National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA 160)

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (TA 161)

The model must not be re-run for purposes other than informing your comments.

Please set out your comments on the model in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response, and only responses on this pro forma will be considered.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to comment on the economic model itself. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as indicated below (please add further tables if necessary).

May 2009

Issue 1 Transparency and validation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The excel model supplied by NICE estimates the cost-effectiveness based on Gaussian regression functions which are derived from an individual state transition model. The source individual state transition model was not supplied until late in the consultation period so that the Gaussian functions could not be evaluated. Thus, it is not possible to fully evaluate the model and it cannot be considered, therefore, to be fully executable. The validity of the model cannot be assessed from the data supplied, nor is there any previous publication available to demonstrate its validity. It is not possible to test the manner by which mortality, fracture risks are accommodated in the model supplied. The model as supplied does not permit alterations to discount rates, body mass index, population mortality, mortality associated with clinical risk factors, time horizon and the estimation of the annual risk of fracture for CRF scenarios other than those pre specified, so that sensitivity analysis around the assumptions cannot be performed.	Amend process to allow full re-assessment and comment on all model used as a part of the current appraisal	Provide an opportunity for an open and educated debate on the validity of the cost effectiveness model used as a basis for Appraisal Committee decisions.

Issue 2 Hip fracture estimates

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The NICE model does not permit the calculation of 10-year fracture probabilities, so that the integrity of the NICE application of FRAX® cannot be directly addressed. For the calculation of annual fracture risk it is not given whether this is applied to specific ages or to an age range. Irrespectively, there are discrepancies between the reviewers and NICE in the calculation of annual risks associated with clinical risk factors (CRFs). There are also discrepancies in the rank order of importance of the CRFs. Possible reasons for the discrepancies may relate to an erroneous assumption that none of the risk factors were associated with excess mortality. An alternative or additional explanation is that NICE derived the risks of clinical spine, forearm and humeral fractures incorrectly by subtracting the risk of hip fracture from the risk of a major fracture. The FRAX® algorithms also assess the probability of death related to any combination CRFs. That is, the FRAX® coefficients should be used to adjust the mortality for a specific patient group. This part of the FRAX® has not been implemented in the NICE model. There are a number of significant interactions that are incorporated into FRAX® that appear to	Correctly utilise FRAX® by using the co-efficients to adjust the mortality for a specific patient group and include the interactions that have been omitted.	Will reduce ICER of SR

have been omitted from the NICE model. These include prior fracture·age and BMD·age, the omission of both will adversely affect cost-effectiveness at younger ages		

Issue 3 Body Mass Index

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Body mass index (BMI) is set at a fixed value by NICE (26kg/$m^{2)}$. The use of a fixed BMI is not consistent with the construct of FRAX®. The deficit decreases the accuracy of all risk estimates except at a BMI of 26kg/m^2. The effect is very marked when BMD is not used to estimate risk	Utilise FRAX ® appropriately to estimate the risk associated with BMI ranges instead of a fixed value.	Underestimates cost effectiveness of SR in patients with lower BMI.

Issue 4 *Intake of alcohol*

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The risk associated with alcohol intake is incorrect for the exposure recommended by NICE and will adversely affect cost-effectiveness.	Correct the accounting for alcohol intake	Improve the cost effectiveness of treatments

Issue 5 Weighting of Risk Factors

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Whereas FRAX® provides the mechanism to compute the cost-effectiveness according to the specific risk factor, NICE weights all risk factors equally. The impact of this on fracture probability is marked. For example the average ten year probability for women aged 65 years with two risk factors and a T-score of -2.0 SD is 20%, but varies more than two-fold (13 to 29%) depending on the risk factor. A similar inaccuracy results from the presentation of age and BMD in categories. Thus NICE present ICERs in age bands (e.g. 55-59 years) and T-score bands (e.g. T= -3.0 to -3.5 SD).	Implement the FRAX algorithm accurately to allow a more accurate assessment of fracture risk and cost effectiveness that aids implementation and deals more fairly with inter-patient variation..	Underestimates cost effectiveness of SR for some patients.

