	Sheffield Teaching Hospitals NHS Foundation Trust	20.24	Full	52	12	The hip fracture risks used in the New Zealand FRAX model are national data. Thus lack of concordance might equally be attributed to mis-calibration of FRAX or selection biases of the cohort [Kanis 2012b]	Thank you for your comment. This has been amended in the quality assessment of the study (appendix D).
237	William Leslie	1.03	Appendix	58		Leslie WD, et al Journal of Clinical Endocrinology & Metabolism. 2007; 92(1):77-81. Ref ID: LESLIE2007D. Excluded "Paper did not report area under curve" but Table 2 gives AUCs.	We had included this study in the review and this reference has been removed from the excluded list of studies.
238	Bone Research Society, the	10.25	Full	58	12	Though not primarily an economic analysis, the effects of screening strategies on resource allocation has been investigated [Johansson 2009, 2011]	Thank you for bringing these studies to our attention. Johansson 2009 has been excluded because it is not an economic evaluation. Johansson 2011 has been excluded because its analysis is not applicable for our purposes (ie an incremental analysis was not conducted). Details for exclusion have been added into the section.
239	British Society for Rheumatology	12.29	Full	58	12	Though not primarily an economic analysis, the effects of screening strategies on resource allocation has been investigated [Johansson 2009, 2011]	Thank you for bringing these studies to our attention. Johansson 2009 has been excluded because it is not an economic evaluation. Johansson 2011 has been excluded because its analysis is not applicable for our purposes (ie an incremental analysis was not conducted). Details for exclusion have been added into the section.
240	Sheffield Teaching Hospitals NHS	20.25	Full	58	12	Though not primarily an economic analysis, the effects of screening strategies on resource allocation has been investigated [Johansson 2009, 2011]	Thank you for bringing these studies to our attention. Johansson 2009 has been excluded because it is not an economic evaluation. Johansson 2011 has been excluded because its

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Foundation Trust						analysis is not applicable for our purposes (ie an incremental analysis was not conducted). Details for exclusion have been added into the section.
241	Technical Adviser (HE)	32.01	Full	58	12	Were there any studies that looked at treatment strategies using different risk assessment tools? This could help inform whether any particular tool was significantly better than others at identifying those most at risk.	Thank you for your comment. We identified one study by Johansson et al (2011) which looked at treatment based on BMD vs FRAX+BMD. However this study has been excluded because its analysis is not applicable for our purposes (ie an incremental analysis was not conducted).
242	Julia Hippisley-Cox, Carol Coupland	18.06	Full	58	Table 36	The key thing about this table is that patients who were high on QFracture and low on FRAX actually had higher risks than those who were high on FRAX and low on QFracture. We think a sentence to this effect would help the reader understand the significance of the reclassification stats.	Thank you for your comment. This information has now been added to the full guideline.
243	Bone Research Society, the	10.26	Full	59	13	See comment to page 43, line 18. It should be noted that the AUCs of the different studies are not comparable because of different follow up times and age ranges both of which affect AUC [Kanis 2012b]	Thank for your comment. To our knowledge, comparing AUC between studies is completely valid and in fact an essential component when evaluating the transportability of a prediction model in patients from other settings, different case-mix and different follow-up times compared to the datasets used to derive the model.
244	British Society for Rheumatology	12.30	Full	59	13	See comment to page 43, line 18. It should be noted that the AUCs of the different studies are not comparable because of different follow up times and age ranges both of which affect AUC [Kanis 2012b]	Thank for your comment. To our knowledge, comparing AUC between studies is completely valid and in fact an essential component when evaluating the transportability of a prediction model in patients from other settings, different case-mix and different follow-up times compared to the datasets used to derive the model.
245	Sheffield Teaching Hospitals NHS Foundatio	20.26	Full	59	13	See comment to page 43, line 18. It should be noted that the AUCs of the different studies are not comparable because of different follow up times and age ranges both of which affect AUC [Kanis 2012b]	Thank for your comment. To our knowledge, comparing AUC between studies is completely valid and in fact an essential component when evaluating the transportability of a prediction model in patients from other settings, different

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	n Trust						case-mix and different follow-up times compared to the datasets used to derive the model.
246	Bone Research Society, the	10.27	Full	60		*Trade-off between clinical benefits and harm:* Absolute risk as an outcome - there is a distinction between the incidence of fracture in an individual who lives for ten years and 10 year fracture probability that should be considered [Kanis 2012b, 2008a. 2011a].	Thank you for your comment. The GDG agreed that absolute risk should be considered when assessing risk of fragility fracture. They also recognised the distinction between 10 year probability and the actual incidence of fracture over 10 years. This information has been added to the "trade off between clinical benefits and harms".
247	Bone Research Society, the	10.28	Full	60		*Economic considerations:* This question has been addressed in a number of economic studies [Borgstrom 2010a, b, 2011, Ivergaard 2010, Kanis 2008b, Jonsson 2011 Strom 2010]	Thank you for bringing these studies to our attention. We have not included these studies since they do not specifically evaluate the measurement of absolute versus relative risk for the assessment of risk of fracture.
248	British Society for Rheumatology	12.31	Full	60		*Trade-off between clinical benefits and harm:* Absolute risk as an outcome - there is a distinction between the incidence of fracture in an individual who lives for ten years and 10 year fracture probability that should be considered [Kanis 2012b, 2008a. 2011a].	Thank you for your comment. The GDG agreed that absolute risk should be considered when assessing risk of fragility fracture. They also recognised the distinction between 10 year probability and the actual incidence of fracture over 10 years. This information has been added to the "trade off between clinical benefits and harms".
249	British Society for Rheumatology	12.32	Full	60		*Economic considerations:* This question has been addressed in a number of economic studies [Borgstrom 2010a, b, 2011, Ivergaard 2010, Kanis 2008b, Jonsson 2011 Strom 2010]	Thank you for bringing these studies to our attention. We have not included these studies since they do not specifically evaluate the measurement of absolute versus relative risk for the assessment of risk of fracture
250	British Thoracic Society	16.09	Full	60		The Guideline is just about calculating risk and does not appear to give any advice about treatment or prophylaxis although the FRAX site refers you online to NOGG site - treatment / prophylaxis is the principal issue for clinicians especially those using steroid therapy.	Thank you for your comment. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools for fragility fracture only. NICE are not involved in the NOGG or RCP guidelines. Intervention and treatment are outside the remit of this guideline.

