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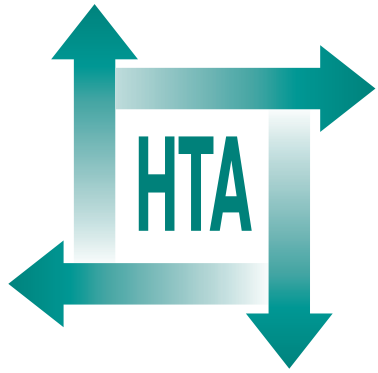

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/28/01. The protocol was agreed in November 2004. The assessment report began editorial review in November 2005 and was accepted for publication in June 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women

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Objectives: To estimate the clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women, at different levels of absolute fracture risk. This considers secondary prevention in women who have sustained a previous fracture and primary prevention in those women without a previous fracture, as women with osteoporosis are asymptomatic until a fracture is sustained.

Data sources: Major electronic bibliographic databases were searched in September 2004 and updated in March 2005.

Review methods: A systematic review was carried out to determine clinical effectiveness using the major electronic bibliographic databases and handsearching reference lists of relevant articles and sponsor submissions. Data from selected studies were assessed and included in the meta-analyses, if appropriate. The model used to calculate cost-effectiveness ratios was an updated version of Sheffield Health Economic Model for Osteoporosis that was populated with absolute risk of fractures using an algorithm being developed for the World Health Organization and supplied in confidence to the authors. The model calculated the number of fractures that occur and provided as output data the costs associated with osteoporotic fractures, and the quality adjusted life-years (QALYs) accrued by a cohort of 100 osteoporotic women, with each fracture being detrimental to health and incurring a cost. When the costs of the intervention were included, the incremental cost compared with no treatment was calculated and divided by the gain in QALYs to calculate cost-effectiveness measures. Treatment with strontium ranelate was calculated against a no-treatment option to evaluate whether it could be given cost-effectively. An incremental analysis against alendronate was also conducted to estimate the cost-effectiveness of strontium ranelate relative to a current standard treatment. The cost-effectiveness of strategies for identifying and treating women without a prior fracture used the risk of fracture as an input to the cost-effectiveness model.

Results: Three trials were identified. Pooled data from two studies indicate that strontium ranelate therapy is associated with a reduction in the risk of vertebral fracture [relative risk (RR) compared with placebo 0.60, 95% confidence interval (CI) 0.53 to 0.69, $p < 0.001$] and non-vertebral fracture (RR 0.84, 95% CI 0.73 to 0.97, $p = 0.01$). In general, strontium ranelate therapy did not seem to be associated with an increased risk of adverse events. However, the risk of one rare but serious adverse event, venous thromboembolism (including pulmonary embolism), was found to be significantly higher in patients receiving strontium ranelate compared with placebo (RR 1.42, 95% CI 1.02 to 1.98, $p = 0.036$). Some nervous system disorders, including mental impairment, disturbed consciousness, memory loss and seizures, were also more common in patients randomised to strontium ranelate. Strontium ranelate provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the absolute risk of fracture. From the algorithm used, it is seen that strontium ranelate can be used cost-effectively in women at relatively high risk of osteoporotic fracture. However, the results of the probabilistic sensitivity analysis, using efficacy data from randomised controlled trials, suggest that it is not as cost-effective as alendronate, a comparator intervention from the bisphosphonate class. The use of strontium ranelate in women without a prior fracture will be dependent on identification algorithms being produced in conjunction with the National Institute for Health and Clinical Excellence Osteoporosis Guidelines Development Group.

Conclusions: Strontium ranelate was shown to be clinically effective in the prevention of osteoporotic fractures. Scenarios have been found where strontium ranelate can be used cost-effectively, however given the probabilistic sensitivity analyses conducted, this intervention appears to be less cost-effective than the bisphosphonate alendronate. The evidence base for the efficacy of fracture prevention for strontium ranelate needs to be strengthened, particularly for hip fractures, where there is currently a non-significant reduction. If it were believed that the efficacy of strontium ranelate is dependent on either age or absolute risk, this would need to be proven. The evidence base on the *T*-score by age of the general female population needs to be strengthened, particularly in women over the age of 80 years. The prevalence of risk factors associated with fracture rates, over and above that provided by bone mineral density, also needs to be significantly strengthened to ensure that the estimated number of women that could be cost-effectively treated is accurate.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Body mass index A person's weight in kilograms divided by height in metres squared. Units are expressed in kg m^{-2}.