Issue 6 Time horizon

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The NICE model uses predominantly a ten-year time horizon which has a large effect on apparent cost-effectiveness. In order to overcome this deficit, the NICE model preserved the time frame but 'bolted on' adjustments to overcome this flaw in the model construct. The estimation of the 'bolt-on' cost consequences which are included in the NICE model are not	Amend or completely re-write the model to account for the ability to include the quality of life and mortality effects as mentioned.	Improve the accuracy of the estimate of costs and benefits and improve the cost effectiveness of treatment.

transparent since they are not mentioned in the HTA report and there is no information on how they are derived. There are no data that test the sensitivity of the NICE model to changes in the time horizon and no way to test the adequacy of the 'bolt-on' to overcome the intrinsic deficit in the model. The publication of the 'bolt-on' states that this took account of deaths occurring after 10 years [Stevenson et al, 2005]. The 'bolt-on' does not appear to accommodate preventable deaths during the offset period or after 10 years. The publication describing the 'bolt-on' states that this took account of deaths, but none of the other consequences of fracture. The spread sheets provided by NICE suggest that this may be untrue in that it may also account for the cost consequences beyond 10 years, though not the long term effects of fracture on quality of life. Some adjustment is made for forearm fractures, the nature of which is not explained. If these adjustments are related to preventable deaths this would assume that wrist, rib, scapular, clavicular and sternal fractures increase mortality, whereas the report indicates otherwise. A comparator model developed by the reviewer revealed discrepancies in the coefficients to calculate both the long term costs and QALYs which adjust a 10-year time horizon to a lifetime horizon. These were consistently higher in the NICE model than that calculated by the comparator model.		

Issue 7 Risk multipliers for fracture risk

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The risk multipliers found in the NICE report differ from those used in the NICE model	Amend the model or the report to gain consistency.	Not known

Issue 8 Discount rates

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Discount rates used are not those recommended by NICE. The model does not allow changes in the discount rates for costs or QALYs	Amend model or consider new model capable of changing discount rates	Probably reduce cost effectiveness of treatment

Issue 9 Compliance

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Compliance is not modelled where all patients are simulated in the model but an adjustment is made on the cost side. The incremental costs and QALYs gained will be overestimated in the initial group of patients that start treatment but do not adhere.	Model compliance appropriately to remove the over estimate of costs and QALYs gained.	Not known

Issue 10 **Side effects**

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
NICE have used same disutility for side effects for all treatments even though SR does not have the same as profile as BPs	Use evidence from SR studies see p 27	Underestimates cost effectiveness of SR

Issue 11 **Costs of fracture**

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Hip fracture costs are out of date	Use new data see p 27	Underestimates cost effectiveness of SR, Will reduce ICER of SR

Issue 12 **QOL for vertebral fractures**

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
QOL data for vertebral fractures appears incorrect	Use best available evidence see p 27	Will reduce ICER of SR

Issue 13 **Cost-effectiveness of identification strategies**

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Identification strategies appear incorrectly costed and inappropriate	see p 40,41	Underestimates cost effectiveness of SR

1 Additional comments received from Servier

Pro-forma field	Comment
Issue	Issue 1Transparency and validation
Description of problem	The following variable cannot be changed for the sensitivity analysis: Baseline population risk of fracture. Nor was it possible to determine the accuracy with which the model reproduced the epidemiology of osteoporosis in the UK.
Description of proposed amendment	Amend process to allow full re-assessment and comment on all model used as a part of the current appraisal
Result of amended model or expected impact on the result	Provide an opportunity for an open and educated debate on the validity of the cost effectiveness model used as a basis for Appraisal Committee decisions.

Pro-forma field	Comment
Issue	Issue 2Hip fracture estimates
Description of problem	The numerous errors found in the accessible parts of the model are likely to impair significantly the stratification of risk and thus the effective targeting of treatment. In the NICE model the annual risks are entered directly as values in the excel sheets and it is not possible, therefore, to evaluate how the actual calculation of the risks were derived. Risks with different risk factors alone or in combination are given in Table 1 and Figure 2. All computations using FRAX® gave different values for annual risks compared to the estimates used in the NICE model. Moreover we could not reproduce the values derived by NICE from the methods described in the HTA report [p6, Stevenson et al, 2007b]. In the case of a major osteoporotic fracture (hip, clinical spine, forearm and humerus fracture), the NICE estimates were higher than those derived from FRAX®. An important exception was the risk estimate associated with a prior fracture where the risk estimate was lower with the NICE assumptions. The same findings were observed when comparing the annual risks in younger ages (Table 2). **Table 1** Annual risk of fracture (%) as given in the NICE model and computed from FRAX®. Risks are given for hip fracture and a major fracture (hip, clinical spine, forearm and humerus)