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						The advice provided on the NOGG website for specific patients, somewhat at odds with other RCP Guidance (Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: Royal College of Physicians, 2002) - if this guidance has changed, this would need emphasised in this document.	In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
251	Sheffield Teaching Hospitals NHS Foundation Trust	20.27	Full	60		*Trade-off between clinical benefits and harm:* Absolute risk as an outcome - there is a distinction between the incidence of fracture in an individual who lives for ten years and 10 year fracture probability that should be considered [Kanis 2012b, 2008a. 2011a].	Thank you for your comment. The GDG agreed that absolute risk should be considered when assessing risk of fragility fracture. They also recognised the distinction between 10 year probability and the actual incidence of fracture over 10 years. This information has been added to the "trade off between clinical benefits and harms".
252	Sheffield Teaching Hospitals NHS Foundation Trust	20.28	Full	60		*Economic considerations:* This question has been addressed in a number of economic studies [Borgstrom 2010a, b, 2011, Ivergaard 2010, Kanis 2008b, Jonsson 2011 Strom 2010]	Thank you for bringing these studies to our attention. We have not included these studies since they do not specifically evaluate the measurement of absolute versus relative risk for the assessment of risk of fracture.
253	Technical Advisers	30.10	full	60	Section 4.7	Does this new recommendation specifically need to mention Qfracture and FRAX?	Thank you for your suggestion. Following debate the developers do not wish to change this wording as it was felt that the current wording is clear. The focus of this recommendation is the need of a formal risk assessment to make the transition from relative risk, based on one risk factor, to absolute risk. QFracture and FRAX are the focus of the next recommendation.
254	Scottish Intercollegiate	4.02	Full	60	12	SIGN agrees with the recommendation to use absolute risk values when assessing risk of fragility fracture. However, we feel that although	Thank you for your comment. We agree that there is currently no published evidence that risk as assessed by risk assessment tools is

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Guidelines Network					the technical mechanics of the process of calculating risk are addressed by this question, a more fundamental question has not been asked – what is the utility of managing patients to effect fracture risk reduction on the basis of these risk assessments? As far as we are aware, there is no published evidence that risk assessed with FRAX or QFracture is amenable to modification with (currently licensed) treatments.	amenable to modification with currently licensed treatments. Treatment options however can also include advice about smoking and alcohol intake and interventions to prevent falls.
255	British Medical Association (BMA) - Clinical and Prescribing Subcommittee of the General Practitioners Committee	17.07	Full	60	12	The web-based assessment tools need to be integrated with existing data on computer systems. This would reduce workload by prompting for missing data as well as facilitating scoring.	Thank you for your comment. We agree that this is likely to be the way forward and already happens with risk assessments for other conditions.
256	National Osteoporosis Society	5.09	Full	61		The guideline recognises that "There is no conclusive evidence that providing treatment on the basis of risk assessment will result in better clinical and cost effective care". It therefore makes the inclusion of BMD (where evidence does exist for treatment reducing fractures) in risk assessment a vital component to in the decision to treat.	Thank you for your comment. The evidence reviews indicated that the addition of BMD did not result in substantial reclassification of risk. The GDG considered that other interventions e.g. prevention of falls were also important.
257	National	5.10	Full	61		"The GDG recognised that until NICE develops	Thank you for your comment. In line with section

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	Osteoporosis Society					further guidance on treatment, the default position for many healthcare practitioners would be to follow guidance set by other organisations or that decisions about which threshold to use will be taken at a local level, in light of characteristics of the high-risk population identified." The National Osteoporosis Society would urge NICE to provide guidance on treatment thresholds to ensure that inconsistent or inappropriate services are not developed in response to this guidance. The utility of the clinical guideline depends on the development in the very near future of updated treatment guidance.	8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
258	Bone Research Society, the	10.29	Full	61		*Other considerations, final paragraph (The GDG had some concerns that, in the absence of evidence…):* This question has been addressed in a number of economic studies [Borgstrom 2010a, b, 2011, Ivergaard 2010, Kanis 2008b; Jonsson 2011 Strom 2010]	Thank you for your comment. We have amended the 'Other considerations' section to clarify that this guideline did not review cost effectiveness and therefore is unable to make recommendations about thresholds. It is anticipated that NICE is preparing for consideration of a review of current related Technology Appraisal guidance (TA160, 161 and 204),
259	British Society for Rheumatology	12.33	Full	61		*Other considerations, final paragraph (The GDG had some concerns that, in the absence of evidence…):* This question has been addressed in a number of economic studies [Borgstrom 2010a, b, 2011, Ivergaard 2010, Kanis 2008b; Jonsson 2011 Strom 2010]	Thank you for your comment. We have amended the 'Other considerations' section to clarify that this guideline did not review cost effectiveness and therefore is unable to make recommendations about thresholds. It is anticipated that NICE is preparing for consideration of a review of current related Technology Appraisal guidance (TA160, 161 and 204).
260	Sheffield	20.2	Full	61		*Other considerations, final paragraph (The*	Thank you for your comment. We have amended

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	Teaching Hospitals NHS Foundation Trust	9				*GDG had some concerns that, in the absence of evidence…):* This question has been addressed in a number of economic studies [Borgstrom 2010a, b, 2011, Ivergaard 2010, Kanis 2008b; Jonsson 2011 Strom 2010]	the 'Other considerations' section to clarify that this guideline did not review cost effectiveness and therefore is unable to make recommendations about thresholds. It is anticipated that NICE is preparing for consideration of a review of current related Technology Appraisal guidance (TA160, 161 and 204).
261	Technical Adviser (HE)	32.02	full	61	Economic considerations	The recommendation to not conduct BMD scans is a good one based on the effectiveness and costing work. The outcomes from the costing analysis should be added to the LETR table	Thank you for your comment. We agree. We have incorporated into the LETR text that our cost analysis showed that risk assessment tools which do not include BMD measurement are less costly than those that include BMD measurement.
262	Scottish Intercollegiate Guidelines Network	4.03	Full	61	1	The FRAX website links to treatment guidance from NOGG that advocates treatment decisions on a basis that widely differs from the evidence-based approach embedded in NICE TA160 & 161; these TAs correctly characterise the vital interaction between treatment & cost-effective benefit in fracture risk reduction - based on confirmation that BMD (measured by DXA) falls below certain thresholds (in the case of alendronic acid (T-score of -2.5 or less)). In clinical practice according to TA161, women with fractures over age of 50 years with osteoporosis should be treated with alendronic acid - a recommendation that reflects published evidence that this approach can reduce fracture risk by ~30-50% (efficacy differs for vertebral and nonvertebral fracture benefit). We cannot understand the sense of advocating prior FRAX in this group - if the implication is that some patients will either not progress to DXA or others might receive treatment without DXA	Thank you for your comment. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools for fragility fracture only. Intervention and treatment are outside the remit of this guideline. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012. In these circumstances we are unable to make comments about the NOGG guideline.