Osteopenia Bone mineral density (BMD) between 1 and 2.5 SD below the young adult mean (*T*-score –1 to –2.5)

Osteoporosis BMD 2.5 SD or more below the young adult mean (*T*-score < –2.5)

Reference nutrient intake (RNI) The level of intake of a nutrient that is sufficient to cover the needs of nearly all the population group for which it is recommended; as it is set 2 SD above the estimated average requirement for that nutrient, it is considerably higher than most people need, and individuals consuming the RNI are most unlikely to be deficient in that nutrient.

Sensitivity The proportion of patients with a specified condition who are diagnosed as such by a test.

Severe osteoporosis BMD 2.5 SD or more below the young adult mean (*T*-score < –2.5) plus at least one documented fracture.

Specificity The proportion of patients without a specified condition who are diagnosed as such by a test.

T-score The number of standard deviations from the average BMD of healthy young women.

Z-score The number of standard deviations that a woman is from the average BMD of women of the same age.

List of abbreviations

AE	adverse event
BMD	bone mineral density
BMI	body mass index
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRF	clinical risk factor
DXA	dual-energy X-ray absorptiometry
FIRST	Fracture International Run-in for Strontium ranelate Trial
HRT	hormone replacement therapy
MAICER	maximum acceptable incremental cost-effectiveness ratio
NA	not applicable
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
NICEGDG	NICE Osteoporosis Guidelines Development Group
NNT	number needed to treat
NR	not reported
QALY	quality-adjusted life-year
RCP	Royal College of Physicians
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SHEMO	Sheffield Health Economic Model for Osteoporosis
SOTI	Spinal Osteoporosis Therapeutic Intervention study
SR	strontium ranelate
STRATOS	Strontium Administration for Treatment of Osteoporosis Study
TROPOS	Treatment of Peripheral Osteoporosis Study
VTE	venous thromboembolism

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Note

In an attempt to produce a readable report within the tight time deadlines, several sentences regarding background information, such as the definition of osteoporosis, and the model structure have been transferred from other reports on which the lead author was an author.

One report is "Glucocorticosteroid-induced osteoporosis: a systematic review and cost–utility analysis", by Kanis JA, Brazier J, Stevenson M, McCloskey EV, Davis S and Lloyd Jones M. *Health Technol Assess* 2006;**10**(7).

Another report is "A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis", by Stevenson M, Lloyd Jones M, de Nigris E, Brewer N, Davis S and Oakley J. *Health Technol Assess* 2005;**9**(22).

Information that was submitted to the National Institute for Health and Clinical Excellence in confidence has been removed from this version of the report.

Executive summary

Objectives

The review aims to estimate the clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women, at different levels of absolute fracture risk. This considers secondary prevention in women who have sustained a previous fracture and primary prevention in those women without a previous fracture, as women with osteoporosis are asymptomatic until a fracture is sustained.

Epidemiology and background

Osteoporosis is a common disease in the elderly, with an estimated 1.1 million female sufferers in England and Wales. It is defined as possessing a *T*-score of –2.5 standard deviations or lower. The main consequence of osteoporosis is an increased incidence of fractures, which increase as a woman ages. These result not only in morbidity for the patient (with a risk of mortality following fractures at some sites), but also in the consumption of scarce NHS resources. A recent estimate of the projected cost in the UK by 2010 of osteoporotic fractures in females put this figure at £2.1 billion.

Methods

A systematic review was carried out to determine clinical effectiveness. Major electronic bibliographic databases were searched in September 2004 and updated in March 2005. In addition, the reference lists of relevant articles and sponsor submissions were handsearched. Data from selected studies were assessed and included in the meta-analyses, if appropriate.

The model used to calculate cost-effectiveness ratios was an updated version of Sheffield Health Economic Model for Osteoporosis. The model calculated the number of fractures that occur and provided as output data the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs) accrued by a cohort of 100 osteoporotic women, with each fracture being detrimental to health and incurring a cost. When the costs of the intervention were included, the incremental cost compared with no treatment was calculated and divided by the gain in QALYs to calculate cost-effectiveness measures. Treatment with strontium ranelate was calculated against a no-treatment option to evaluate whether it could be given cost-effectively. An incremental analysis against alendronate was also conducted to estimate the cost-effectiveness of strontium ranelate relative to a current standard treatment. The cost-effectiveness of strategies for identifying and treating women without a prior fracture used the risk of fracture as an input to the cost-effectiveness model.