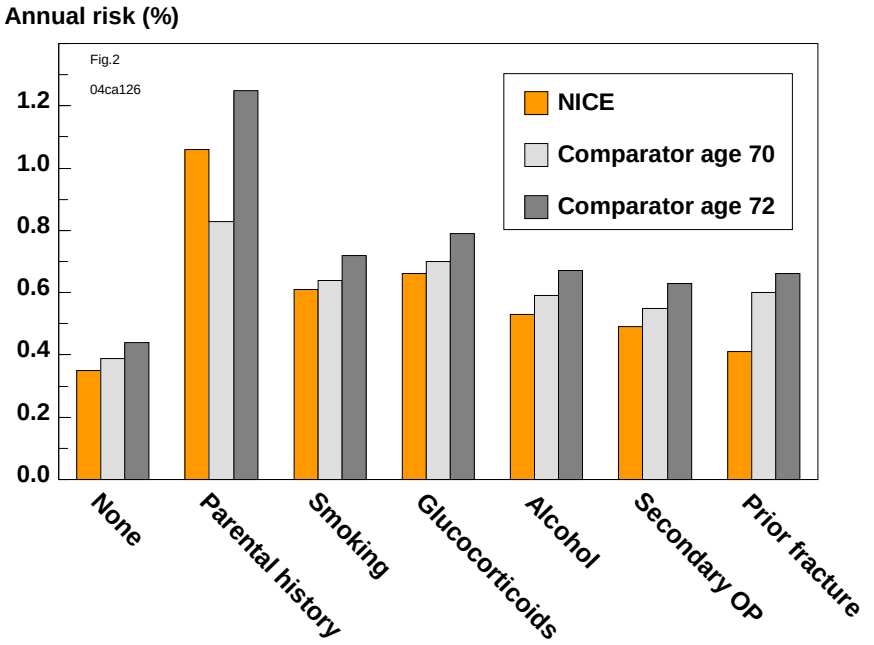
	NICE FRAX		Review FRAX 70-year		Review FRAX 72-year	
CRFs	major	hip	major	hip	major	hip
None	1.66	0.35	1.52	0.39	1.58	0.44
Parental history	2.82	1.06	2.58	0.83	2.78	1.25
Smoking	1.86	0.61	1.68	0.64	1.75	0.72
Glucocorticoids	2.80	0.66	2.47	0.70	2.53	0.79
Alcohol	2.07	0.53	1.92	0.59	2.00	0.67

Pro-forma field	Comment

Secondary OP	2.19	0.49	2.01	0.55	2.08	0.63
Prior fracture	2.38	0.41	2.47	0.60	2.50	0.66
Parental history + smoking	3.54	1.86	2.95	1.37	3.38	2.03
Parental history + Glucocorticoids	4.89	2.02	4.17	1.49	4.49	2.21
Parental history + alcohol	3.69	1.63	3.29	1.26	3.66	1.90
Parental history + secondary OP	3.78	1.52	3.41	1.17	3.71	1.77

Table 2 Annual risk of fracture (%) as given in the NICE model and computed from FRAX® in women at the age of 50 years. Risks are given for hip fracture and a major fracture (hip, clinical spine, forearm and humerus)

	NICE FRAX		Review FRAX 50-year	
CRFs	major	hip	major	hip
None	0.64	0.18	0.61	0.13
Parental history	1.17	0.19	1.16	0.14
Smoking	0.76	0.32	0.68	0.23
Glucocorticoids	1.09	0.35	1.03	0.24
Alcohol intake	0.82	0.28	0.76	0.20
Secondary	0.85	0.26	0.80	0.18

Pro-forma field	Comment
	osteoporosis Prior fracture 1.06 0.27 1.17 0.28 **Figure 1** Annual risk of hip fracture (%) computed by NICE and our comparison at the age of 70 and 72 years 

Pro-forma field	Comment
Description of proposed amendment	Correctly utilise FRAX® by using the co-efficients to adjust the mortality for a specific patient group and include the interactions that have been omitted.
Result of amended model or expected impact on the result	Will reduce ICER of SR