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						(and to do so in patients who might by DXA be shown to have T-scores > -2.4 then they won't benefit from treatment that nevertheless might do harm). The authors should include a cautionary note to avoid using the NOGG treatment guidance if they are keen to recommend FRAX.	
263	Scottish Intercollegiate Guidelines Network	4.04		61	1	It is not clear why recommendation 5 contains an upper age threshold of 84 years. The rationale presented in the guideline does not adequately account for this. The FRAX tool allows entry of data up to age 90. Furthermore, recommendation 6 advises caution when assessing fracture risk in those aged 85 and over due to prediction tools potentially underestimating risk, but one or other of these statements would have to be revised to allow them to co-exist. You can't exercise caution about a derived fracture risk score, in those over 85 if you do not recommend the use of the risk estimation tool in this age group.	Thank you for your comment. We have amended the recommendation to say 'within their allowed age range' and have specified the age ranges for the two tools in the footnotes.
264	Bone Research Society, the	10.30	Full	62	.	*Quality of evidence - There are no other validation studies available in the UK for FRAX.* This is untrue. THIN and the YORK cohort were examined in the validation of FRAX [Kanis 2007, 2008a]	Thank you for your comment. FRAX UK validation cohorts (THIN and YORK) were indeed included in Kanis 2007, but the paper examined the prediction of fracture risk with the use of clinical risk factors alone and clinical risk factors with BMD and it was not clear which clinical risk factors were included in the final model.
265	Bone Research Society, the	10.31	Full	62		*Other considerations. "The GDG considered that the information available to assess tools was suboptimal. The method of development and coefficients used in the FRAX equation are not publicly available, how FRAX treats risk factors and interactions between risk factors (for example, secondary causes of osteoporosis*	Thank you for your comment. To our knowledge, the WHO Technical Report (Kanis 2008a): 'Assessment of osteoporosis at the primary health-care level' was published in 2007. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf The 10-year probability data reported in this

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						and BMD) is not known." This is well described in the technical report which is widely available [Kanis 2008a]	paper are adjusted for at least age, and univariate analysis are not available. This paper does not state that the hazard ratios reposted are in fact the regression coefficients for FRAX. This study is listed as an excluded study in Appendix C (paragraph C.5).
266	British Society for Rheumatology	12.34	Full	62	.	*Quality of evidence - There are no other validation studies available in the UK for FRAX.* This is untrue. THIN and the YORK cohort were examined in the validation of FRAX [Kanis 2007, 2008a]	Thank you for your comment. FRAX validation cohorts (THIN and YORK) were indeed included in Kanis 2007, but the paper examined the prediction of fracture risk with the use of clinical risk factors alone and clinical risk factors with BMD and it did not state which clinical risk factors were included in the final model.
267	British Society for Rheumatology	12.35	Full	62		*Other considerations. "The GDG considered that the information available to assess tools was suboptimal. The method of development and coefficients used in the FRAX equation are not publicly available, how FRAX treats risk factors and interactions between risk factors (for example, secondary causes of osteoporosis and BMD) is not known."* This is well described in the technical report which is widely available [Kanis 2008a]	Thank you for your comment. In the Kanis 2007 paper it is not clear the data refers to the FRAX tool (which was released in 2008). The results report the gradient of risk and AUC for prediction of hip and other osteoporotic fractures on the basis of risk factors alone and risk factors plus BMD.
268	Sheffield Teaching Hospitals NHS Foundation Trust	20.30	Full	62	.	*Quality of evidence - There are no other validation studies available in the UK for FRAX.* This is untrue. THIN and the YORK cohort were examined in the validation of FRAX [Kanis 2007, 2008a]	Thank you for your comment. FRAX validation cohorts (THIN and YORK) were indeed included in Kanis 2007, but the paper examined the prediction of fracture risk with the use of clinical risk factors alone and clinical risk factors with BMD and it did not state which clinical risk factors were included in the final model.
269	Sheffield Teaching Hospitals NHS	20.31	Full	62		*Other considerations. "The GDG considered that the information available to assess tools was suboptimal. The method of development and coefficients used in the FRAX equation are*	Thank you for your comment. In the Kanis 2007 paper it is not clear the data refers to the FRAX tool (which was released in 2008). The results report the gradient of risk and AUC for prediction

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	Foundation Trust					*not publicly available, how FRAX treats risk factors and interactions between risk factors (for example, secondary causes of osteoporosis and BMD) is not known."* This is well described in the technical report which is widely available [Kanis 2008a]	of hip and other osteoporotic fractures on the basis of risk factors alone and risk factors plus BMD.
270	Technical Advisers	30.11	full	62	Recommendation 5	Other considerations. Discussion needs to justify why only FRAX and Qfracture were considered. Is the evidence strong enough to support use of these two tools only compared with any alternatives? Also more discussion need on why BMD is not needed – this is covered under recommendation7 but, for completeness, I think something is needed here.	Thank you for your comment, these are the tools listed in the scope. There are other tools available, but the stakeholders during the scoping workshop indicated that FRAX and QFracture are the ones the guideline should focus on: http://www.nice.org.uk/nicemedia/live/13281/56271/56271.pdf. We have now added more discussion about this in the 'Other consideration' box for recommendation 5.
271	Julia Hippisley-Cox, Carol Coupland	18.08	Full	62	8	We'd like to clarify that the validation on the QResearch database was based on a separate set of practices to that used to develop the model and so would meet the definition of external validation (internal validation is usually taken to mean validations which have been conducted on the SAME data as that which was used to develop the model.	Thank you for your comment. The derivation and validation paper (BMJ 2009;339:b4229) reports that two thirds of Qresearch practices were randomly assigned to the derivation dataset and one third to the validation dataset. Collins et al (BMC Medicine 2011,9;103) use the term internal validation to describe 'split samples' and comment that randomly splitting sample can produce overly optimistic performance data.
272	Bone Research Society, the	10.32	Full	63	.	*Trade-off between benefit and harm*. This limitation may be true for QFracture but not for FRAX. FRAX reports the probability of fracture i.e. integrates the death and fracture hazard [Kanis 2008a, 2012a]. After about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability [Kanis 2000]. Thus the older the patient the shorter the time horizon.	Thank you for your comment. We recognised that FRAX has taken into account the death and fracture hazards in the model. However, there is still a potential issue of over-estimating individual risk as it is based on a 10 year probability at the population level. In addition, there is no further data available as to how this is incorporated into the FRAX algorithm.
273	British	12.3	Full	63	.	*Trade-off between benefit and harm*.	Thank you for your comment. We recognised that

