NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal Consultation Document

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

The Department of Health and the National Assembly for Wales have asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct an appraisal of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women and provide guidance on their use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted and the views put forward by the representatives nominated for this appraisal by professional organisations and patient/carer and service user organisations. The Committee has developed preliminary recommendations on the use of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

This document has been prepared for consultation with the formal consultees. It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk).

Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in Section 1 are preliminary and may change after consultation.

The process the Institute will follow after the consultation period is summarised below. For further details, see the *Guide to the Technology Appraisal Process* (this document is available on the Institute's website, www.nice.org.uk).

- The Appraisal Committee will meet again to consider the original evidence and this Appraisal Consultation Document in the light of the views of the formal consultees.
- At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.
- After considering feedback from the consultation process, the Committee will prepare the Final Appraisal Determination (FAD) and submit it to the Institute.

- Subject to any appeal by consultees, the FAD may be used as the basis for the Institute's guidance on the use of the appraised technology in the NHS in England and Wales.

The key dates for this appraisal are:
Closing date for comments: 21 October 2005
Second Appraisal Committee meeting: 1 November 2005

Details of membership of the Appraisal Committee are given in Appendix A and a list of the sources of evidence used in the preparation of this document is given in Appendix B.

Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in Section 1 are preliminary and may change after consultation.

1 Appraisal Committee's preliminary recommendations

This guidance covers the primary prevention of osteoporotic fragility fractures in postmenopausal women who have not sustained a clinically apparent osteoporotic fracture.

This guidance covers the treatment of postmenopausal women who have normal levels of calcium and/or vitamin D. Unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete, calcium and/or vitamin D supplementation should be prescribed.

This guidance does not cover the prevention and treatment of corticosteroid-induced osteoporosis in women who are on systemic long-term corticosteroid therapy.

T-score relates to the measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) scanning at the femoral neck.

1.1 Bisphosphonates (alendronate, etidronate and risedronate) are recommended as treatment options for the primary prevention of osteoporotic fragility fractures:

- in women aged 70–74 years
  - if they have one clinical risk factor (see Section 1.3) and a T-score of -3.5 SD or below, or
  - if they have two clinical risk factors and a T-score of -3 SD or below, or
  - if they have three or more clinical risk factors and a T-score of -2.5 SD or below;
- in women aged 75 years and over

- if they have one clinical risk factor and a T-score of –3 SD or below
- if they have two clinical risk factors and a T-score of –2.5 SD or below, or
- if they have three or more clinical risk factors, and in this case a DXA scan is not necessary.

1.2 In choosing which bisphosphonate to use, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.

1.3 Clinical risk factors to be considered are parental history of hip fracture; low body mass index (in the absence of knowledge about BMD and defined as less than 19 kg/m^2); and medical conditions independently associated with bone loss, such as rheumatoid arthritis.

1.4 Strontium ranelate is recommended as an alternative treatment option, under the circumstances specified in Section 1.1 in women:

- for whom bisphosphonates are contraindicated (see Summaries of Product Characteristics), or
- who are unable to comply with the special instructions for the administration of bisphosphonates, or
- who are intolerant of bisphosphonates (as defined in Section 1.6).

1.5 Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fractures.

1.6 For the purpose of this guidance, intolerance of bisphosphonates is defined as oesophageal ulceration, erosion or stricture, any of which is sufficiently severe to warrant discontinuation of treatment with a bisphosphonate.

2 Clinical need and practice

2.1 Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

2.2 Bone formation exceeds bone resorption in youth, but by the third decade of life there is a gradual loss of bone mass. Osteoporosis is therefore usually an age-related disease. It can affect both sexes, but women are at greater risk because bone loss is accelerated, to a variable degree, after the menopause because of a decrease in oestrogen production.

2.3 Diagnosis of osteoporosis is based on the measurement of BMD, with reference to the number of standard deviations (T-score) from the BMD in an average 25-year-old woman:

- normal: T-score of –1 or above
- osteopenia: T-score of between –1 and –2.5
- osteoporosis: T-score of –2.5 or below
- established/severe osteoporosis: T-score of –2.5 or below with one or more associated fractures.

2.4 T-score measurements vary by site and method. It has been recommended that BMD should be measured at the femoral neck using DXA to estimate fracture risk.

2.5 It has frequently been quoted that over 2 million women have osteoporosis (that is, have a T-score below –2.5) in England and Wales. However, recent epidemiological data based on a UK sample indicate that this figure may be closer to 1.1 million. Osteoporosis is most common in older white women. Prevalence of osteoporosis increases markedly with age after the menopause, from approximately 2% at 50 years of age rising to over 25% at 80 years.

2.6 Fragility fracture is the clinically apparent and relevant outcome in osteoporosis (referred to as ‘fracture’ or ‘osteoporotic fracture’ in the

following). In the absence of fracture the condition is asymptomatic and often remains undiagnosed. Osteoporotic fractures occur most commonly in the vertebrae, hip and wrist, and are associated with substantial disability, pain and reduced quality of life.

2.7 In women aged over 50 years, the lifetime risk of a vertebral fracture is estimated to be one in three, and one in five for hip fracture. Postmenopausal women with an initial fracture are at substantially greater risk of subsequent fractures. For instance, a woman with a vertebral fracture has an increased relative risk (RR) of 4.4 for a further vertebral fracture, 2.3 for a hip fracture, and 1.4 for a wrist fracture.

2.8 It is estimated that annually there are 180,000 osteoporosis-related symptomatic fractures in England and Wales. Of these, 70,000 are hip fractures, 25,000 are clinical vertebral fractures, and 41,000 are wrist fractures.

2.9 After a hip fracture, a high proportion of women are permanently unable to walk independently or perform other activities of daily living and, consequently, many are unable to live independently. Hip fractures are also associated with increased mortality; estimates of the relative mortality risk vary from 2 to greater than 10 in the 12 months following hip fracture. However, it is unclear to what the extent this can be attributed to fracture alone as opposed to pre-existing comorbidity.

2.10 Vertebral fractures are associated with loss of height and curvature of the spine and result in pain, breathing difficulties, gastrointestinal problems and difficulties performing activities of daily living. It is thought that the majority of vertebral fractures (50–70%) do not come to clinical attention. Vertebral fractures are also associated with increased mortality; UK-specific data indicate a 4.4-fold increase in mortality due to vertebral fractures. However, as with hip fractures, it is unclear to what extent this may be due to comorbidities.

2.11 In addition to increasing age and low BMD, other clinical factors have been associated with an increased fracture risk, such as prior fracture, parental history of hip fracture; low body mass index (in the absence of knowledge about BMD and defined as less than 19 kg/m^2); long-term systemic use of corticosteroids and medical conditions independently associated with bone loss such as rheumatoid arthritis. A full review of risk factors associated with osteoporotic fracture has been carried out for the development of the NICE Clinical Guideline *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk*.

2.12 Under the auspices of the World Health Organization (WHO), an algorithm is currently being developed that quantifies the absolute risk of osteoporotic fracture on the basis of risk factors.

