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 NICE model was made available to the BRS on 15th May 2009. It would not run because 4 code characters were deleted in one macro. This error was found and corrected in 48 hours from receipt, allowing the BRS 27 working days to investigate the model (for those unfamiliar with the UK University/NHS systems, no "time out" from other work was provided to the BRS evaluators).

Initially we concentrated on identifying model inputs, adjusting them if they deviated from the current published literature and determining if the NICE model performed more similarly to FRAX-NOGG in adjusted form. Subsequently we identified potential structural defects, attributable to first the grouping of all potential candidates for treatment by age group and the calculation of a mean ICER, which if greater than £30,000 (£20,000 for primary protection) led to treatment being denied to all subgroups. Finally over-simplifications were discovered in the way certain risk factors were modelled, which require correction to avoid unfairness to minority groups of (mainly younger) women with osteoporosis.

We note that the current cost of alendronic acid is set at about £55, against a current cost to the NHS of £25. Since up to 15% of alendronate-takers might suffer side effects that could be alleviated by switching to another anti-resorptive agent (at a cost of up to £300 pa), we strongly suggest that in line with current equality legislation and to avoid legal challenges on the grounds of discrimination NICE should advise PCTs to make alendronic acid the first choice treatment with the possibility of the GP switching to a drug in the same class with an annual cost of up to £300 in the event of unacceptable side-effects. This results in a weighted mean cost for "anti-bone resorbers" of (0.85*£25+0.15*£300) = £66, close to the somewhat inflated (or outdated) value of £55 used currently by NICE for alendronic acid.

The BRS wish to draw the attention of the National Institute for Health and Clinical Excellence (NICE) to a variety of other concerns with the model used by NICE:

(a) *Transparency and validation*: The Excel model supplied by NICE estimates the cost-effectiveness based on Gaussian regression functions which are derived from an individual state transition model. This model was only made available late in the consultation period and the coefficients utilised could not be assessed from the data supplied. It does not permit alterations to discount rates, body

mass index, population mortality, mortality associated with clinical risk factors, or the time horizon.

(b) *The utilisation of FRAX*: The NICE model does not permit the calculation of 10 year fracture probabilities as is the case with the appropriate application of FRAX. Discrepancies thus arise with other estimates of cost-effectiveness utilising the model. Possible reasons for these relate to the erroneous assumption that risk factors are not associated with excess mortality; and that a number of significant interactions observed in the original FRAX model, for example fracture/age and BMD/age, appear to have been omitted from the NICE model. Furthermore, body mass index is set at a fixed value by NICE and this deficiency results in erroneous risk estimates except at a BMI of 26 kg/m^2.

(c) The NICE model uses predominantly a 10 year time horizon, with an adjustment to permit alterations in their sensitivity analysis. This adjustment is not described, and does not appear to take account of preventable deaths beyond the 10 year time frame.

(d) *Risk multipliers for fracture risk*: These coefficients appear to be different in the report and in the model.

(e) *Compliance*: Compliance does not appear to have been modelled, whereas adverse effects of treatment appear to have been multiplied.

(f) *Guidance for treatment based on technology appraisal*: We remain of the opinion that there are ethical questions regarding the derivation of guidance for treatment in osteoporosis which is driven exclusively by cost effectiveness. Thus, the appropriateness of treatment with a generic agent to an individual at a given risk level, but the lack of provision to utilise an alternative licence to agent, should there be a failure to tolerate the initial agent, or should adverse effects be observed, appears to us unsustainable.

2nd July 2009

Prepared by the BRS subcommittee on economic modelling:

[redacted],

Please feel free to get in touch if you want other model outputs. The model will be disabled on 5PM 3rd July 2009 as requested.

Issue 1 Alendronic acid assumed to have 10-fold the actual risk of side-effects that reduce quality of life

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model and expected impact on the results.