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	Society for Rheumatology	6				This limitation may be true for QFracture but not for FRAX. FRAX reports the probability of fracture i.e. integrates the death and fracture hazard [Kanis 2008a, 2012a]. After about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability [Kanis 2000]. Thus the older the patient the shorter the time horizon.	FRAX has taken into account the death and fracture hazards in the model. However, there is still a potential issue of over-estimating individual risk as it is based on a 10 year probability at the population level. In addition, there is no further data available as to how this is incorporated into the FRAX algorithm.
274	ProStrakan Group	14.02	Full	63	1- Rec 6	Recommendation 6: Assessing 10 year risk in this age group is problematic due to life expectancy. However it is imperative that this group is not simply ignored due to not being included in a risk assessment cohort. It would be preferable to include firm guidance on how to manage this most vulnerable group of individuals in the absence of using risk assessment tools.	Thank you for your comment. We have clarified the recommendations indicating that risk assessment tools can be used in older population (currently up to 90 years for FRAX and 84 years for QFracture) and that that people above the age limit of the tools are considered at high risk in virtue of their age alone. We have added a separate recommendation to highlight the point that over the age of 80 years, 10 year risk should be interpreted with caution as 10 year risk is likely to underestimate short term risk.
275	Sheffield Teaching Hospitals NHS Foundation Trust	20.32	Full	63	.	*Trade-off between benefit and harm*. This limitation may be true for QFracture but not for FRAX. FRAX reports the probability of fracture i.e. integrates the death and fracture hazard [Kanis 2008a, 2012a]. After about the age of 80 years, the 10 year probability is equal to the remaining lifetime probability [Kanis 2000]. Thus the older the patient the shorter the time horizon.	Thank you for your comment. We recognised that FRAX has taken into account the death and fracture hazards in the model. However, there is still a potential issue of over-estimating individual risk as it is based on a 10 year probability at the population level. In addition, there is no further data available as to how this is incorporated into the FRAX algorithm.
276	Technical Adviser (HE)	32.03	full	63	Economic considerations	68% referral rate is only useful when put into some clinical context. I.e. is 68% unfeasibly high or low. Some clinical context would strengthen this comment.	Thank you for your comment. We agree. We have amended the text to indicate that recent research shows the actual referral rate is well below 68% for women without prior fracture aged 50-85.
277	Scottish	4.05	Full	63	1	"Do not routinely measure BMD to assess	Thank you for your comment. The guideline is not

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	Intercollegiate Guidelines Network					fracture risk without prior assessment using FRAX (without a BMD value) or QFracture." It is unclear whether the guideline is suggesting that there is a FRAX value or QFracture value below which BMD should not be measured. If so it would be useful to know what fracture risk value would trigger a BMD measurement.	suggesting that there is a FRAX value or QFracture value below which BMD should not be measured. The guideline is recommending that the first step for fragility fracture risk assessment is to estimate the absolute risk using FRAX (without a BMD value) or QFracture (which does not take BMD into account).
278	Technical Advisers	30.12	full	63	Recommendation 6	Trade off between benefits and harms. 'In older age groups, death is a competing risk' – this sentence needs clarifying, does it mean that patients might die before they experience a fracture?	Thank you, this has been clarified in the guideline.
279	Technical Advisers	30.13	full	63	Recommendation 7	This is a strong recommendation in spite of the evidence being at risk of bias. Need to emphasis the reasons for making a strong recommendation.	Thank you for the comment. The recommendation says 'do not routinely' which allows the healthcare professional discretion in using their clinical judgement. We have added further information, in particular about the cost analysis to the evidence to recommendations to make the rationale clearer.
280	Bone Research Society, the	10.33	Full	64		*Quality of evidence – arbitrary threshold and correct classifications.* The Canadian study used the thresholds recommended in the Canadian guidelines [Papaioannou 2010]. The same group has also reported patients correctly reclassified [Leslie 2012a,b]	Thank you for your comment. We have amended the text accordingly. With regard to correct classification, methods such as net reclassification improvement and the integrated discrimination improvement are shown to provide useful and accurate predictions as to whether adding a factor (BMD) would improve the accuracy of model prediction. Details can be found in Appendix C.
281	British Society for Rheumatology	12.37	Full	64		*Quality of evidence – arbitrary threshold and correct classifications.* The Canadian study used the thresholds recommended in the Canadian guidelines [Papaioannou 2010]. The same group has also reported patients correctly reclassified [Leslie	Thank you for your comment. We have amended the text accordingly. With regard to correct classification, methods such as net reclassification improvement and the integrated discrimination improvement are shown to provide useful and accurate predictions as to whether