3 The technologies

Bisphosphonates: alendronate, etidronate, risedronate

3.1 Bisphosphonates are inhibitors of bone resorption and increase BMD by altering osteoclast activation and function. Alendronate, etidronate and risedronate are licensed in the UK for the management of osteoporosis.

3.2 Alendronate (Merck Sharp & Dohme Ltd) is an oral bisphosphonate licensed in the UK at a dose of 10 mg/day for the treatment of osteoporosis in postmenopausal women to prevent fractures. A once-weekly preparation (70 mg) is also licensed for the treatment of postmenopausal osteoporosis. Prices are £23.12 for 28 10-mg tablets and £22.80 for four 70-mg tablets (excluding VAT; *British National Formulary* 49th edition [*BNF 49*]). This equates to £301.38 per annum for the once-daily treatment or £297.21 per annum for the once-weekly treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.3 Etidronate (Procter & Gamble Pharmaceuticals UK Ltd) is an oral bisphosphonate licensed in the UK for the treatment of osteoporosis. The drug is administered in 90-day cycles, with each cycle consisting of etidronate

(400 mg daily) for 14 days followed by calcium carbonate (1.25 g daily) for the remaining 76 days. The price per 90-day pack is £37.39 (excluding VAT; *BNF 49*), which equates to £151.64 per annum. Costs may vary in different settings because of negotiated procurement discounts.

3.4 Risedronate (Procter & Gamble Pharmaceuticals UK Ltd) is an oral bisphosphonate licensed in the UK at a dose of 5 mg/day and at 35 mg/week for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures, and for the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prices are £19.10 for 28 5-mg tablets and also £20.30 for four 35-mg tablets (excluding VAT; *BNF 49*), which equates to £248.98 per annum for the daily treatment or £264.63 per annum for the once weekly treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.5 Gastrointestinal side effects are common with bisphosphonates. In people with oesophageal abnormalities and other factors that delay oesophageal transit or emptying, risedronate should be used cautiously and alendronate is contraindicated. For full details of side effects and contraindications, see the Summaries of Product Characteristics.

3.6 Bisphosphonates have relatively complex instructions for administration. Alendronate and risedronate must be taken with 200 ml and 120 ml of water, respectively. Before and immediately after administration patients may not eat or drink, and must remain upright for stipulated time periods. Etidronate should be taken at the midpoint of a 4-hour fast (that is, 2 hours before and 2 hours after food or medication).

Selective oestrogen receptor modulators (SERMs): raloxifene

3.7 SERMs are a class of drugs with selective activity in various organ systems, acting as weak oestrogen receptor agonists in some systems and as oestrogen antagonists in others. The aim of treatment with SERMs is to

maximise the beneficial effects of oestrogen on bone and to minimise the adverse effects on the breast and endometrium.

3.8 Raloxifene (Eli Lilly and Company Ltd) is the only SERM licensed for the treatment of osteoporosis in postmenopausal women. The recommended dose is 60 mg/day. The prices of 28- and 84-tablet packs are £19.86 and £59.59, respectively (excluding VAT; *BNF 49*), which equates to £258.89 per annum. Costs may vary in different settings because of negotiated procurement discounts.

3.9 Raloxifene is contraindicated in people with a history of venous thromboembolism, hepatic impairment, cholestasis, severe renal impairment, undiagnosed uterine bleeding, and endometrial cancer. Raloxifene should not be co-administered with systemic oestrogens and, in patients with breast cancer, it should not be used for osteoporosis treatment and prevention until treatment of the breast cancer, including adjuvant therapy, has been completed. Raloxifene is associated with an increased risk of venous thromboembolic events, particularly during the first 4 months of treatment, which is similar to the reported risk associated with hormone replacement therapy. For full details of side effects and contraindications, see the Summary of Product Characteristics.

Strontium ranelate

3.10 Strontium ranelate (Servier Laboratories Ltd) is composed of two atoms of stable strontium (an element with properties similar to calcium) and one molecule of ranelic acid. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption. It is licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. The recommended dose is one 2 g sachet/day, taken as a suspension in water. The price of a 28-sachet pack is £25.60 (excluding VAT; *BNF 49*), which equates to £333.71 per annum. Costs may vary in different settings because of negotiated procurement discounts.

3.11 The absorption of strontium ranelate is reduced by food, milk and derivative products. It should therefore be administered between meals, preferably at bedtime or at least 2 hours after eating.

3.12 Strontium ranelate is not recommended in patients with severe renal impairment and should be used with caution in patients at increased risk of venous thromboembolism. Treatment with strontium ranelate should be discontinued during treatment with oral tetracycline or quinolone antibiotics. For full details of side effects, drug interactions and contraindications, see the Summary of Product Characteristics.

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Report reviewed data from published randomised controlled trials (RCTs) in postmenopausal women where fracture or health-related quality of life was an endpoint and where one of the five drugs of interest was compared with a relevant comparator including: no treatment, placebo, or one of the other included interventions. The majority of studies used placebo or no treatment as a control. Most studies ensured that women in all arms had normal calcium levels or adequate supplementation, and some studies used additional dietary supplementation with vitamin D.

4.1.2 For this appraisal, reductions in RRs associated with treatment were pooled regardless of the baseline BMD and fracture status of the participants in the studies. It was also assumed that these reductions in RR remain constant at all ages, although there was little evidence for the effectiveness of the drugs in women aged 80 years and older.

4.1.3 For vertebral fractures, some studies used clinical (that is, symptomatic) fractures as their endpoint while others used fractures that were identified

radiographically; such fractures, which are termed radiographic or morphometric, include both symptomatic and asymptomatic fractures. Various definitions of radiographic fractures have been developed, but those definitions that require a 20% reduction in vertebral height are generally recognised as producing more reliable results than those that require a 15% reduction.

4.1.4 For non-vertebral fracture types, individual data on hip, leg, pelvis, wrist, hand, foot, rib and humerus were sometimes provided, while some studies only presented data for all non-vertebral fractures grouped together.

4.1.5 **Alendronate**

4.1.5.1 Sixteen RCTs of alendronate in postmenopausal women were included in the Assessment Report: two studies in women with low or normal BMD; one in women with osteopenia; eight in women with osteopenia or osteoporosis; four in women with osteoporosis; and one in women with established osteoporosis. Overall, 15 studies compared alendronate with placebo or with no treatment; and two used active comparators. All the studies were conducted in women who had adequate levels of calcium from dietary intake or were receiving calcium supplementation.

4.1.5.2 Two studies, one comparing alendronate with oestrogen or oestrogen/alendronate combined and the other comparing alendronate with teriparatide (licensed only for secondary and not primary prevention), found no statistically significant differences in clinically apparent fractures of any type in women with osteoporosis. However, back pain was reported less frequently by women in the teriparatide group compared with women in the alendronate group (6% vs 19%, p = 0.012).

4.1.5.3 In addition to the 16 RCTs, a 2-year study demonstrated the equivalence of weekly and daily doses of alendronate, in terms of clinical fracture incidence and gastrointestinal adverse events. However, this study was not included in the analysis, as it did not have the specified comparators.