Results

Number and quality of studies, and direction of evidence

Three trials (the STRATOS, SOTI and TROPOS studies) were identified which compared strontium ranelate with placebo in postmenopausal women with osteoporosis and reported fracture outcomes. Participants also received calcium and vitamin D supplements, with the exception of participants in SOTI and TROPOS, whose daily dietary calcium intake exceeded 1000 mg; these women only received vitamin D supplements.

Pooled data from SOTI and TROPOS indicate that strontium ranelate therapy is associated with a significant reduction in the risk of vertebral fracture [relative risk (RR) compared with placebo 0.60, 95% confidence intervals (CI) 0.53 to 0.69, $p < 0.001$] and non-vertebral fracture (RR 0.84, 95% CI 0.73 to 0.97, $p = 0.01$). The studies were not powered to identify a statistically significant difference in the incidence of fracture at any specific peripheral fracture site.

Safety

In general, strontium ranelate therapy did not seem to be associated with an increased risk of adverse events. Most adverse events were mild and transient. However, the risk of one rare but serious adverse event, venous thromboembolism (including pulmonary embolism), was found to be significantly higher in patients receiving strontium ranelate compared with placebo (RR 1.42, 95% CI 1.02 to 1.98, $p = 0.036$). Some nervous system

disorders, including mental impairment, disturbed consciousness, memory loss and seizures, were also more common in patients randomised to strontium ranelate. Both of these issues are being addressed in the ongoing extension of the SOTI and TROPOS studies and by postmarketing surveillance.

Summary of benefits

Benefits were measured in terms of QALYs. Strontium ranelate provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the absolute risk of fracture.

Cost-effectiveness of identification and treatment strategies

The report used a modified version of a soon-to-be published algorithm that estimates absolute fracture risk from patient characteristics. Risk factors used within the algorithm were age, gender, bone mineral density (BMD), prior fracture history, parental history of hip fracture, smoking status, alcohol consumption, rheumatoid arthritis and corticosteroid use. The results show that strontium ranelate can be used cost-effectively in women at relatively high risk of osteoporotic fracture. However, the results of the probabilistic sensitivity analysis, using efficacy data from randomised controlled trials, suggest that it is not as cost-effective as alendronate, a comparator intervention from the bisphosphonate class.

The use of strontium ranelate in women without a prior fracture will be dependent on any identification algorithms that are implemented. Such algorithms are being produced in conjunction with the National Institute for Health and Clinical Excellence Osteoporosis Guidelines Development Group (NICEGDG), and a preliminary version is reproduced in this report. It is likely that any identification strategy aimed at reducing the incidence of osteoporotic fractures will use bisphosphonates as the first line therapy. Given this, the use of strontium ranelate in such patients is likely to be low.

Costs

Since, on the basis of the probabilistic sensitivity analyses, strontium ranelate is not expected to be the first line therapy, the introduction of this intervention is unlikely to change significantly the overall costs associated with current osteoporosis treatments such as bisphosphonates. The acquisition cost of strontium ranelate is greater than that for bisphosphonates, and where the intervention is prescribed the cost of purchasing drugs will increase.

Conclusions

Strontium ranelate was shown to be clinically effective in the prevention of osteoporotic fractures. Scenarios have been found where strontium ranelate can be used cost-effectively; however, given the probabilistic sensitivity analyses conducted, this intervention appears to be less cost-effective than the bisphosphonate alendronate.

Work has been presented on the cost-effectiveness of identifying asymptomatic women who could be treated cost-effectively. This work is part of an ongoing project undertaken with the NICEGDG and will be further reviewed and be used as part of the guidelines issued for the management of women at high risk of osteoporotic fracture.

Recommendations for research

The evidence base for the efficacy of fracture prevention for strontium ranelate needs to be strengthened, particularly for hip fractures, where there is currently a non-significant reduction.

If it were believed that the efficacy of strontium ranelate is dependent on either age or absolute risk, this would need to be proven.

The evidence base on the *T*-score by age of the general female population needs to be strengthened, particularly in women over the age of 80 years. The prevalence of risk factors associated with fracture rates, over and above that provided by BMD, also needs to be significantly strengthened to ensure that the estimated number of women that could be cost-effectively treated is accurate.