Pro-forma field	Comment
Issue	Issue 3Body Mass Index
Description of problem	It is not known how the BMI value was set by NICE, nor could this be tested since BMI cannot be changed in the NICE model. It is evident that the use of BMI as a fixed variable is not consistent with the construct of FRAX®. The deficit decreases the accuracy of all risk estimates except at the value used by NICE. The effect is very marked when BMD is not used to estimate risk. This will have implications where management decisions are given for women without BMD (e.g. with a prior fracture aged 70 years or more). Though the impact is less, there are errors of accuracy incurred when BMD is added to the model. The use of a fixed BMI introduces other errors of accuracy in the computation of fracture probability. There is a significant interaction of BMI with BMI and for some outcomes with age [De Laet et al, 2005]. Thus the significance of a step change in BMI differs at different values of BMI and age. There is also an important effect of BMI on mortality. The phenomenon is illustrated in Table 4 which gives the ratio of fracture probabilities at low values for BMI compared to average values (25kg/m^2) at the ages of 50 and 70 years. At the age of 50 years and a BMI of 15kg/m^2 the 10 year probability of a major fracture is increased by 40%. At the age of 70 years the probability of a major fracture is decreased by 22%. These important interactions do not appear to be accommodated in the NICE model. **Table 3** The effect of low BMI on fracture probability ratios for women aged 50 or 70 years with a prior fracture and with a T-score for femoral neck BMD set at -2.5 SD. The ratio of ten-year fracture probabilities are shown at each BMI compared to a BMI of 25kg/m2 in an individual of the same age.

	Age 50 years		Age 70 years	
BMI	Major	Hip	Major	Hip
15	1.4	1.2	0.78	0.88
20	1.2	1.1	0.92	0.94
25	-	-	-	-

Pro-forma field	Comment
Description of proposed amendment	Utilise FRAX ® appropriately to estimate the risk associated with BMI ranges instead of a fixed value.
Result of amended model or expected impact on the result	Underestimates cost effectiveness of SR in patients with lower BMI.

Pro-forma field	Comment
Issue	Issue 4 Intake of alcohol
Description of problem	The FRAX® model accommodates alcohol intake as a dichotomous risk variable. The threshold is set at an average intake of 3 or more units daily and is associated with an increased risk of hip fracture and a major fracture [Kanis et al, 2005f]. The HTA report indicates incorrectly that a threshold value of >2 units daily was used. Notwithstanding, the NICE appraisal chose a threshold of >4 units daily. This is associated with a higher relative risk for fracture than either of the thresholds given above (Table 5). For example, the relative risk of hip fracture (without BMD) is 1.92 for an intake of 3 or more units daily, but 2.26 at an average intake of 4 or more units daily. Thus the use of the original FRAX® coefficient by NICE underestimates the fracture risk when the threshold is altered.

Table 4 Risk ratio for fracture and 95% confidence intervals according to the intake of alcohol with and without adjustment for femoral neck BMD [Kanis et al, 2005f].

Consumption	Without BMD		Adjusted for BMD	
(units/day)	RR	95% CI	RR	95% CI
Osteoporotic fracture				
>2	1.38	1.16-1.65	1.36	1.13-1.63
>3	1.55	1.26-1.92	1.53	1.23-1.91
>4	1.70	1.30-2.22	1.64	1.24-1.27
Hip fracture				
>2	1.68	1.19-2.36	1.70	1.20-2.42
>3	1.92	1.28-2.88	2.05	1.35-3.11
>4	2.26	1.35-3.79	2.39	1.39-4.09

Pro-forma field	Comment
Description of proposed amendment	Correct the accounting for alcohol intake
Result of amended model or expected impact on the result	Improve the cost effectiveness of treatments

Pro-forma field	Comment
Issue	Issue 5Weighting of Risk Factors
Description of problem	Whereas FRAX® provides the mechanism to compute the cost-effectiveness according to the specific risk factor, NICE weights all risk factors equally. The impact of this on fracture probability is shown in Table 6. For example the average ten year probability for women aged 65 years with two risk factors and a T-score of -2.0 SD is 20%, but varies more than two-fold (13 to 29%) depending on the risk factor. Other examples are available on the FRAX® web site. The impact of this on resource use is discussed towards the end of the report

Table 5 Ten-year probability of osteoporotic fractures (%) according to BMD T-score at the femoral neck in women aged 65 years from the UK. [Data from FRAX® web site]

Number of CRFs	BMD T-score (femoral neck)					
	-4.0	-3.0	-2.0	-1.0	0	1.0
0	27	15	9.7	7.1	5.9	5.0
1	37 (33-41)	22 (18-26)	14 (10-18)	10 (7.1-14)	8.5 (5.7-12)	7.3 (4.8-10)
2	49 (42-58)	30 (23-40)	20 (13-29)	15 (8.6-23)	12 (6.8-19)	10 (5.6-17)
3	62 (53-72)	41 (30-55)	27 (17-42)	20 (11-34)	17 (8.7-29)	15 (7.2-26)
4	73 (63-81)	52 (42-65)	36 (26-51)	27 (18-41)	23 (14-36)	20 (11-32)

A similar situation pertains when CRFs are accorded equal weights in the absence of BMD. For example, the average ten year probability for women aged 65 years with two risk factors and a BMI of 25 kg/m2 is 19%, but varies more than two-fold (11 to 29%) depending on the risk factor. Other examples are given in Table 7 and on the FRAX® web site.