4.1.5.4 The meta-analysis for alendronate relative to placebo, carried out by the Assessment Group, resulted in an RR of vertebral fracture of 0.56 (95% confidence interval [CI] 0.46 to 0.68, 4 RCTs, n = 7039); an RR of hip fracture of 0.62 (95% CI, 0.40 to 0.98, 4 RCTs, n = 7881), an RR of wrist fracture of 0.67 (95% CI, 0.34 to 1.31, 4 RCTs, n = 7931) and an RR for other non-vertebral fractures of 0.81 (95% CI, 0.68 to 0.97; 6 RCTs, n = 9973).

4.1.5.5 Gastrointestinal adverse events including nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain were reported in at least one third of the participants in studies of alendronate. However, only one study found the increased frequency of these symptoms to be statistically significant relative to placebo. This is consistent with post-marketing studies indicating that around one-third of alendronate users experience gastrointestinal adverse events. In order to avoid oesophagitis, the Summary of Product Characteristics now recommends that alendronate should be taken, upon rising for the day, with a full glass of water. It is possible that these instructions were not followed in all of the studies, particularly the earlier ones.

4.1.5.6 One study reported health-related quality of life outcomes. At 12 months there were statistically significant improvements in the alendronate group but not in the control group in scores for pain, social isolation, energy level and physical ability.

4.1.6 **Etidronate**

4.1.6.1 Twelve RCTs of etidronate in postmenopausal women were reviewed: three studies in women with low-to-normal BMD; two in women with osteopenia or osteoporosis; one in women with osteoporosis; one in women with osteoporosis or established osteoporosis, and five in women with established osteoporosis. Four studies included active comparators, and eight compared etidronate with placebo or with no treatment (although in six of these, subjects in all arms received calcium, either alone or with

vitamin D). Some studies did not use the exact treatment regimen currently licensed in the UK (that is, a 90-day cycle comprising 400 mg etidronate for 14 days, followed by calcium carbonate 1.25 g for the remaining 76 days). None of the studies reported health-related quality of life outcomes.

4.1.6.2 The meta-analysis of RCTs for etidronate relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.40 (95% CI, 0.20 to 0.83, 3 RCTs, n = 341); an RR of hip fracture of 0.50 (95% CI, 0.05 to 5.34, 2 RCTs, n = 180), and an RR for other non-vertebral fractures of 1.04 (95% CI, 0.64 to 1.69; 5 RCTs, n = 490). There were no data for wrist fracture.

4.1.6.3 An observational study in a general practice setting in the UK reported on fracture rates in people with a diagnosis of osteoporosis who were receiving cyclical etidronate compared with those who were not taking a bisphosphonate. People taking etidronate had an RR of non-vertebral fracture of 0.80 (95% CI, 0.70 to 0.92). The RR of hip fracture was 0.66 (95% CI, 0.51 to 0.85) and that of wrist fracture, 0.81 (95% CI, 0.58 to 1.14).

4.1.6.4 Higher rates of gastrointestinal adverse effects were found in the etidronate groups of four RCTs, although the differences were not always statistically significant. However, non-RCT evidence and testimonies from clinical experts and patient experts suggested that etidronate may be associated with fewer gastrointestinal adverse effects than are other bisphosphonates.

4.1.7 **Risedronate**

4.1.7.1 Seven RCTs of risedronate in postmenopausal women were reviewed: one study in women with normal BMD; one in women with osteopenia; one in women with osteopenia or osteoporosis; one in women with osteoporosis or specific risk factors for hip fracture such as a recent fall;

and three in women with established osteoporosis. All compared risedronate with placebo (although, with the exception of those in the normal BMD study, all women also received calcium) and none reported on health-related quality of life.

4.1.7.2 The meta-analysis for risedronate relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.61 (95% CI, 0.50 to 0.75, 3 RCTs, n = 2301); an RR of hip fracture of 0.74 (95% CI, 0.59 to 0.93, 3 RCTs, n = 11,770), an RR of wrist fracture of 0.68 (95% CI, 0.43 to 1.08, 2 RCTs, n = 2439) and an RR for other non-vertebral fractures of 0.76 (95% CI, 0.64 to 0.91; 5 RCTs, n = 12,399).

4.1.7.3 Overall and gastrointestinal adverse events were similar in the risedronate and placebo groups in all of the studies.

4.1.8 **Raloxifene**

4.1.8.1 Three RCTs of raloxifene in postmenopausal women were identified, but only two were included in the Assessment Group's meta analysis: the largest study (the Multiple Outcomes of Raloxifene Evaluation study – MORE) was in women with osteoporosis, of whom 37% had a vertebral fracture at entry, and a smaller study was in women all of whom had established osteoporosis. Both compared raloxifene with placebo (in both studies, women in both arms received calcium and vitamin D). Both studies examined raloxifene at doses of 60 mg/day (UK licensed dose for treatment of postmenopausal osteoporosis) and 120 mg/day. Neither reported on health-related quality of life. The mean age in the studies was 67–68 years. The MORE study was extended to further assess fracture, breast cancer, and cardiovascular and uterine safety outcomes. A third study examined the additive effect of raloxifene, compared with placebo, in women with a femoral neck T-score of –2.0 or lower, with or without prior fracture, who were also receiving fluoride, calcium and vitamin D. Because of the use of fluoride as a co-intervention, these results were not included in the Assessment Group's meta-analysis.

4.1.8.2 The meta-analysis for raloxifene relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.65 (95% CI, 0.53 to 0.79, 1 RCT, n = 4551); an RR of hip fracture of 1.13 (95% CI, 0.66 to 1.96, 2 RCTs, n = 6971), an RR of wrist fracture of 0.89 (95% CI, 0.68 to 1.15,1 RCT, n = 6828) and an RR for other non-vertebral fractures of 0.92 (95% CI, 0.79 to 1.07; 1 RCT, n = 6828).

4.1.8.3 The most serious adverse effect associated with raloxifene is the approximately three-fold increased risk of venous thromboembolism. Statistically significantly higher incidences of hot flushes, arthralgia, dizziness, leg cramps, influenza-like symptoms, endometrial cavity fluid, peripheral oedema and worsening diabetes were also found with raloxifene compared with placebo.

4.1.8.4 The MORE study shows that raloxifene protects against breast cancer, with the RR at 4 years, for all types of breast cancer, reported as 0.38 (95% CI, 0.24 to 0.58) and for invasive breast cancer as 0.28 (95% CI, 0.17 to 0.46). The impact of raloxifene on cardiovascular disease is unclear, although there is evidence that it lowers fibrinogen and both total and LDL cholesterol without increasing HDL cholesterol.

4.1.9 **Strontium ranelate**

4.1.9.1 Three RCTs of strontium ranelate in postmenopausal women were identified: one study in women with osteoporosis and two in women with osteoporosis or established osteoporosis. All three studies compared strontium ranelate against placebo. All three studies provided calcium and vitamin D supplementation to ensure an adequate intake.