Until head-to-head comparisons of strontium ranelate and bisphosphonates are undertaken, decision-makers will have to make choices based on indirect evidence; for example, comparing the results for bisphosphonates plus calcium and vitamin D versus calcium and vitamin D, with those for strontium ranelate plus calcium and vitamin D versus calcium and vitamin D. Given the large number of patients that would be needed to show statistical difference in efficacy between patients these trials are unlikely to be conducted; however, high-quality observational databases may provide further insight into relative efficacies.

Chapter 1

The aim of the review

The review aims to estimate the clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women, at different levels of absolute fracture risk. This is divided into secondary prevention in women who have sustained a previous fracture and primary prevention in those women without a previous fracture. For the latter group the costs of identifying these women must also be considered as women with osteoporosis are asymptomatic until a fracture is sustained. Once women have been identified for treatment, the cost-effectiveness at different levels of absolute fracture risk can be calculated. This analysis therefore has two components:

- establishing the cost-effectiveness of strontium ranelate at different levels of absolute fracture risk in postmenopausal women with osteoporosis, who have and have not had a fracture
- estimating how alternative approaches for the identification of osteoporotic women who have not had a fracture impact on the cost-effectiveness of strontium ranelate.

Chapter 2
Background

The internationally agreed definition of osteoporosis is: a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone and susceptibility to fracture.[1]

The clinical significance of osteoporosis lies in the fractures that arise; without a fracture a person suffering from osteoporosis will not suffer morbidity. The most common fractures are vertebral compression fractures, and fractures of the distal radius and the proximal femur (hip fracture). In addition, when the skeleton is osteoporotic, fractures occur more commonly at many other sites, including the pelvis, proximal humerus, distal femur and ribs.

The incidence of fracture is strongly related to age, with a fairly linear increase as a person ages. The exception is for hip fracture, where the rise appears to be more exponential.[2]

Fractures of the spine often go undetected; it is estimated that only one-third of fractures seen in trials, where morphometric criteria are used to establish the presence of a fracture, come to clinical attention.[3] This report focuses on clinically apparent vertebral fractures, with a sensitivity analysis conducted on the impact of including morphometric fractures.

Osteoporotic fractures occurring at the spine and the proximal humerus are associated with significant morbidity and some mortality, but the most serious consequences arise in individuals with hip fracture, which is associated with a large increase in mortality in the year following the hip fracture.[4] However, some of the associated mortality is confounded owing to underlying co-morbidities.

It has been estimated that the cost of treating osteoporotic fractures in postmenopausal women was approximately £1.5–1.8 billion in the UK per annum in 2000.[5,6] These costs have been estimated to increase to £2.1 billion by 2010.[6] The key components of the costs associated with this estimate were hip fractures and the subsequent nursing home care that is required for a proportion of these women.

This report is focused on postmenopausal women owing to the deterioration of bone quality following the menopause, which is strongly correlated with a rise in fracture incidence.

Description of osteoporosis, osteopenia and severe osteoporosis

The definition of osteoporosis has been developed since bone mineral can be measured with precision and accuracy. However, it is acknowledged that other factors such as abnormalities within the skeleton and risk of falls are also important in determining the risks of fracture. Nevertheless, bone mineral density (BMD) alone forms the basis for the diagnosis of osteoporosis.

The units used in this report for assessing the BMD of a woman will be *T*-scores and *Z*-scores. A *T*-score is defined as the number of standard deviations (SDs) from the average BMD of healthy young women. A *Z*-score is defined as the number of SDs that a woman is from the average BMD of women of the same age.

Two thresholds of BMD have been proposed for Caucasian women based on the *T*-score.[7,8] The first, osteoporosis, denotes a value for BMD that is two and a half standard deviations or more below the young adult mean value (*T*-score < -2.5 SD). The second, osteopenia, denotes a *T*-score that lies between –1 and –2.5 SD.

The class of osteoporosis is further divided into patients with severe osteoporosis, which is defined as a *T*-score of or below –2.5 SD plus at least one documented fracture. In this report the term severe osteoporosis will be used to define women who have a *T*-score equal to or less than –2.5 SD with a clinically apparent prior fracture. The term osteoporosis will be used to define women with a *T*-score equal to or less than –2.5 SD, without a clinically apparent prior fracture.