Table 6 Ten-year probability of osteoporotic fractures (%) according to body mass index (BMI) in women aged 65 years from the UK. [Data

<table>
<tr><th>Pro-forma field</th><th>Comment</th></tr>
<tr><td></td><td>from FRAX web site]
<table>
<tr><td rowspan="2">Number of CRFs</td><td colspan="7">BMI (kg/m²)</td></tr>
<tr><td>15</td><td>20</td><td>25</td><td>30</td><td>35</td><td>40</td><td>45</td></tr>
<tr><td>0</td><td>11</td><td>9.3</td><td>8.6</td><td>7.4</td><td>6.5</td><td>5.6</td><td>4.9</td></tr>
<tr><td>1</td><td>16 (12-21)</td><td>14 (10-18)</td><td>13 (9.2-16)</td><td>11 (7.9-14)</td><td>9.8 (6.9-12)</td><td>8.5 (5.9-11)</td><td>7.4 (5.1-9.5)</td></tr>
<tr><td>2</td><td>24 (16-34)</td><td>21 (13-31)</td><td>19 (11-29)</td><td>17 (9.8-26)</td><td>14 (8.4-23)</td><td>13 (7.3-20)</td><td>11 (6.3-18)</td></tr>
<tr><td>3</td><td>35 (24-49)</td><td>30 (19-45)</td><td>27 (16-43)</td><td>24 (14-38)</td><td>21 (12-34)</td><td>18 (10-30)</td><td>16 (8.7-27)</td></tr>
<tr><td>4</td><td>48 (35-62)</td><td>42 (30-57)</td><td>38 (26-54)</td><td>34 (22-49)</td><td>30 (19-44)</td><td>26 (16-39)</td><td>23 (14-35)</td></tr>
</table></td></tr>
<tr><td>Description of proposed amendment</td><td>Implement the FRAX algorithm accurately to allow a more accurate assessment of fracture risk and cost effectiveness that aids implementation and deals more fairly with inter-patient variation..</td></tr>
<tr><td>Result of amended model or expected impact on the result</td><td>Underestimates cost effectiveness of SR for some patients.</td></tr>
</table>

Pro-forma field	Comment
Issue	Issue 6Time horizon
Description of problem	However, in the model there are two values called *wristbonusat2.5* and *phbonusat2.5* that are also added on to the QALYs which are not described in the report. If these bonuses are also related to preventable deaths it seems to have been assumed that wrist, rib, scapular, clavicular and sternal fractures increase mortality, whereas the report [Stevenson et al, 2007b] indicates otherwise. Another issue is that these adjustments only are related to preventable deaths during the 5 years of treatment
Description of proposed amendment	Amend or completely re-write the model to account for the ability to include the quality of life and mortality effects as mentioned.
Result of amended model or expected impact on the result	Improve the accuracy of the estimate of costs and benefits and improve the cost effectiveness of treatment.

Pro-forma field	Comment
Issue	Issue 9 Compliance
Description of problem	In the HTA reports it is assumed that 50% of the patients stop treatment within the first month. The patients that drop out of treatment are not simulated in the model. The patients that are simulated in the model are only those that persist on treatment for the whole intervention period. This is probably because compliance functionality was not implemented at the time it was decided to produce the Gaussian functions. Instead, an adjustment is made on the cost side to account for non-compliers by adding on one additional month of intervention costs. Any adjustment on the effect side is not necessary since non-compliers are not assumed to have any effect of treatment. This approach to account for compliance will overestimate both the incremental costs and QALYs gained [Ström et al, 2009] so that there may not be a major impact on the ICER compared to an approach where all patients are simulated in the model. This has, however not been tested.
Description of proposed amendment	Model compliance appropriately to remove the over estimate of costs and QALYs gained.
Result of amended model or expected impact on the result	Not known

Pro-forma field	Comment
Issue	Issue 11 Costs
Description of problem	Costs of fracture were taken from Stevenson et al [2006] as used previously to determine cost-effectiveness of intervention in glucocorticoid-induced osteoporosis [Kanis et al, 2007b]. These differ somewhat from those used by NICE, which were based on now out-dated Health Resource Group codes and are unrealistically low as judged by empirical data in the case of hip fracture, unavailable for vertebral fractures and inappropriate for forearm fractures in the elderly, since a substantial proportion of forearm fractures occur in young individuals [Stevenson et al, 2006]. In addition the incorrect HRG coding was chosen for hip fracture.
Description of proposed amendment	
Result of amended model or expected impact on the result	Underestimates cost effectiveness of SR