4.1.9.2 The Assessment Group reported the results of a published meta-analysis, which resulted in an RR for vertebral fracture of 0.60 (95% CI 0.53 to 0.69, 2 RCTs, n = 6551); and an RR for all non-vertebral fractures (including wrist fracture) of 0.84 (95% CI 0.73 to 0.97, 2 RCTs, n = 6551). Hip fracture efficacy was established in one study: The RR for hip fracture in

the whole study population was 0.85 (95% CI 0.61 to 1.19, 1 RCT, n = 4932). A post-hoc subgroup analysis in women over 74 years of age and with a T-score of –2.4 resulted in an RR for hip fracture of 0.64 (95% CI 0.41 to 0.98, 1 RCT, n = 1977).

4.1.9.3 In general, strontium ranelate was not associated with an increased risk of adverse effects and for the most part adverse effects were mild and transient. Transient nausea, diarrhoea and creatine kinase elevations were the most commonly reported clinical adverse effects. A serious adverse event associated with strontium ranelate therapy was an increased incidence (RR = 1.42) of venous thromboembolism (VTE) and pulmonary embolism. This is being addressed with the extension of ongoing studies and by post-marketing surveillance.

4.1.9.4 One study published results on health-related quality of life. Strontium ranelate was said to benefit quality of life when compared with placebo, as assessed by the QUALIOST osteoporosis-specific questionnaire and by the general health perception score of the SF-36 general scale.

4.2 Cost effectiveness

The Assessment Group's economic model

4.2.1 The Assessment Group provided a cost–utility model in which the cost effectiveness of the individual drugs was estimated for women at different levels of annual absolute risk of fracture and different ages (from age 50, in 5-year age bands). This was done because the cost-effectiveness of interventions at a given age is not only determined by total absolute fracture risk but also by the proportion of fractures at each site within a given absolute risk, the mortality hazard over the treatment period, the baseline utility values and the probability of entering a nursing home with associated cost and utility consequences.

4.2.2 The RR reductions for fracture were taken from the meta-analyses described above. Based on the advice from the Guideline Development Group, it was

assumed that RRs remain constant across all ages, T-scores and fracture status.

4.2.3 All osteoporotic fractures were included in the modelling. The RR for hip fracture was assumed to apply also to pelvis and other femoral fractures. The RR for non-vertebral fracture was assumed to apply to proximal humerus, rib, sternum, scapula, tibia, fibula and wrist fracture. Where confidence intervals spanned unity, no effect was assumed. For strontium ranelate, however, a non-significant RR for hip fracture was used in order to acknowledge a statistically significant effect reported in a subgroup of older women. The model used UK-specific epidemiological data on femoral neck BMD.

4.2.4 The model assumed an initial utility in the year of fracture and a higher utility in subsequent years. The time horizon was 10 years, consisting of 5 years treatment with sustained efficacy plus 5 years linear decline to no effect. The percentage of women that are assumed to move from community living to a nursing home following a hip fracture increased with increasing age. An age-dependent gradient of hip fracture risk was used. An association between vertebral or proximal humerus fracture and increased mortality in osteoporotic patients was included. No follow-up BMD scans were included in the model, reflecting clinical practice in the UK, based on the limited DXA availability.

4.2.5 A number of clinical risk factors were aggregated and quantified as absolute risk. The model used a fracture-risk algorithm derived from a study carried out under the auspices of the WHO. This study analysed the effect of age, sex, T-score and several other clinical risk factors on fracture incidence in 12 cohorts from Europe, North America and Asia, with a total of 60,000 people and 250,000 patient-years of observation. The risk factors included body mass index, previous fracture, ever use of corticosteroids, parental history of fracture, current smoking, alcohol intake of more than 2 units per day, and rheumatoid arthritis. The study provided prevalence data for the different risk factors, and risk ratios for hip fracture and osteoporotic fracture for each risk

factor, including T-score and age. From these risk ratios an algorithm was developed that integrates all risk factors into absolute risk of fracture.

4.2.6 In the absence of any additional risk factor a woman with a T-score of –2.5 has an absolute annual risk of fracture of 0.9% at the age of 50-54 rising to 2.8% at the age of 80. A woman aged 65-69 has an absolute annual risk of fracture of 0.8% at a T-score of –1 rising to 5.9% at a T-score of –5. A 50-54 year-old woman with a T-score of –4 has the same absolute annual risk of fracture (2.3%) as a 75-79 year-old woman with a T-score of –2.5.

4.2.7 The estimates of cost effectiveness were generated for different levels of absolute risk derived from a large number of combinations of T-scores, ages and risk factors. For practical reasons relating to the number of potential combinations, only single-point RRs of fracture calculated from the log-normal efficacy distributions were used in the model.

4.2.8 For raloxifene, the cost effectiveness was modelled both including and excluding the breast cancer benefit. Four-year follow-up data from the MORE study were used, and it was assumed that women with low BMD have a lower breast cancer risk than women with normal BMD. Due to the small absolute risk of venous thrombosis in women, and the non-significant effect on cardiovascular events for all women, neither effect was incorporated into the model.

4.2.9 As women without fracture do not usually present to clinicians, the Assessment Group also estimated the impact of identification costs on the cost effectiveness of the drugs. Identification of women at high risk was modelled using the selective case-finding approach currently recommended by the Royal College of Physicians (RCP) and a new case-finding approach based on the WHO study results. For this the net-benefit approach was used, whereby the total net benefit for each identification approach and age band was calculated by subtracting the cost of identification (risk assessment and DXA scanning) from the net benefit of treating all women that can be treated cost effectively. Where the total net benefit is positive, the identification and

treatment approach is cost effective on a population level. The net benefit approach requires an assumption about the willingness to pay. The Assessment Group modelled this for two maximum acceptable Incremental Cost Effectiveness Ratios (ICERs), £20,000 and £30,000 per quality-adjusted life year (QALY), in accordance with the NICE *Guide to the Methods of Technology Appraisal*.

Cost per QALY without including identification costs

4.2.10 The cost per quality-adjusted life-year gained, compared with no treatment, (CQG) became more favourable with increasing age and decreasing T-score, that is with increasing annual absolute risk of fracture (abbreviated to 'risk' in the following) for the bisphosphonates and strontium ranelate. This was also the case for raloxifene, when the breast cancer benefit was excluded. However, when the breast cancer benefit for raloxifene was included, the CQG became less favourable with increasing risk.

4.2.11 Alendronate is taken as a proxy for the bisphosphonates because the data for alendronate generally provide the best case in terms of cost effectiveness.

4.2.12 For women aged 60-64 with a T-score of –2.5 and no clinical risk factors (equivalent to a risk of 1.05%), the CQG was £77,000 for alendronate, £245,000 and £27,000 for raloxifene (excluding and including the breast cancer benefit respectively), and £128,000 for strontium ranelate. For women aged 60-64 with a T-score of –3 and no clinical risk factors (equivalent to a risk of 1.34%), the CQG was £52,000 for alendronate, £212,000 and £30,000 for raloxifene (excluding and including the breast cancer benefit respectively), and £95,000 for strontium ranelate. For women aged 60-64 with a T-score of –3.5 and no clinical risk factors (equivalent to a risk of 1.78%), the CQG was £32,000 for alendronate, £184,000 and £34,000 for raloxifene (excluding and including the breast cancer benefit respectively), and £67,000 for strontium ranelate.