Since the introduction of working definitions of osteoporosis, much attention has focused on their

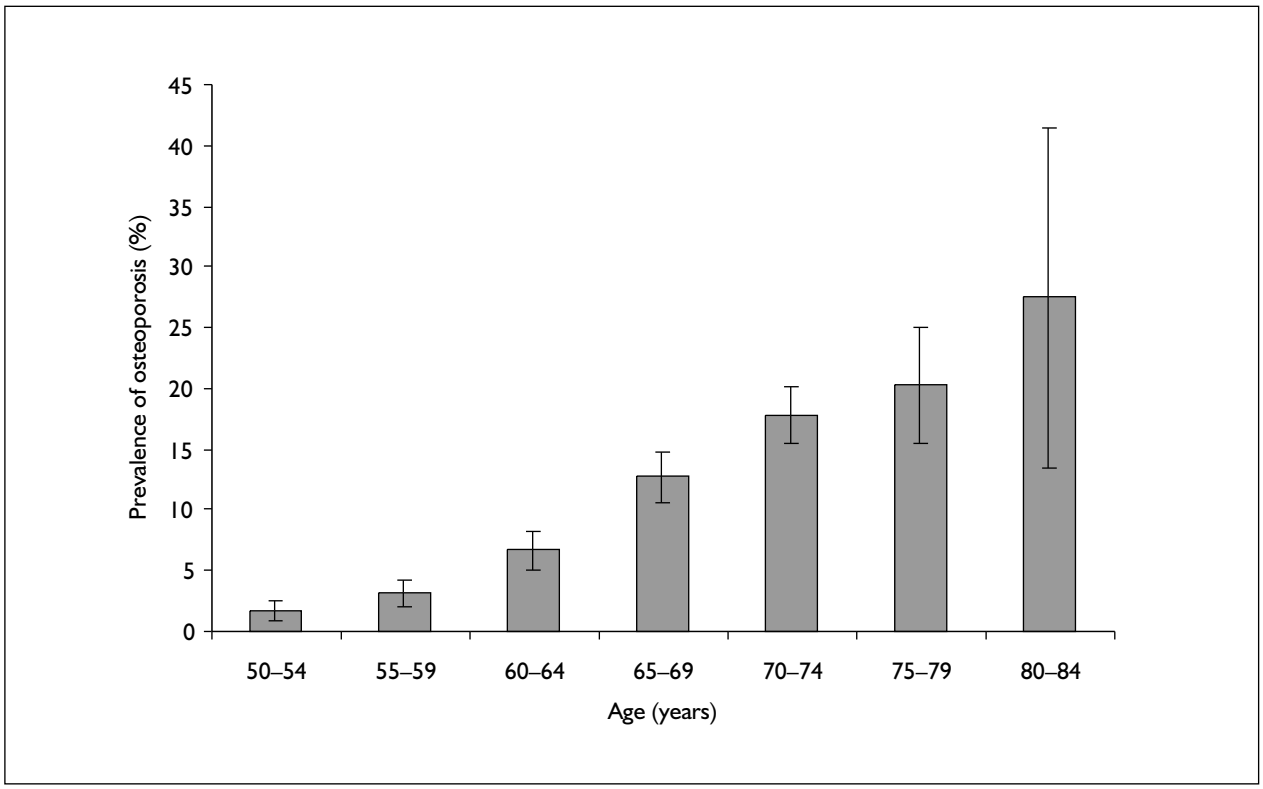

FIGURE 1 *Estimated prevalence of female osteoporosis by age band*

application to epidemiology, clinical trials and patient care. Several problems have emerged, however, largely owing to the development of new measurement techniques applied to many different sites. It is now clear that the same *T*-score derived from different sites and techniques yields different information on fracture risk, even when adjustments are made for age. Thus, the *T*-score cannot be used interchangeably with different techniques and at different sites.

The site chosen for use in this review is measurement at the femoral neck, since this is the reference site for diagnosis.[9] The statistical relationships that have been established between increased fracture risk at the hip and *Z*-score (the *T*-score of the woman minus the average *T*-score for that age and gender) have been undertaken at this site.[10,11]

Epidemiological data

Prevalence of female osteoporosis by age

Raw data were taken from a UK population-based study by Holt and colleagues[12] and used to calculate the relationship between *T*-score and age. The prevalence of osteoporosis within the UK has also been estimated from these data. This data set contained observations on 5713 women aged between 50 and 85 years and used the National Health and Nutrition Examination Survey III (NHANES III) reference data for women aged 20–29 years.