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						2012a,b]	adding a factor (BMD) would improve the accuracy of model prediction. Details can be found in Appendix C.
282	ProStrakan Group	14.03	Full	64	34-	Recommendation 8: The Cochrane review (Cochrane Review, Calcium and Vitamin D for corticosteroid induced osteoporosis (Review) 1998. Homik J et al. The Cochrane Collaboration, published by John Wiley and sons Ltd) clearly states that when commencing glucocorticosteroid treatment (high dose for a period of time) it is sensible to commence calcium and vitamin D supplementation immediately. Consideration of the addition of bone sparing treatment is well documented in the RCP guideline on glucocorticosteroid induced osteoporosis (1999) on the basis of age, previous fragility fracture history, and other parameters. It is felt that a DXA scan for confirmation may be an expensive 'nice to have' which does not offer substantial clinical gain, and that a pragmatic risk benefit assessment may serve better.	Thank you but the evidence and GDG consensus did not support your recommendation. The Cochrane review you mention was not included in this guideline as it is about intervention for osteoporosis and not about risk assessment tools for fragility fracture, therefore outside the scope of this guideline.
283	Sheffield Teaching Hospitals NHS Foundation Trust	20.33	Full	64		*Quality of evidence – arbitrary threshold and correct classifications.* The Canadian study used the thresholds recommended in the Canadian guidelines [Papaioannou 2010]. The same group has also reported patients correctly reclassified [Leslie 2012a,b]	Thank you for your comment. We have amended the text accordingly. With regard to correct classification, methods such as net reclassification improvement and the integrated discrimination improvement are shown to provide useful and accurate predictions as to whether adding a factor (BMD) would improve the accuracy of model prediction. Details can be found in Appendix C.
284	Scottish Intercollegiate Guideline	4.07		64	1	Recommendation 8 is only implementable with the definition of a threshold intervention which is claimed to be outside of the remit of this guideline. We suggest it is incorporated to allow	Thank you for your comment. We appreciate your concern; however an intervention threshold cannot be specified in this guideline, as explained by the footnote to this recommendation.

N.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	s Network					this recommendation to be acted on.	
285	NHS Trafford	23.00	Full	64	1	NICE TA 160,161 and 204 recommends use of pharmacological agents for the primary and secondary prevention of osteoporosis according to the patient's T-score on DXA scanning. There is no reference in these existing TA's to guide the use of these treatments according to % fracture risk. This new short clinical guideline on assessing fracture risk in patients with or at risk of osteoporosis recommends the use of the FRAX or QFracture risk assessment tool to assess the risk of fracture in patients above 40, with BMD calculation only recommended for patients who are at the threshold for any proposed treatment or before starting drugs which may adversely affect bone, as the use of BMD in the calculation is more accurate. This summary of the evidence behind the recommendation is explicit that people well above the threshold can be treated without measurement of BMD. This is not explicit in the summary on page 12 (lines 1-6) and creates doubt for many people who only read the summary of the guideline. This recommendation to treat patients who which is in contrary to TA 160/161/204 where only patients with relevant T scores are recommended to receive treatment. This will cause confusion for prescribers and difficulties complying with NICE TAs and will ultimately mean that DXA scanning will continue for those patients who are being considered for treatment	Thank you for your comment. Intervention and treatment are outside the remit of this guideline. In line with section 8 of the currently published related Technology Appraisal guidance (TA160, 161 and 204), NICE is preparing for the consideration of a review of the guidance in light of the forthcoming publication of this short guideline. It is anticipated that a review proposal paper will be issued for consultation with stakeholders in June 2012.
286	Spinal	9.06	Full	65	1	Do the GDG regard spinal cord injury as a	Thank you for your comment. The GDG

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	Injuries Association					major risk factor, and would they include spinal cord injured people in the recommendation to have a BMD measurement?	considered spinal cord injury as a cause of secondary osteoporosis (immobility due to neurological injury or disease), and not a major risk factor.
287	ProStrakan Group	14.04	Full	66	10	Recommendation 10: Could this be addressed in a more systematic manner – we know that even patients with previous fracture history are not all assessed and treated (RCP report May 11, Falling Standards Broken Promises). What is the likelihood of these threshold patients being reassessed after 2 years, or even have their risk factors reassessed in this time?	Thank you for your comment. We acknowledge the issues you raise in terms of follow up of patients. We have indicated to the NICE implementation team that this is an important area to consider for guideline implementation.
288	Bone Research Society, the	10.34	Full	67		*Other considerations, second paragraph:* There is no convincing evidence that femoral neck BMD underperforms for vertebral fracture risk. See also comment to page 12, line 19.	Thank you for your comment. The GDG agree that femoral neck BMD is a good predictor of vertebral fractures, and the statement has been removed from the guideline.
289	Bone Research Society, the	10.35	Full	67		*Other considerations, fourth paragraph:* An adjustment to FRAX to take account of dose response is published and noted on the web site [Kanis 2011b]	Thank you for your comment. We were aware that information about the dose-dependent effect of oral glucocorticoids was included in the "notes on risk factors" on the FRAX website and we agreed that clinical judgement is needed. However, it does not quantify risk (increase by how much) and cannot be put in the algorithm.
290	Bone Research Society, the	10.36	Full	67		*Other considerations, fifth paragraph:* This is explicit in the technical report and review literature [Kanis 2008a, 2011a]	Thank you for your comment. We have reviewed the references and they outlined the potential limitations of the risk factors included in the FRAX model. However, there was no information on how FRAX dealt with these issues.
291	British Society for Rheumatology	12.38	Full	67		*Other considerations, second paragraph:* There is no convincing evidence that femoral neck BMD underperforms for vertebral fracture risk. See also comment to page 12, line 19.	Thank you for your comment. The GDG agree that femoral neck BMD is a good predictor of vertebral fractures, and the statement has been removed from the guideline.

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292	British Society for Rheumatology	12.39	Full	67		*Other considerations, fourth paragraph:* An adjustment to FRAX to take account of dose response is published and noted on the web site [Kanis 2011b]	Thank you for your comment. We were aware that information about the dose-dependent effect of oral glucocorticoids was included in the "notes on risk factors" on the FRAX website and we agreed that clinical judgement is needed. However, it does not quantify risk (increase by how much) and cannot be put in the algorithm.
293	British Society for Rheumatology	12.40	Full	67		*Other considerations, fifth paragraph:* This is explicit in the technical report and review literature [Kanis 2008a, 2011a]	Thank you for your comment. We have reviewed the references and they outlined the potential limitations of the risk factors included in the FRAX model. However, there was no information on how FRAX dealt with these issues.
294	Sheffield Teaching Hospitals NHS Foundation Trust	20.34	Full	67		*Other considerations, second paragraph:* There is no convincing evidence that femoral neck BMD underperforms for vertebral fracture risk. See also comment to page 12, line 19.	Thank you for your comment. The GDG agree that femoral neck BMD is a good predictor of vertebral fractures, and the statement has been removed from the guideline.
295	Sheffield Teaching Hospitals NHS Foundation Trust	20.35	Full	67		*Other considerations, fourth paragraph:* An adjustment to FRAX to take account of dose response is published and noted on the web site [Kanis 2011b]	Thank you for your comment. We were aware that information about the dose-dependent effect of oral glucocorticoids was included in the "notes on risk factors" on the FRAX website and we agreed that clinical judgement is needed. However, it does not quantify risk (increase by how much) and cannot be put in the algorithm.
296	Sheffield Teaching Hospitals NHS Foundation Trust	20.36	Full	67		*Other considerations, fifth paragraph:* This is explicit in the technical report and review literature [Kanis 2008a, 2011a]	Thank you for your comment. We have reviewed the references and they outlined the potential limitations of the risk factors included in the FRAX model. However, there was no information on how FRAX dealt with these issues.
297	Technical	30.1	full	67	Recommenda	Does this recommendation need to specifically	Thank you, the recommendation has been