4.2.13 For women aged 75-79 with a T-score of –2.5 and no clinical risk factors (equivalent to a risk of 2.32%), the CQG was £27,000 for alendronate, £73,000 and £35,000 for raloxifene (excluding and including the breast cancer benefit respectively),) and £46,000 for strontium ranelate. For women aged 75-79 with a T-score of –3.0 and no clinical risk factors (equivalent to a risk of 2.94%), the CQG was £19,000 for alendronate, £61,000 and £34,000 for raloxifene (excluding and including the breast cancer benefit respectively),and £35,000 for strontium ranelate.

4.2.14 When it was assumed that the maximum amount that it is acceptable to pay for an additional QALY is £20,000, intervention thresholds, based on risk derived from T-score and age alone, were between 2.5 and 3% for alendronate, and between 4.1 and 4.7% for strontium ranelate. Absolute risk intervention thresholds were not calculated for raloxifene as its cost-effectiveness was inversely proportional to absolute risk of fracture when the breast cancer benefit was included, and intervention thresholds were over 10% when the breast cancer benefit was excluded.

4.2.15 Clinical risk factors other than age and T-score also contribute to the risk of fracture. Although absolute risk of fracture provides an overall measure of fracture risk, the economic modelling revealed that absolute risk is not a precise indicator of cost effectiveness. This is because absolute risk covers all fracture sites included in the analysis, but different fracture sites have different impacts on quality of life, costs and mortality; the ratio of the risks for hip to non-hip fracture changes with age; different risk factors have different effects on hip and non-hip fractures, and this effect changes with age. Every possible combination of age, T-score and risk factor(s) therefore has a different absolute risk intervention threshold.

Manufacturers' models

4.2.16 For alendronate, the manufacturer's model provided a CQG of £8,622 for 70-year-old women with a T-score below –2.5. The manufacturer's results were more favourable than the Assessment Group's model. This could be because

of different assumptions used for baseline fracture prevalence (not adjusted in the manufacturer's model), different utilities for vertebral fractures and efficacy data, different risk groups used, or the longer time horizon used in the manufacturer's model.

4.2.17 For etidronate the manufacturer's model provided a CQG of £18,634 for 70-year-old women with a T-score below –2.5. The manufacturer's model included morphometric vertebral fractures and corticosteroid use as risk factors for further fractures. It is unclear whether the manufacturer's CQG figure was for women with or without osteoporotic fragility fracture.

4.2.18 For risedronate, the manufacturer provided data from two models. The CQG derived from the manufacturer's own model was £577 for age 74. In the second model provided by the manufacturer, which was commissioned from an external body, the CQG was more than £35,000 for all women without fragility fracture and with a T-score of –2.5. However, for those at slightly higher risk, and age 70 and older, the corresponding CQG was £13,500 or less. The CQG figure calculated by the manufacturer's own model is difficult to substantiate from the information given. The CQG figures generated by the second model are more consistent with the figures provided by the Assessment Group's model though they do differ somewhat. This may be due to differing cost and RR inputs.

4.2.19 For raloxifene, the manufacturer provided data, all including the breast cancer benefit, for different age groups and different risk levels. It was not clear how the different risk levels were defined. The CQG figures varied from £12,000 to £22,000. The manufacturer's results were more favourable than the Assessment Group's analysis, even when the Assessment Group included the breast cancer benefit. In the Assessment Group's model, the RR for the breast cancer effect was higher (0.38) than the RR of invasive breast cancer used in the manufacturer's model (0.28) and the breast cancer risk was adjusted for the association between low BMD and decreased risk of breast cancer. Additionally, the manufacturer's model used different assumptions for

baseline fracture prevalence (not adjusted in the manufacturer's model), different utilities for vertebral fractures, different efficacy data, different risk groups, and a longer time horizon.

4.2.20 For strontium ranelate, the manufacturer provided a model developed by an external organisation. This resulted in a CQG of £45,028 for 65-year-old women decreasing to £26,686 for 80-year-old women, all with a T-score of –2.5. The manufacturer's results were more favourable than the Assessment Group's results because different modelling assumptions were used. For example, a limited number of health-state transition possibilities were incorporated. The model provided by the manufacturer used more favourable hip-fracture efficacy data from a subgroup of patients aged over 74 and slightly more favourable efficacy data for wrist and proximal humerus fracture. Higher hip-fracture costs were used.

Cost effectiveness including identification costs

4.2.21 The Assessment Group modelled the costs from two identification approaches: the RCP selective case-finding approach (currently standard practice) and a new approach based on the data from the WHO study. Both approaches are based on opportunistic case finding through a risk assessment, undertaken during a GP visit arranged for a different reason.

4.2.22 Under the RCP selective case-finding approach, patients in whom any risk factor is present are referred for DXA scan. If the T-score is –2.5 or less, treatment is prescribed. Under the alternative approach based on the WHO algorithm, risk is estimated based on the presence or absence of six risk factors (parental hip fracture, alcohol consumption, corticosteroid use, rheumatoid arthritis, smoking and prior fracture). No treatment (or investigation) is given if the risk is low (that is, much below the intervention threshold). Treatment is given without DXA scan if the risk is high (that is, much above the intervention threshold). For all other women, a DXA scan is carried out and treatment is given if the absolute risk is above the intervention threshold. In order to establish if women should be given no treatment,

treatment without a DXA scan or a DXA scan, the Assessment Group ran the model for each age band and risk-factor combination, and calculated which of the three options gave the highest net benefit.

4.2.23 In women under the age of 70, identification based on the RCP and on the WHO algorithm-based approaches resulted in negative net benefits, that is were not cost-effective, assuming a maximum acceptable ICER of £20,000 for an additional QALY. At age 70 and above both approaches resulted in a positive net benefit (i.e. the benefits of the identification and treatment strategy outweighed the costs).

4.2.24 For the WHO approach, the Assessment Group estimated the identification strategy with the highest net benefit for all risk factors and T-score combinations. This led to a complex matrix of DXA scan decisions and intervention thresholds, as each risk factor is associated with its own intervention threshold. The Assessment Group therefore simplified the approach as follows: using average T-scores across risk factors; weighting according to the prevalence of those risk factors or combinations; giving more impact to the risk factor 'parental history of hip fracture'; and by excluding corticosteroid use as a risk factor.

4.2.25 In women over the age of 70 the following approach led to the highest net benefit.

- Women aged 70–74, who have at least one risk factor, receive DXA scanning, and treatment at or below T-scores of –2.8, –2.3 or –1.7 when one, two or three risk factors are present, respectively.

- Women aged 75–79 with three risk factors are treated without DXA scanning. All other women aged 75–79 receive DXA scanning, and treatment at or below T-scores of –3, –2.3 or –1.5 when zero, one or two risk factors are present, respectively.