The percentage of women with a *T*-score of –2.5 SD or below, as measured at the femoral neck, was recorded. These data are shown in *Figure 1* and exhibit a marked increase with age. The database taken from the Holt study[12] had relatively few women (40) aged between 80 and 84 years. The confidence interval around the prevalence at this age is wide and is shown in *Figure 1*. Assuming, however, that the midpoint values were correct, multiplying these prevalence rates by the respective population of England and Wales[13] results in an estimate of 1.14 million women suffering with osteoporosis.

The average *T*-score at the femoral neck in each age band was calculated from the UK population data in the Holt study.[12] A linear relationship was assumed and *T*-score was assumed to be 2.0251 – (0.0512 × Age, in years). The assumed average *T*-score at the midpoint of the age band is given in *Table 1*. Above 85 years of age, the *T*-score for the average woman almost reaches the threshold for osteoporosis.

TABLE 1 *Average* T*-scores for women by age band*

Age (years)	Average UK *T*-score, Holt[12a]	*Z*-score at threshold of osteoporosis (*T*-score of –2.5 SD)[a]
50–54	–0.66	–1.84
55–59	–0.92	–1.58
60–64	–1.17	–1.33
65–69	–1.43	–1.07
70–74	–1.69	–0.81
75–79	–1.94	–0.56
80–84	–2.20	–0.3
85–89	–2.45	–0.05

[a] Compared with the NHANES III reference data for women aged 20–29 years.

Prevalence of clinical risk factors for osteoporotic fractures

Data on the prevalence of clinical risk factors (CRFs) for osteoporotic fracture are estimated from summarised data taken from the WHO study, which considered cohorts from a number of countries, including England. These data are assumed to be applicable to the UK. The CRFs included are age, gender, BMD, body mass index (BMI), prior fracture, parental fracture, smoking, corticosteroid use, rheumatoid arthritis and alcohol consumption (>2 units per day). The data provided by the WHO study were broken into age bands of 5 years and *T*-score bands of 0.5 SD. The data were aggregated across the *T*-score bands. The WHO study was a multicentre study and not all risk factors were recorded at every centre, meaning that the number of patients with data available varies for each risk factor combination. It was assumed that there was no correlation between whether patients had a particular risk factor and whether the risk factor was recorded by the centre. This was used to normalise the prevalence across all possible CRF combinations.

Table 2 gives the prevalence of CRFs provided by the WHO data for women by age band. The cohort size is indicated in brackets for single risk factors. The prevalence given is for all women regardless of their BMD or BMI.

TABLE 2 *Prevalence of CRFs for osteoporotic fracture in women [academic in confidence]*
[Confidential information removed]

Incidence of osteoporotic fractures by age

In previous NICE assessments of interventions for the prevention of osteoporotic fractures in postmenopausal women, fractures of the hip, spine, wrist and proximal humerus were considered to be related to osteoporosis. These four fracture types were assumed to be the most prevalent and were the only sites included in recent submissions to the National Institute for Health and Clinical Excellence (NICE) by manufacturers of the drugs.[14–19] To present as accurate results as possible, the NICE Osteoporosis Guidelines Development Group (NICEGDG) advised that further fracture sites, which are also considered to be related to osteoporosis,[20] should be included in the modelling. These are fractures of the pelvis, humeral shaft, tibia, fibula, scapula, ribs, sternum and other femoral fractures.

Data on the estimated incidence of hip fractures and the combined incidence of vertebral, wrist and proximal humerus fractures for an individual woman are provided by the WHO algorithm. The WHO study is the first to provide UK-specific fracture risk for an individual based on a large number of CRFs. The WHO study provides separate algorithms for calculating an individual's hip fracture risk and combined vertebral, wrist and proximal humerus fracture risk, resulting in four separate algorithms. Separate algorithms are provided for when BMD is known or unknown and whether the patient is male or female.

A traditional stepwise approach was used to remove non-significant coefficients, with the slight modification that coefficients were included in all four algorithms if the variables were significant, at a 10% level, in any one of the algorithms. This resulted in risk factors being included in some algorithms when their *p*-values were non-significant. For example, current smoking was significant for hip fracture but not for other fracture types, and a coefficient of less than one, implying a protective effect, has been used. This is non-significant and traditionally would be set to one. Despite this, the WHO risk algorithm appears to be the best risk assessment tool currently available.