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	Advisers	4			tion 11	mention FRAX and Qfracture?	changed to reflect your suggestion.
298	British Pain Society	25.06	x	68 Rec 12	1	No mention of effect of antiepileptic drugs until this page- may prevent those being treated for epilepsy from being screened, causing increased pain and morbidity.	Thank you for your comment. The GDG did not consider that effect of anti-epileptic drugs warranted additional assessment below the age of 50 years.
299	William Leslie	1.02	Full	69	2-12	This question is addressed in a recent paper published by JBMR (in press, online [Epub] late Feb 2012).	Thank you for bringing this paper to our attention. The GDG reviewed the paper and considered that it does not validate the tool in this population and that further research is required. The preferred methodologies to validate the risk prediction tools are outlined in Appendix C of the guideline. This paper has now been noted in the research recommendation.
300	ProStrakan Group	14.05	Full	69	2	The only evidence recommending a 'drug holiday' relates to bisphosphonates. This research recommendation has grouped all bone sparing agents in the same class, and this is not evidence based.	Thank you for your comment. The GDG made this research recommendation because there is a lack of evidence on whether the tools accurately predict risk of fragility fracture in people at the end of their treatment period. The GDG therefore felt there was a need for prospective studies to investigate the predictive power of these tools to assess fracture risk in patients after a period of bone protective therapy.
301	UCB Pharma Ltd	26.04	Full	69	4	It is critical that physicians are empowered to rely on individual clinical assessment of fracture risk (at the end of a therapeutic cycle) informed by changes in bone mass (cause of osteoporosis, decrease of BMD > 5%, new or worsening fracture, biomarkers, etc.) rather than rely on (non-validated) risk assessment tools to evaluate treatment effect. FRAX and QFracture have not been validated as tools for monitoring change in risk in patient receiving treatment for their osteoporosis; therefore their use can add confusion rather than supplement information already provided	Thank you for your comment. We have included a research recommendation to consider the performance of these tools in patients who are already on treatment.

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						by change in BMD. These tools should be validated in patients receiving treatment before any consideration of widespread implementation as a tool to evaluate treatment effect. If validated, there is the opportunity to identify therapeutic non-responders earlier and switch to more appropriate therapies.	
302	UCB Pharma Ltd	26.05	Full	69	16	It is important to consider the individual's aetiology for secondary osteoporosis in the overall assessment. Clinical assessment (vs. risk assessment tools) is also important. Each cause of secondary osteoporosis should be considered a separate entity that contributes to the overall risk profile. Early and accurate diagnosis is good medical practice and will facilitate access to proven and effective therapies for patients at increased risk of fracture.	Thank you for your comment. Risk tools do include some secondary causes of osteoporosis in their risk equations and we have included a research recommendation to assess the validity of tools in these groups. The GDG considered that risk assessment using tools should be performed first and then amended using clinical judgement.
303	UCB Pharma Ltd	26.06	Full	69	16	The FRAX model's calculator does not permit combinations of secondary risk factors; for example, a patient with two or more causes of secondary osteoporosis has the same relative risk results from the (FRAX calculator) as either one alone, thus underestimating the relative risk of fragility fracture.	Thank you for your comment. This is the reason we have indicated that risk tools are likely to underestimate risk in people with secondary causes of osteoporosis.
304	UCB Pharma Ltd	26.07	Full	69	27	BMD is significant in the assessment of fracture risk and should complement patient history, physical findings, laboratory and radiological evaluations. By adding BMD to FRAX, one is reassured that risk categorization for a given patient is further supported by a widely accepted and validated objective parameter.	Thank you for your comment. As explained in the subsequent paragraph, there are no definitive studies in primary or secondary care evaluating whether the addition of BMD to FRAX improves the accuracy of the predicted fracture risk. There is a need for studies to examine whether adding BMD to FRAX results in the correct reclassification of patients from low risk to high risk (and vice-versa). Furthermore, studies are also needed to evaluate the clinical usefulness

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							(net benefit) of adding BMD to FRAX; that is, how many more patients are correctly classified as high risk (true positives) at the same rate of correctly classifying patients as low risk (true negatives).
305	UCB Pharma Ltd	26.08	Full	69	40	Women, typically of advanced age, in long term residential care are at high risk of fracture. Physicians need to review clinically relevant risk factors such as medical conditions or therapies that are associated with increased fracture risk.	Thank you, we acknowledge your point, however, the aim of this research recommendation is to assess whether care home residents should have targeted fracture risk assessment and whether residents at higher risk of fracture can be identified, using FRAX or QFracture. This could result in a more effective and efficient strategy for fracture prevention targeting health service resources on those at the very highest fracture risk.
306	UCB Pharma Ltd	26.09	Full	69	40	FRAX will provide little new or useful information in describing risk for long term care residents who are currently taking osteoporosis medication.	Thank you for your comment. We recognise these issues. The research recommendations include research on long term care residents and the use of risk tools when people are already taking osteoporosis medication.
307	UCB Pharma Ltd	26.10	Full	70	12	All women at increased risk of fragility fracture in the UK regardless of race, ethnicity, or presumed fracture risk should have equal access to information, diagnosis and treatment for their osteoporosis (i.e. equity of access).	Thank you for your comment. We agree with your comments and are aware of potential inequalities and inequities in relation to osteoporosis and fracture risk in ethnic groups in the England and Wales. We agree, as you have outlined in your comments, that it is important to understand ethnic and racial influences on osteoporotic fractures and to validate risk assessment tools. This is why we have included a research recommendation to assess the use of risk assessment tools in detecting fragility fracture risk in different ethnic groups in the UK.
308	UCB Pharma Ltd	26.11	Full	70	12	Ethnic minority groups have poorer health than others (i.e. health inequalities) and have poorer access to health services in the UK. It is	Thank you for your comment.