- Women above the age of 80 with two or more risk factors are treated without DXA scanning. All other women over the age of 80 receive DXA scanning and treatment at or below T-scores of –2.3 or –1.5 when zero or one risk factor is present, respectively.

4.2.26 The model indicated that the WHO-algorithm-based approach led to higher net benefits than the RCP-recommendation based approach, that is was more cost effective, because DXA scans would be targeted more efficiently and because treatment would be given on cost-effectiveness grounds.

4.2.27 Sensitivity analysis revealed that the cost effectiveness of the WHO approach was sensitive to compliance with treatment. When compliance fell below 25–50% the approach led to negative net benefits, i.e. was no longer cost effective.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of alendronate, etidronate, risedronate, raloxifene and strontium ranelate, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people with osteoporosis, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the effective use of NHS resources.

4.3.2 As women who have not had a fracture do not present to clinicians, the Committee considered it necessary to include the cost involved in the assessment of fracture risk in the total cost that is included in the cost-effectiveness modelling. The Committee was made aware of a previous decision of the National Screening Committee not to recommend DXA scanning as screening to prevent osteoporotic fracture because of concerns about the accuracy of BMD assessment for the prediction of fracture and because there was no trial evidence indicating that such screening would reduce the incidence of fractures.

4.3.3 The Committee agreed that its previous decisions, which had been accepted at appeal and for which there was no new evidence, should stand. The Committee had previously concluded that all the bisphosphonates should be considered together in terms of cost-effectiveness in preventing vertebral fractures and hip fractures (*NICE Technology Appraisal* No. 87). It also had previously concluded that raloxifene's effects on breast cancer should not be the sole factor in deciding whether or not raloxifene is a cost-effective option for the treatment of osteoporosis.

Clinical effectiveness

4.3.4 The Committee reviewed the (updated) evidence base for the bisphosphonates and raloxifene, which had previously been appraised in the context of secondary prevention. It then considered the clinical evidence for strontium ranelate from RCTs and heard statements from experts. It noted that strontium ranelate was effective in preventing vertebral and pooled non-vertebral fractures, and resulted in a non-significant 15% reduction in hip-fracture incidence. The Committee also noted the result of a post-hoc subgroup analysis showing a statistically significant reduction in the incidence of hip fractures in women over the age of 74 and with low BMD. The Committee concluded that the hip-fracture efficacy evidence was less robust for strontium ranelate than for alendronate and risedronate.

4.3.5 The Committee heard that, for all the drugs, efficacy tends to be greatest at lower BMDs (osteoporosis and established osteoporosis, equivalent to a T-score ≤ –2.5). It noted that, in osteopenic women (equivalent to a T-score between –2.5 and –1), efficacy in reducing fracture-risk was less well established. The Committee concluded that any recommendation for the use of the drugs would be less soundly based in people with osteopenia than in people with osteoporosis.

Risk factors

4.3.6 The Committee discussed the importance of risk factors in addition to age and low BMD. The Committee had previously considered a number of risk factors for which there was qualitative evidence that the presence of the risk factor increased the risk of fracture (*NICE Technology Appraisal* No. 87). The Committee noted that, since this appraisal, several risk factors had been assessed by the WHO study, as being independent of BMD and their effects on risk were quantified. These were prior fracture (not relevant for this appraisal), parental history of hip fracture, ever use of corticosteroids, rheumatoid arthritis, current smoking and alcohol intake of more than 2 units per day. The Committee noted that the WHO study also indicated that low BMI was a risk factor, but was not independent of BMD.

4.3.7 The Committee was concerned about recommending the use, as risk factors, of current smoking and alcohol intake because their effects on fracture risk were relatively small, and such behavioural risk factors are difficult to confirm reliably. However, the Committee noted that medical conditions which are independently associated with bone loss, such as rheumatoid arthritis, are important for risk assessment. The Committee was also mindful that long-term systemic corticosteroid use, as a principal risk factor, requires separate consideration and is not covered in this guidance, and that a full review of other risk factors was carried out as part of the Clinical Guideline Development.

4.3.8 ***Cost-effectiveness modelling***

4.3.9 The Committee considered the willingness to pay for an additional QALY gained through primary prevention of osteoporotic fracture, and did not consider there to be compelling additional considerations that would lead them to adopt a threshold higher than £20,000 per QALY. The target population consists of women who are well and asymptomatic, and do not generally present seeking medical help for the condition (unlike in secondary prevention where the women who receive treatment have sustained a fracture).

4.3.10 The Committee acknowledged the efforts of the Assessment Group to build on the model used previously, particularly in using the so-far unpublished and complex WHO data to calculate transition probabilities and for modelling the identification approaches. The Committee had previously concluded that the Assessment Group's model was likely to give the best estimates of cost effectiveness because it used data for a wide age range (age 50–80 years), was updated to use all fracture sites and more recent utility, prevalence and risk-factor data, and an adjusted prevalence of fractures in the average population. Although the Assessment Group's model considered a shorter time period (10 years) than the manufacturers' models, the Committee thought that this was appropriate considering the age groups involved and the uncertainties around health effects over a longer period.

4.3.11 The Committee noted that the relationship between absolute risk and cost effectiveness is not constant because each risk factor has a different impact on cost effectiveness. Therefore, the Committee considered it inappropriate to recommend intervention thresholds based on absolute risk. The Committee considered the complex results related to the inclusion of different risk factors and combinations of risk factors and agreed that a simplified strategy, grouping the effects of risk factors, is the only practical way forward.

Bisphosphonates

4.3.12 Given the evidence on clinical effectiveness and cost effectiveness without the inclusion of identification costs, the Committee concluded that bisphosphonates show the best cost-effectiveness profile across all ages, T-scores and absolute risks, when compared to no treatment, and should be recommended for women who are at sufficiently high risk and who can be identified cost effectively.

4.3.13 The Committee considered the economic modelling of the identification approaches and noted that neither the current RCP selective case-finding

approach, nor the approach based on the WHO algorithm was cost effective for women below the age of 70. The Committee noted that, for certain groups of women aged 70 and above, identification and treatment can be cost effective. However, the Committee considered that some of the assumptions underpinning these results were associated with uncertainty and were optimistic. In particular, the Committee noted that compliance with antiresorptive therapy is generally low, and there is evidence that cost effectiveness is sensitive to compliance. It also noted that costs relating to adverse effects of treatment were excluded, that there was a lack of trial evidence for the effectiveness of identification strategies in fracture prevention, and that the accuracy of DXA scanning was imperfect. Additionally, the Committee was aware that treatment of otherwise healthy women requires caution, particularly if the treatments can confer adverse effects.

4.3.14 The Committee heard that expert opinion was divided about replacing the current RCP recommendations, which do not favour the treatment of women without at least one risk factor, with an approach based on the so-far unpublished WHO study.

4.3.15 The Committee considered the T-score thresholds used in the simplified identification strategy modelled by the Assessment Group. In view of the optimistic assumptions discussed in 4.3.12, the Committee decided to exercise caution in the formulation of recommendations, and to recommend identification and making intervention available only for women over 70 with at least one additional risk factor. It reached the following conclusions.