NB in tables below the SE disutility column shows the current NICE Model value of 10 and also the values of unity (current evidence) and 2 (as part of a reasonable sensitivity analysis). The first table shows the calculated ICERS (note that values with exclamation marks are cost ineffective) and the second table shows the categories of women referred for BMD tests. CPQ - cost (£) per QALY; is it CE – yes if lower than £20,000; CRF - number of clinical risk factors</th></tr>
<tr><td>The disutility associated with bisphosphonate use (eg alendronic acid) was over-estimated by a factor of 10 compared to the published literature. For those not familiar with the terminology of health economic modelling, disutility refers to the extent to which taking the drug is useless or counterproductive. It is quantitated according to the associated add-on costs of dealing with the disutility plus the reduction in quality-adjusted life years (QALYs) resulting from treatment that is attributable to the disutility. Thus, when the disutility factor is increased for alendronic acid by a factor of 10, the benefits of treating those who receive treatment and still suffer no ill effects remain the same, while the numbers suffering disutility (or alternatively the impact of the disutility on the individual) are/is amplified ten-fold. The effect is to remove and sometimes reverse the benefit of treatment in those who stand to gain moderately from treatment in terms of fractures avoided.</td><td>Restore the side effect disutility to unity from its current value of 10-fold</td><td>
<table>
<tr><th></th><th colspan="2">SE disutility = 10</th><th colspan="2">SE disutility = 2</th><th colspan="2">SE disutility = 1</th></tr>
<tr><th></th><th>CPQ</th><th>is it CE</th><th>CPQ</th><th>is it CE</th><th>CPQ</th><th>is it CE</th></tr>
<tr><td>Age 50</td><td>#DIV/0!</td><td>#DIV/0!</td><td>#DIV/0!</td><td>#DIV/0!</td><td>#DIV/0!</td><td>#DIV/0!</td></tr>
<tr><td>Age 55</td><td>#DIV/0!</td><td>#DIV/0!</td><td>£113,616</td><td>-</td><td>£105,301</td><td>-</td></tr>
<tr><td>Age 60</td><td>£267,461</td><td>-</td><td>£31,753</td><td>-</td><td>£27,534</td><td>-</td></tr>
<tr><td>Age 65</td><td>£18,391</td><td>1</td><td>£15,301</td><td>1</td><td>£14,542</td><td>1</td></tr>
<tr><td>Age 70</td><td>£9,290</td><td>1</td><td>£8,562</td><td>1</td><td>£8,199</td><td>1</td></tr>
<tr><td>Age 75</td><td>£1,060</td><td>1</td><td>£2,172</td><td>1</td><td>£2,084</td><td>1</td></tr>
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<tr><th>BMD?</th><th colspan="4">SE disutility = 10</th><th colspan="4">SE disutility = 2</th><th colspan="4">SE disutility = 1</th></tr>
<tr><th>CRFs</th><th>0</th><th>1</th><th>2</th><th>3</th><th>0</th><th>1</th><th>2</th><th>3</th><th>0</th><th>1</th><th>2</th><th>3</th></tr>
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<tr><td>Age 60</td><td></td><td></td><td></td><td>1</td><td></td><td></td><td>1</td><td>1</td><td></td><td></td><td>1</td><td>1</td></tr>
<tr><td>Age 65</td><td></td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Age 70</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Age 75</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
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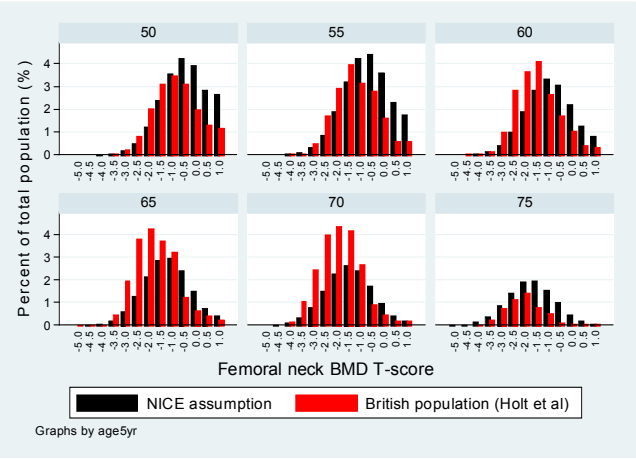
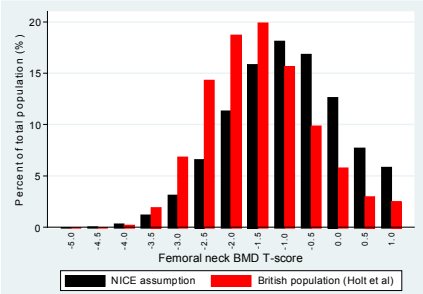
Issue 2 British women assumed to be at far less risk of osteoporosis at a given age than shown by the observational data, making identification less cost-effective than is actually the case.