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						important to support initiatives aimed at reducing health inequalities and inequities.	
309	UCB Pharma Ltd	26.12	Full	70	12	Ethnic minority groups are growing quickly and account for the majority of Britain's overall population growth thus presenting a complex challenge to health care practitioners and policy makers in terms of achieving equitable access.	Thank you for your comment.
310	UCB Pharma Ltd	26.13	Full	70	12	Osteoporosis is underdiagnosed and often ignored in ethnic minority women. Understanding the ethnic and racial influences on osteoporotic fractures is critical to decreasing the burden of such fractures on patients and society.	Thank you for your comment.
311	UCB Pharma Ltd	26.14	Full	70	19	Further work needs to be done to validate the risk assessment tools (FRAX and Q Fracture) in different ethnic groups in England and Wales. These tools must first be validated retrospectively against available data such as GP listings and subsequent long term outcomes to evaluate their potential deterministic accuracy in ethnic groups.	Thank you for your comment.
312	British Thoracic Society	16.06	Full	84	Appendix A	Require to see DOI	Thank you for your enquiry, Appendix A of the guideline does contain all the DoIs recorded during the development process.
313	William Leslie	1.01	Full and Appendix	46, 47, 88		Cited reference #54 (Leslie WD, et al. Bone. 2007; 40(4):991-996) does not correspond to the study data summarized for Leslie 2007A (Manitoba) in Tables 23-24. Data appear to be from: Leslie WD, et al Journal of Clinical Endocrinology & Metabolism. 2007; 92(1):77-81. Ref ID: LESLIE2007D.	Thank you for your comment, this has been amended.
314	Technical Adviser (HE)	32.05	Appendix E	241	4	It would be helpful to explain why, or if, studies on treatment were not examined.	Thank you for your comment. We have amended the relevant section accordingly.
315	Technical	30.0	Full	423	10	Cross-refer to full methodology in Appendix C	Thank you but we would need more information

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	Advisers	8					to answer your comment, we do not understand where you would like us to insert the cross-reference on page 423. The Guideline is 91 pages long, the appendices 250 pages.

These organisations were approached but did not respond:

Abbott GmbH & Co KG

Abbott Laboratories

Action on Pain

Adults Strategy and Commissioning Unit

Age Related Diseases and Health Trust

Age UK

Airedale NHS Trust

Alder Hey Children's NHS Foundation Trust

All About Nocturnal Enuresis Team

All Wales Dietetic Advisory Committee

Alpro UK Ltd

Amgen UK

AMORE Studies Group

Anglesey Local Health Board

Arrowe Park Hospital

Arthritis and Musculoskeletal Alliance

Arthritis Research UK

Association of Anaesthetists of Great Britain and Ireland

Association of British Clinical Diabetologists

Association of British Healthcare Industries

Association of British Insurers

Association of Clinical Pathologists

Association of Dance Movement Therapy UK

Astrazeneca UK Ltd

Autistic People Against Neuroleptic Abuse

Barnet Primary Care Trust

Barnsley Hospital NHS Foundation Trust

Barnsley Primary Care Trust

Bayer HealthCare

BEAT

Bedfordshire Primary Care Trust

Boehringer Ingelheim

Bolton Primary Care Trust

Bonesupport AB

Bradford and Airedale Primary Care Trust

Bradford District Care Trust

Breast Cancer Care

Brighton and Sussex University Hospital NHS Trust

Britannia Health Products Ltd

British Association for Counselling and Psychotherapy

British Association of Oral and Maxillofacial Surgeons

British Association of Prosthetists & Orthotists

British Dental Health Foundation

British Dietetic Association

British Geriatrics Society

British Geriatrics Society-Special Interest Group in Diabetes

British Lung Foundation

British Medical Association

British Medical Journal

British Menopause Society

British National Formulary

British Nuclear Medicine Society

British Orthopaedic Association

British Psychological Society

British Society for Rheumatology

British Society of Gastroenterology

British Society of Paediatric Gastroenterology Hepatology and Nutrition

British Society of Rehabilitation Medicine

British Society of Skeletal Radiologists

Buckinghamshire Primary Care Trust

BUPA Foundation

Calderdale Primary Care Trust

Camden Link

Camden Provider Services

Cardiff and Vale NHS Trust

Care Quality Commission (CQC)

Chartered Society of Physiotherapy

Chesterfield Primary Care Trust

City and Hackney Teaching Primary Care Trust

Coeliac UK

College of Occupational Therapists

Commission for Social Care Inspection

Community District Nurses Association

Community Practitioners' & Health Visitors Association

Cook Medical Inc.

Co-operative Pharmacy Association

Countess of Chester Hospital NHS Foundation Trust

County Durham Primary Care Trust

Cumberland Infirmary

Cytyc UK Limited

Daiichi Sankyo UK

David Lewis Centre, The

Department for Communities and Local Government

Department of Health, Social Services and Public Safety - Northern Ireland

Derbyshire County Primary Care Trust

Derbyshire Mental Health Services NHS Trust

Doddmed Ltd

Doncaster Primary Care Trust

Dorset Primary Care Trust

Eaton Foundation

Eli Lilly and Company

Epilepsy Action

Equalities National Council

Faculty of Dental Surgery

Faculty of Family Planning & Reproductive Healthcare

Faculty of Pain Medicine of the Royal College of Anaesthetists

Faculty of Public Health

Federation of Ophthalmic and Dispensing Opticians

Fibroid Network Charity

Food Standards Agency

Galen Ltd

GE Healthcare

Gelita UK Limited

Genzyme Therapeutics

George Eliot Hospital NHS Trust

GlaxoSmithKline

Gloucestershire LINk

GP Care

Great Western Hospitals NHS Foundation Trust

Greater Manchester West Mental Health NHS Foundation Trust

Grunenthal Ltd

Guerbet Laboratories Ltd

Guy's and St Thomas' NHS Foundation Trust

Hammersmith and Fulham Primary Care Trust

Hampshire Partnership NHS Trust

Hayward Medical Communications

Health Protection Agency

Health Quality Improvement Partnership

Healthcare Improvement Scotland

Heart of England NHS Foundation Trust

Hertfordshire Partnership NHS Trust

Hindu Council UK

Humber NHS Foundation Trust

Imaging Equipment Ltd

Independent Healthcare Advisory Services

Institute of Biomedical Science

Institute of Physics and Engineering in Medicine

Institute of Sport and Recreation Management

Internis Pharmaceuticals Ltd

Isle of Wight NHS Primary Care Trust

Janssen

JRI Orthopaedics

KCARE

Kimal PLC

koGEN Limited

Kyphon Inc.