- Women aged 70 and above should be assessed for the presence of risk factors.
- Women aged 70–74 should receive treatment if they have one clinical risk factor (see Section 1.3) and a T score of –3.5 or below, if they have two

clinical risk factors and a T score of –3 or below, or if they have three or more clinical risk factors and a T score of –2.5 or below.

- Women aged 75 years and over should receive treatment if they have one clinical risk factor and a T score of –3 or below; if they have two clinical risk factors and a T score of –2.5 or below; or if they have three or more clinical risk factors, without the need for a DXA scan.

4.3.16 The Committee further recognised that treatment with bisphosphonates does not confer absolute protection against further fracture, and that the beneficial effect on BMD accrues over many months. It was persuaded that even if a woman sustains a fracture within the first few months of bisphosphonate therapy, continuation with bisphosphonate treatment is likely to be the most appropriate therapy in many women.

Strontium ranelate

4.3.17 For strontium ranelate, the Committee agreed that, on balance, the RR for hip fracture used in the modelling could be accepted but it did not accept an even more favourable but potentially biased estimate of efficacy in preventing hip fracture from a post-hoc subgroup analysis. Based on the incremental analysis carried out by the Assessment Group, the Committee agreed that strontium ranelate was likely to be dominated by bisphosphonates. Therefore, the Committee concluded that strontium ranelate should only be a treatment option for women who cannot take bisphosphonates because of intolerance to bisphosphonates or inability to comply with the special recommendations for use of bisphosphonates, or because bisphosphonates are contraindicated.

Raloxifene

4.3.18 For raloxifene, the Committee had previously decided that the breast cancer benefit should not be a driver of any positive recommendation (*NICE Technology Appraisal* No. 87). The Committee noted that the cost

effectiveness of raloxifene, in terms of fracture prevention, was very unfavourable relative to the bisphosphonates and strontium ranelate. The existence of strontium ranelate as an option in women for whom bisphosphonates are inappropriate, and the older age group brought into consideration in primary prevention made the consideration of raloxifene less relevant than in the original appraisal of secondary prevention. The Committee concluded that raloxifene should not be recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

Calcium and vitamin D prerequisites for treatment

4.3.19 The Committee has previously considered the effect of calcium and vitamin D on the clinical effectiveness of the drugs considered (*NICE Technology Appraisal* No. 87) and concluded that calcium and/or vitamin D supplementation should be provided unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete.

5 Proposed recommendations for further research

5.1 To enable direct comparisons of efficacy to be made between the different drugs for osteoporosis, the Committee recommends that head-to-head studies should be conducted.

5.2 Given the emergence of evidence from one bisphosphonate that the benefits of the drug may continue for several years beyond treatment cessation, the Committee recommends that research should be carried out to define the optimal duration of treatment with individual bisphosphonates.

5.3 The Committee recommends research into the long-term effects of bisphosphonates on bone quality, given the inhibitory effects on bone resorption of these drugs.

5.4 There is some evidence that strontium ranelate may interfere with the results of DXA scanning as it has similar properties to calcium. It may also affect the measurement of calcium levels in the blood. This could have implications in the clinical care setting and further research is recommended.

5.5 The Committee notes that there is an ongoing study to investigate the clinical and cost effectiveness of identifying women at high risk in the prevention of osteoporotic fracture.

6 Preliminary views on the resource impact for the NHS

The NICE Costing Unit is currently developing this section. A costing template and report will be available at the time of publication of the final guidance.

7 Proposals for implementation and audit

This section presents proposals for implementation and audit based on the preliminary recommendations for guidance in Section 1.

7.1 All clinicians in NHS Hospital and Primary Care Trusts who care for postmenopausal women who are at risk of osteoporotic fragility fractures should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 Local guidelines, protocols or care pathways that refer to the care of postmenopausal women who are at risk of osteoporotic fragility fractures should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

7.3.1 For a woman aged 70–74 years, bisphosphonates are considered as treatment options for the primary prevention of osteoporotic fragility fractures if she meets any of the following:

- She has one clinical risk factor and a T-score of –3.5 or below **or**
- She has two clinical risk factors and a T-score of –3 or below **or**
- She has three or more clinical risk factors and a T-score of –2.5 or below.

7.3.2 For a woman aged 75 years or older, bisphosphonates are considered as treatment options for the primary prevention of osteoporotic fragility fractures if she meets any of the following:

- She has one clinical risk factor and a T-score of –3 or below **or**
- She has two clinical risk factors and a T-score of –2.5 or below **or**
- She has three or more clinical risk factors.

7.3.3 The woman participates with her clinician in choosing a bisphosphonate. In making the choice, the woman and her clinician consider the drugs' overall proven effectiveness profiles against tolerability and adverse effects.

7.3.4 Strontium ranelate is considered as a treatment option for a woman if she meets the circumstances specified in 7.3.1 or 7.3.2 **and** any of the following:

- She has a contraindication to bisphosphonates **or**
- She is unable to comply with the special instructions for administration of bisphosphonates **or**
- She is intolerant of bisphosphonates.

7.3.5 Raloxifene is not prescribed as a treatment option for the primary prevention of osteoporotic fractures.

7.4 Local clinical audits on the care of women at risk of osteoporotic fragility fractures could also include criteria related to the prevention of falls based on the standards in the National Service Framework for Older People or criteria based on the clinical guidelines for prevention and treatment of osteoporosis published by the Royal College of Physicians. Issues that could be addressed in local clinical audits on osteoporosis include, maintaining patient adherence with bisphosphonate drug therapy, educating patients about the condition and treatments, and the involvement of the multiprofessional team in managing patients with osteoporosis.

8 Related guidance

8.1 The Institute has issued guidance on technologies for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

National Institute for Clinical Excellence (2005) Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathryroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, *NICE Technology Appraisal Guidance* No. 87, London: National Institute for Clinical Excellence.

8.2 NICE plans to publish the guideline '*Osteoporosis: a*ssessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' in June 2006.

8.3 NICE plans to publish the guidance '*Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women'* in March 2006.

9 Proposed date for review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be

reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 It is proposed that the guidance on this technology is considered for review in March 2009.

Andrew Stevens
Chair, Appraisal Committee
September 2005

Appendix A. Appraisal Committee members and NICE team members

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets regularly and membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley

Vice Chairman, InContact

Professor John Cairns
Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Peter I Clark
Honorary Chairman, Association of Cancer Physicians

Ms Donna Covey

Chief Executive, Asthma UK

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Professor Jack Dowie
Health Economist, London School of Hygiene and Tropical Medicine

Professor Gary A. Ford

Professor of Pharmacology of Old Age/Consultant Physician, Royal Victoria Infirmary, Newcastle upon Tyne

Dr Fergus Gleeson
Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Former Director of Nursing & Workforce Development, Mid Essex Hospital Services NHS Trust

Ms Linda Hands

Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford

Professor Peter Jones
Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

Professor Robert Kerwin
Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Rachel Lewis
Nurse Advisor to the Department of Health

Professor Jonathan Michaels
Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner
General Medical Practitioner, Sheffield

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr Rubin Minhas

General Practitioner, Primary Care Cardiovascular Society

Mr Miles Scott
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Dr Ken Stein
Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)
Professor of Public Health, University of Birmingham

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Kate Burslem

Technical Lead, NICE project team

Elisabeth George

Technical Lead, NICE project team

Janet Robertson

Technical Advisor, NICE project team

Cathryn Fuller

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee for the appraisal of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fractures in postmenopausal women

A The assessment reports for this appraisal were prepared by The University of Sheffield, School of Health and Related Research (ScHARR).