Description of problem	Description of proposed amendment	Result of amended model: Primary prevention Compare these results with those given previously (Issue 1) column headings unchanged
The proportions of women with low BMD (as estimated by BMD T-score) as input into the NICE model was output graphically and in tabular form and found to be substantially underestimated for England and Wales. The effect of this is to increase costs of identifying those needing treatment because more screening is required for each woman identified for treatment. We could not identify where the grossly elevated BMD T-score distributions came from; we substituted the distribution published by Holt et al (see below) which remains the largest database of T-scores for British women recruited from population registers and therefore as far as possible free from the effect of volunteer bias. Comparison of population distribution by 5-year age-group over femoral neck BMD T-score group in the NICE model versus observed distribution in 5173 British women aged 50-85 years from 7 centres across the UK (Aberdeen, Bath, Cambridge (City), Cambridge (Rural), Harrow, Norfolk, and Truro. [Holt G et al Br J Radiol. 2002 Sep;75(897):736-42]).   	Set the population distribution of T-scores for the femoral neck to be the same as those published by Holt et al (and also restore the numbers of women to those actually known to be living in England and Wales in 2007 from the substantial underestimate found in the model)	

	SE disutility = 2		SE disutility = 1	
	CPQ	is it CE	CPQ	is it CE
Age 50	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Age 55	£65,686	-	£27,470	-
Age 60	£18,623	1	£17,523	1
Age 65	£10,650	1	£10,207	1
Age 70	£5,975	1	£5,716	1
Age 75	£668	1	£648	1

BMD?	SE disutility = 2				SE disutility = 1			
CRFs	0	1	2	3	0	1	2	3
Age 50								
Age 55				1			1	1
Age 60		1	1	1		1	1	1
Age 65	1	1	1	1	1	1	1	1
Age 70	1	1	1	1	1	1	1	1
Age 75	1	1	1	1	1	1	1	1

Issue 3 Incremental Cost-Effectiveness Ratios assumed to be identical for all subgroups of women in a 5-year age band, irrespective of their BMD-independent risk factors. This excludes women from treatment with non-BMD related higher than average risk

Description of problem	Description of proposed amendment	Expected impact on the results if a more sophisticated model assessing groups of women with 0, 1, 2 or 3 risk factors were each assessed separately
Use of mean population ICERS at each BMD level to determine whether an age-cohort was eligible for treatment, irrespective of numbers of clinical risk factors additional to a specific BMD level	Where mean ICER shows non-cost effectiveness, proceed to sub-group ICER analysis (as shown in table to right) before excluding subgroups from treatment.	Median ICERs by No of CRFs, age, and BMD T-score assuming SE disutility factor of 1

No of CRFs and age	BMD T-score -5	-4.5	-4	-3.5	-3	-2.5	-2	-1.5	-1	-.5	0	.5	1
0 CRF													
50	-8,702	-7,051	-4,084	1,078	9,636	23,015	42,565	69,404	104,792	151,418	189,506	223,218	257,140
55	-9,049	-7,232	-4,282	305	7,040	16,355	28,476	43,507	61,660	80,690	94,927	108,796	122,750
60	-8,171	-6,445	-3,787	177	5,833	13,599	23,852	36,983	53,542	68,380	82,877	97,911	113,826
65	-9,392	-7,745	-5,395	-2,129	2,257	8,003	15,338	24,525	34,764	44,137	53,957	64,284	75,287
70	-9,090	-7,574	-5,651	-3,250	-337	3,179	7,394	12,431	16,976	21,661	26,599	31,846	37,490
75	-9,731	-8,581	-7,163	-5,422	-3,326	-782	2,309	5,770	9,177	12,986	17,156	21,737	26,805
1 CRF													
50	-9,035	-7,667	-5,227	-1,028	5,851	16,748	31,450	50,833	74,983	105,336	129,134	149,141	168,183
55	-9,462	-7,933	-5,440	-1,545	4,028	11,519	21,255	32,758	46,207	59,387	69,675	79,426	88,962
60	-8,616	-7,157	-4,903	-1,527	3,316	9,561	18,073	28,340	40,529	51,142	61,387	71,737	82,660
65	-9,877	-8,462	-6,440	-3,719	-103	4,931	11,431	18,900	26,712	33,967	41,438	49,162	57,256
70	-9,779	-8,491	-6,856	-4,778	-2,111	1,168	5,139	9,274	12,966	16,764	20,720	24,877	29,734
75	-10,343	-9,356	-8,142	-6,656	-4,834	-2,503	359	3,627	6,679	9,851	13,283	17,010	21,087
2 CRF													
50	-9,415	-8,376	-6,474	-3,110	2,352	11,063	22,806	35,784	55,118	76,513	92,562	105,594	117,530
55	-9,933	-8,742	-6,788	-3,628	817	7,617	14,485	22,875	34,134	44,691	52,399	59,553	66,398
60	-9,122	-7,981	-6,211	-3,463	307	5,817	12,201	19,120	29,300	37,968	45,957	53,852	61,783
65	-10,527	-9,445	-7,903	-5,756	-2,780	1,332	6,166	11,673	18,380	25,026	31,637	38,370	45,294
70	-10,860	-9,834	-8,483	-6,729	-4,620	-2,089	964	4,536	7,686	10,948	15,112	19,838	24,412
75	-11,406	-10,615	-9,614	-8,354	-6,790	-4,946	-2,757	-249	2,342	5,013	7,832	10,855	14,251
3 CRF													
50	-9,636	-8,803	-7,330	-4,814	-735	5,465	14,199	25,599	39,541	55,939	68,683	79,089	88,395
55	-10,194	-9,222	-7,669	-5,292	-1,846	2,860	8,895	16,206	24,694	33,285	39,764	45,703	51,266
60	-9,403	-8,471	-7,063	-4,998	-2,096	1,826	6,908	13,248	20,934	27,889	34,501	40,990	47,409
65	-11,038	-10,198	-8,993	-7,301	-4,994	-1,933	2,009	6,945	12,528	17,873	23,363	28,929	34,581
70	-11,692	-10,962	-9,996	-8,737	-7,126	-5,099	-2,584	493	3,658	7,035	10,596	14,308	18,168
75	-12,446	-11,934	-11,284	-10,460	-9,421	-8,121	-6,495	-4,540	-2,361	163	3,019	6,213	9,758