Lambeth Community Health

Lancashire Care NHS Foundation Trust

Leeds Community Healthcare NHS Trust

Leeds Primary Care Trust (aka NHS Leeds)

Liverpool Community Health

Liverpool PCT Provider Services

Liverpool Primary Care Trust

Lothian University Hospitals Trust

Luton and Dunstable Hospital NHS Trust

Maidstone and Tunbridge Wells NHS Trust

Medicines and Healthcare products Regulatory Agency

Medtronic

Medway NHS Foundation Trust

Menarini Pharma U.K. S.R.L.

Merck Sharp & Dohme UK Ltd

Mid Staffordshire NHS Foundation Trust

midwifeexpert.com

Ministry of Defence

MRC Human Nutrition Research

Napp Pharmaceuticals Ltd

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Institute for Health Research Health Technology Assessment Programme

National Patient Safety Agency

National Pharmacy Association

National Public Health Service for Wales

National Rheumatoid Arthritis Society

National Treatment Agency for Substance Misuse

NeuroDiversity International(NDI)/NeuroDiversity Self-Advocacy Network

NHS Birmingham East and North

NHS Bournemouth and Poole

NHS Clinical Knowledge Summaries

NHS Connecting for Health

NHS Cornwall and Isles Of Scilly

NHS Derbyshire county

NHS Direct

NHS Hampshire

NHS Herefordshire

NHS Hertfordshire

NHS Kensington and Chelsea

NHS Kirklees

NHS Manchester

NHS Milton Keynes

NHS Newcastle

NHS Nottinghamshire County

NHS Plus

NHS Plymouth

NHS Richmond

NHS Sefton

NHS Sheffield

NHS Warwickshire Primary Care Trust

NHS Worcestershire

Norfolk and Norwich University Hospital

North East Lincolnshire Care Trust Plus

North Yorkshire & York Primary Care Trust

Norwich Primary Care Trust

Nottingham City Hospital

Novartis Pharmaceuticals

Nuffield Orthopaedic Centre

Nutricia Clinical Care

Nutrition and Diet Resources UK

Nutrition Society

Nycomed UK Ltd

Optasia Medical Ltd

Patients Watchdog

Pelvic Pain Support Network

PERIGON Healthcare Ltd

Peterborough Primary Care Trust

Pfizer

Pharmaceutical Services Negotiating Committee

Pharmametrics GmbH

Poole Hospital NHS Trust

Powys Local Health Board

Primary Care Pharmacists Association

Primary Care Rheumatology Society

Primary Sclerosing Cholangitis Support

Proprietary Association of Great Britain

Public Health Wales NHS Trust

QResearch

Retreat, The

RioMed Ltd.

Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust

Robinson Healthcare Ltd

Roche Diagnostics

Roche Products

Rotherham Primary Care Trust

Royal Berkshire NHS Foundation Trust

Royal Brompton Hospital & Harefield NHS Trust

Royal College of Anaesthetists

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Nursing

Royal College of Obstetricians and Gynaecologists

Royal College of Paediatrics and Child Health

Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition

Royal College of Pathologists

Royal College of Physicians of Edinburgh

Royal College of Psychiatrists

Royal College of Radiologists

Royal College of Surgeons of England

Royal Liverpool and Broadgreen University Hospitals NHS Trust

Royal National Hospital for Rheumatic Diseases NHS Foundation Trust

Royal National Institute of Blind People

Royal National Orthopaedic Hospital NHS Trust

Royal Pharmaceutical Society

Royal Society of Medicine

Rupanyup Hospital/Nursing Home

Sacyl

Salford Primary Care Trust

Sandwell Primary Care Trust

Sanofi

Schering Health Care Ltd

Scottish Clinical Biochemistry Managed Diagnostic Network

Scottish Dental Clinical Effectiveness Programme

Scottish Oral Health Group

SEE BETSI CADWALADR - North Wales NHS Trust

Sheffield Primary Care Trust

Shire Pharmaceuticals Ltd

SNDRi

Social Care Institute for Excellence

Society for Endocrinology

Society of British Neurological Surgeons

Society of Orthopaedic Medicine

Solent Healthcare

Solvay

South Essex Partnership NHS Foundation Trust

South Staffordshire Primary Care Trust

South West London Elective Orthopaedic Centre

Spinal Injuries Association

St Helens and Knowsley Teaching Hospitals NHS Trust

Stockport Primary Care Trust

Strakan Limited

Stryker

Surgical Dressing Manufacturers Association

Synthes Ltd

Tameside Hospital NHS Foundation Trust

Teva UK

The Association for Clinical Biochemistry

The Association of the British Pharmaceutical Industry

The British In Vitro Diagnostics Association

The College of Chiropractors

The Food Commission

The Princess Alexandra Hospital NHS Trust

The Relatives and Residents Association

The Rotherham NHS Foundation Trust

The Whittington Hospital NHS Trust

Trinity Pharmaceuticals Limited

Trinity-Chiesi Pharmaceuticals

Tunstall Healthcare UK Ltd

UK National Screening Committee

UK Specialised Services Public Health Network

UK Thalassaemia Society

United Lincolnshire Hospitals NHS

University College London Hospital NHS Foundation Trust

University Hospital Aintree

University Hospital Birmingham NHS Foundation Trust

University of Nottingham

Vertec Scientific Ltd

Wakefield District NHS Primary Care Trust

Wales Osteoporosis Advisory Group

Walsall Teaching Primary Care Trust

Warner Chilcott UK

Welsh Endocrine and Diabetes Society

Welsh Government

Welsh Scientific Advisory Committee

West Hertfordshire Primary Care Trust

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

Wiltshire Primary Care Trust

Worcestershire Acute Hospitals Trust

York Hospitals NHS Foundation Trust