Stevenson M, Davis S, Lloyd Jones M and Beverley C. *Strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women,* July 2005.

Stevenson M, Davis S. *Addendum to the Assessment Report: The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women,* July 2005

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report. They are also invited to comment on the Appraisal Consultation Document and consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- Alliance for Better Bone Health
- Eli Lilly & Company Ltd
- Merck Sharp & Dohme Ltd
- Proctor & Gamble Pharmaceuticals
- Servier Ltd

II Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance

- Bone and Tooth Society
- British Geriatrics Society
- British Menopause Society
- British Orthopaedic Association
- British Society for Rheumatology
- Department of Health
- Institute for Ageing and Health
- National Osteoporosis Society
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- RADAR (The Royal Association for Disability and Rehabilitation)
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Society for Endocrinology
- Southwark Primary Care Trust
- The Society and The College of Radiographers
- Women's Health
- Women's Health Concern
- Women's Nutritional Advisory Service

III Commentator organisations (without the right of appeal):

- British National Formulary
- National Collaborating Centre for Nursing and Supportive Care
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals Ltd
- Research Institute for the Care of the Elderly
- Strakan Group Ltd
- Welsh Assembly Government

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on technologies for the primary prevention of osteoporotic fractures in postmenopausal women by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the Appraisal Consultation Document:

- Mrs Jackie Parrington, Deputy Chief Executive, National Osteoporosis Society – Patient Expert nominated by the National Osteoporosis Society
- Mrs Anthea Franks – Patient Expert nominated by the National Osteoporosis Society
- Professor Juliet Compston, Professor Bone Medicine, Bone and Tooth Society – Clinical Expert nominated by the Royal College of Physicians
- Dr R.M. Francis, Reader in Medicine (Geriatrics) and Honorary Consultant Physician, British Geriatrics Society – Clinical Expert nominated by the British Geriatrics Society and the National Osteoporosis Society
- Dr Caje Moniz, Consultant and Clinical Director, King's Healthcare NHS Trust – Clinical Expert nominated by the National Osteoporosis Society
- Dr Peter Selby, Consultant Physician, Central Manchester and Manchester Children's University Hospitals NHS Trust – Clinical Expert nominated by the Society of Endocrinology and the National Osteoporosis Society

Appendix C. Detail on criteria for audit of the use of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fractures in postmenopausal women

Possible objectives for an audit

An audit could be carried out to ensure the appropriateness of the consideration of technologies, specifically bisphosphonates (alendronate, etidronate, risedronate) raloxifene and strontium ranelate, for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

Possible patients to be included in the audit

An audit could include all women aged 70 and over who attend a GP consultation for any purpose and who have not previously sustained a clinically apparent osteoporotic fracture. Women who have corticosteroid-induced osteoporosis should be excluded from this audit.

The audit assumes that postmenopausal women included in the audit have normal levels of calcium and/or vitamin D. If they do not, other audit measures related to calcium and/or vitamin D supplements should be added.

Measures that could be used as a basis for an audit

The measures that could be used in an audit on the appropriate consideration of prescribing bisphosphonates, raloxifene and strontium ranelate are as follows.

Criterion	**Standard**	**Exception**	**Definition of terms**
1. For a woman aged 70–74 years, bisphosphonates are considered as treatment options if she meets any of the following: a. She has one clinical risk factor and a T-score of –3.5 or below **or** b. She has two clinical risk factors and a T-score of –3 or below **or** c. She has three or more clinical risk factors and a T-score of –2.5 or below	100% of woman aged 70–74 years who meet any of 1 a–c	A. The woman has a contraindication to bisphosphonates B. The woman is unable to comply with the special instructions for administration of bisphosphonates C. The woman is intolerant of bisphosphonates D. The woman declines treatment after discussion with her clinician (see 3 below)	Bisphosphonates are alendronate, etidronate or risedronate. Clinical risk factors include the following: parental history of hip fracture; low body mass index (in the absence of knowledge about bone mineral density and defined as less than 19 kg/m^2); and medical conditions independently associated with bone loss, such as rheumatoid arthritis. T-score relates to measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) scanning at the femoral neck. See Summaries of Product Characteristics for a description of contraindications for bisphosphonates and special instructions for administration of bisphosphonates. 'Intolerance of bisphosphonates' is defined as oesophageal ulceration, erosion or stricture, any of which is sufficiently severe to warrant discontinuation of treatment with a bisphosphonate.

			Clinicians will need to agree locally on how consideration of bisphosphonates as treatment options is documented for audit purposes.
2. For a woman aged 75 years or older, bisphosphonates are considered as treatment options if she meets any of the following: a. She has one clinical risk factor and a T-score of –3 or below **or** b. She has two clinical risk factors and a T-score of –2.5 or below **or** c. She has three or more clinical risk	100% of women aged 75 years and over who meet any of 2a–c	A. The woman has a contraindication to bisphosphonates B. The woman is unable to comply with the special instructions for administration of bisphosphonates C. The woman is intolerant of bisphosphonates D. The woman declines treatment after discussion with her clinician (see 3 below)	See above for relevant definitions. For 2c, the woman does not need to have a DXA scan.
3. The woman participates with her clinician in choosing a bisphosphonate	100% of women who meet 1a–c or 2a–c and who do not meet Exceptions A–C in 1 or 2 above	A. The woman declines participating in discussion about the options with her clinician	Clinicians will need to agree locally on how discussion between the woman and the clinician is documented for audit purposes. The discussion should reflect consideration of the drugs' overall proven effectiveness profiles, tolerability and adverse effects.
4. Strontium ranelate is considered as a treatment option if a woman is 70-74 years of age and meets 1a–c above or is 75 or more years of age and meets 2a–c above and any of the following: a. She has a contraindication to	100% of women who meet any of 1a–c above or any of 2a–c above and any of 4a–c	A. The woman has a contraindication to strontium ranelate	See above for relevant definitions. See the Summary of Product Characteristics for contraindications to strontium ranelate.

bisphosphonates **or** b. She is unable to comply with the special instructions for administration of bisphosphonates **or** c. She is intolerant of bisphosphonates			
5. Raloxifene is prescribed as a treatment option for the primary prevention of osteoporotic fractures	0% of women considered for primary prevention of osteoporotic fractures	None	Clinicians will need to agree locally on how women considered for primary prevention of osteoporotic fractures are identified for audit purposes.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{criterion} \textit{ plus } \text{number of patients who meet any } \textbf{exception} \text{ listed}}{\text{Number of patients to whom the } \textbf{measure} \text{ applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.