Issue 4 Absence of modelling of continuous variables known to the GP that confer risk independently of BMD

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr>
<td>Continuous variables that confer risk independently of BMD are un-modelled (such as lower BMI, eg under 25 which independently increases risk of hip fracture by up to two-fold: de Laet et al 2005 Osteoporos Int 2005 16:1330-8). This disadvantages some high risk subjects</td>
<td>Risk attributable to various levels of BMI independently of BMD may be modelled by rescaling the currently assumed age-specific absolute fracture risks at a given BMD level by the relative risk appropriate for each BMI level. This would only apply to low BMI values.</td>
<td>ICERs after scaling the age-specific 1-year hip fracture probabilities by 2.0 to reflect the hip fracture risk of a woman with BMI of 15 kg/m^2.
<table>
<tr><th></th><th colspan="2">SE disutility = 2</th><th colspan="2">SE disutility = 1</th></tr>
<tr><th></th><th>CPQ</th><th>is it CE</th><th>CPQ</th><th>is it CE</th></tr>
<tr><td>Age 50</td><td>#DIV/0!</td><td>#DIV/0!</td><td>#DIV/0!</td><td>#DIV/0!</td></tr>
<tr><td>Age 55</td><td>£17,825</td><td>1</td><td>£16,646</td><td>1</td></tr>
<tr><td>Age 60</td><td>£12,361</td><td>1</td><td>£11,582</td><td>1</td></tr>
<tr><td>Age 65</td><td>£4,436</td><td>1</td><td>£4,227</td><td>1</td></tr>
<tr><td>Age 70</td><td>£743</td><td>1</td><td>£736</td><td>1</td></tr>
<tr><td>Age 75</td><td>-£4,406</td><td>1</td><td>-£4,222</td><td>1</td></tr>
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<tr><th>BMD?</th><th colspan="4">SE disutility = 2</th><th colspan="4">SE disutility = 1</th></tr>
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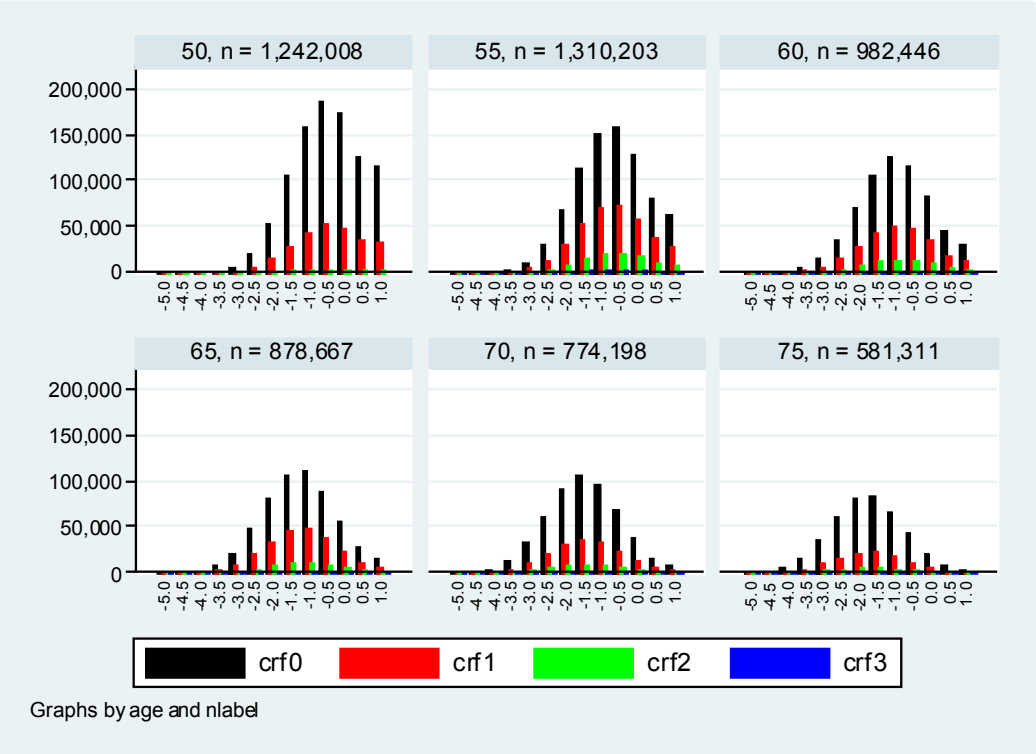
Issue 5 Absence of the required interaction between BMD and BMI (this absence was a necessary consequence of Issue 4)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Distribution of BMD values according to numbers of clinical risk factors as output by the NICE model. Unexpectedly (based on our reading of the evidence) we found that distributions were very similar (see histograms below).  We searched through the model spreadsheets for appropriate interactions as detailed in the individual-level meta-analysis of Kanis et al (Osteoporos. Int 2007 18: 1033-46) and found no evidence of their presence in the model in active form	Implement key interactions, such as the one between low BMD and low BMI (which increase risk above that expected for low BMD in presence of a normal BMI, which appears to be 26 in all simulations, whether BMI is 26 or some other figure.	The minority of very high risk younger women with low BMI and low BMD would get a more appropriate recommendation for alendronate.