Pro-forma field	Comment
Issue	Issue 12 QOL for vertebral fractures
Description of problem	The impact on quality of life the first year after a fracture (hip, vertebral and forearm) was based on empirical estimates [Borgström et al, 2006d]. The quality of life estimates for other fractures were based on expert opinion [Kanis et al, 2004b]. The quality of life in subsequent years after a hip fracture was assumed to be 91% of that of a healthy individual. Forearm fractures were estimated to have no quality of life reduction in the second and subsequent years. The quality of life in subsequent years after a vertebral fracture was reduced by 7.1% derived from empirical observations. In an international study when the clinical vertebral fracture may have occurred at a previously unknown time [Oleksik et al, 2000], the utility loss was 9%. These multipliers were used together with the population tariff values for the UK [Kind et al, 1998]. These values are similar to those used by NICE except for vertebral fracture where the utility multiplier in the first year was arbitrarily reduced by the appraisal committee by 27% from 0.626 to 0.792, despite empirical evidence to the contrary at the time of the assessment and now supported by a systematic review by ScHARR [Peasgood et al, 2009].
Description of proposed amendment	
Result of amended model or expected impact on the result	Will reduce ICER of SR

Pro-forma field	Comment
Issue	Issue 13 Cost-effectiveness of identification strategies
Description of problem	Contrary to the claim by NICE, the approach does not follow the guidance of the Royal College of Physicians, so that the acquisition costs are inflated with an adverse effect on cost-effectiveness There are several limitations in this approach. Firstly, an average ICER is used to determine the population that would be identified as suitable for treatment. The use of the average ICER assumes that the prevalence of each CRF is equal. This is clearly not the case [Kanis et al, 2008b, d], and weighted averages should have been used. A further error is that in the derivations of the identification strategy, cost-effectiveness the NICE model also included the ICERs based on alcohol intake (where the incorrect coefficient was used), and smoking and exposure to glucocorticoids which were CRFs not considered to be relevant risk factors in the NICE appraisal. It further did not include a low BMI as a risk variable – a weakness acknowledged in the HTA report to disadvantage younger women with CRFs, and a low BMI. A third error is that the distribution of clinical risk factors over T-score and age (said to be based on the data used to develop the FRAX® algorithm). This assumes an identical prevalence of CRFs over the entire range of T-score (see Table 20 above) which is clearly inappropriate. Indeed women with above a threshold of probability on the basis of CRFs have a T-score that is approximately 1 SD lower than women below the threshold [Johansson et al, 2004]. The distribution of risk factors by age does not conform to their known distribution [Kanis et al, 2008i, 2004c]. A further error is in the distribution of the T-score in the population which does not conform to the population from which it was derived [Holt et al, 2002]. The assumed distribution adversely affects cost-effectiveness, particularly in younger women. In the case of alendronate, the cost of drug is modelled at twice its actual cost which will adversely affect cost-effectiveness. A further flaw is that the acquisition algorithm claims to follow the guidance of the Royal College of Physicians. This guidance indicates that women with CRFs would be eligible for a BMD test, and treatment offered to those with a T-score of -2.5 SD. But an important exception is given for women with a prior fragility fracture where intervention may be considered without recourse to BMD testing [RCP, 1999, 2000]. The guidance of the RCP mirrors that of many other clinical guidelines in Europe and North America [Kurth et al, 2006; Kanis et al, 2008h; NOGG, 2008; Lippuner et al, 2009; Siminoski et al, 2007; Dawson-Hughes et al, 2009; EC, 1998; NOF, 2003]. The omission of this aspect of the guidance increases the requirement for BMD tests in the identification strategy and thus inflates the cost. For example, the number of BMD tests to identify a patient for treatment between the ages of 70-74 years is given as 4.6

Pro-forma field	Comment
	with a WTP of £20,000 and 5.8 with a WTP of £30,000 [Stevenson et al, 2007b, Table 59]. By contrast, when the WHO approach is used for the same age range, the average requirement is 0.4 BMD scans per patient identified for treatment [Kanis et al, 2008i]
Description of proposed amendment	
Result of amended model or expected impact on the result	Underestimates cost effectiveness of SR