Issue 6 Inadequate documentation of the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Documentation of the model is sketchy. If another modeller took over from Dr Stevenson, there appears a serious risk of mistakes being made through misunderstanding of the sometimes non-existent and sometimes ultra-cryptic comment fields.	Matt Stevenson should be commissioned to document the model thoroughly, in its final form, assuming that NICE TA 160/1 in final form are based on a revised version of this model. The model should then be subjected to external, independent peer review and published in a high grade scientific journal under the names of the modeller and the commissioning Chair to establish scientific responsibility.	Reduction in the risk of serious future errors by up to an order of magnitude.

Issue 7 Alcohol intake

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The rationale for the choice of 4 or more units per day intake is not justified anywhere within the NICE documentation. Even if the choice is made to use this threshold, then the coefficient for alcohol intake is incorrect e.g. for hip fracture the coefficieint appears to be 1.53, whereas the published literature (Kanis et al, Osteoporos Int. 2005;16: 737-42) demonstrates that the coefficient for 4 units or more should be 2.26-2.39..	The alcohol threshold should be modelled at the FRAX threshold of 3 units or more daily and the correct coefficient should be applied	The ICER will improve

Issue 8 Smoking and glucocorticoids

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
It is unclear but the spreadsheets appear to suggest that the risks attributable to smoking and glucocorticoid use are included in the identification strategies, but these CRFs are not considered by NICE to be relevant risk factors in the appraisal.	The model should embrace these risk factors and include the full FRAX algorithm in the strategy for osteoporosis management	

Issue 9 Lack of interactions between risk factors in the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There is compelling evidence of significant interactions between several of the risk factors that impact on risk assessment. These interactions are incorporated within FRAX but not within the NICE model and will have an adverse effect on cost-effectiveness especially at younger ages. For example a prior fracture has greater significance at younger ages than in the more elderly population.	The NICE model should be adapted to accommodate interactions such as BMD and fracture, BMD and BMI etc.	The ICER at younger ages will be improved