TABLE 3 *Risk coefficients derived from the WHO cohort analysis*

	Without BMD		With BMD	
	OWH fracture	**Hip fracture**	**OWH fracture**	**Hip fracture**
Gender (1/2)	**[Confidential information removed]**			
Min. (BMI, 25)	**[Confidential information removed]**			
Max. (BMI-25,0)	**[Confidential information removed]**			
Previous fracture (0/1)	**[Confidential information removed]**			
Mother/father (0/1)	**[Confidential information removed]**			
Current smoke (0/1)	**[Confidential information removed]**			
Corticosteroids (0/1)	**[Confidential information removed]**			
Rheumatoid arthritis (0/1)	**[Confidential information removed]**			
Alcohol (0/1)	**[Confidential information removed]**			
Gender × Current age	**[Confidential information removed]**			
Previous fracture x min. (current age, 80)	**[Confidential information removed]**			
Mother/father × max. (0, min (age-65, 10))	**[Confidential information removed]**			
Min. (Z-score, 0)	**[Confidential information removed]**			
Max. (Z-score, 0)	**[Confidential information removed]**			
Z-Score × Current age	**[Confidential information removed]**			

OWH, vertebral, wrist and proximal humerus.

The annual risks of fracture was calculated from the algorithm used by the assessment team as follows. More detail is given in Appendix 1.

For each patient the following variables were input: gender (2 for women in these analyses), current age (in years), BMI (assumed to be 26 for all women in the analyses), and whether any of the following variables were present: has the patient sustained a previous fracture, did either parent suffer a previous hip fracture, does the patient smoke, does the patient consume an average of more than 2 units of alcohol per day, has the patient ever used corticosteroids and does the patient suffer from rheumatoid arthritis (0 = no, 1 = yes)?

These values were multiplied by the appropriate coefficients contained in *Table 3*, to give the risk of hip fracture and to give vertebral, proximal humerus and wrist fracture depending on whether BMD was known or not.

Once all products of input values and coefficients had been calculated these were summed and the resulting value was exponentiated.

The reviewers were also provided with age normalising factors and UK normalising factors (*Table 4*). The analysis assumed a normalising factor that is an average of the 5-year band (i.e. for a woman aged 68, the mean from 65–70 would be used). These factors were chosen so that the data are calibrated against the data presented by Singer and colleagues.[21]

Thus, for a woman aged 75, with a BMI of 26, who smoked, and with unknown BMD, the basic risk of a vertebral, wrist or proximal humerus fracture would be, ignoring zeros, **[confidential information removed]**.

If her *Z*-score was –1, the risk would become: **[confidential information removed]**.

From communication with Professor Kanis, all covariates are significant in at least one model, but not all the variables included in the models are significant; however, these have been retained for symmetry in the overall model. Further, according to Professor Kanis, the effect of these insignificant coefficients is negligible.

These algorithms have been supplied to ScHARR confidentially, and have been described as final. Some details on the methodology and calibration of the data to the UK population have been provided; however, the full write-up of the methodology (including normalising factors) and of the final algorithm had not been published as of October 2006.

The WHO algorithm gives the total fracture risk for vertebral, wrist and proximal humerus fractures, but does not break this into constituent parts. As the cost and utilities of fractures are different, the combined data need to be separated into a fracture risk for each of these individual sites. The proportions of this total, using the numbers of proximal humerus and wrist fractures

TABLE 4 *Normalising factors for the UK population and for normalising the risk*

Age (years)	Factor reflecting the risk in UK		Factor for normalising the risk			
	For OWH fracture	For hip fracture	For OWH without BMD	For OWH with BMD	For hip without BMD	For hip with BMD
[Confidential information removed]						

TABLE 5 *Proportion of total vertebral, wrist and proximal humerus fractures by fracture site*

Age (years)	Proportion of total vertebral, wrist and proximal humerus fractures that are vertebral fractures (%)	Proportion of total vertebral, wrist and proximal humerus fractures that are wrist fractures (%)	Proportion of total vertebral, wrist and proximal humerus fractures that are proximal humerus fractures (%)
50–54	20	65	15
55–59	26	60	14
60–64	22	61	18
65–69	29	58	13
70–74	36	47	17
75–79	38	43	19
≥ 80	39	41	20

reported by Singer and colleagues,[21] and assuming that the ratio of hip to vertebral fractures seen in Malmö, Sweden,[22] was applicable to the UK, are shown in *Table 5*. These proportions are used to divide the total number of vertebral, wrist and proximal humerus fractures. It is noted that in applying these fractures the incidence of vertebral, wrist and proximal humerus fractures is greater than that previously used in economic evaluations.[23] This will be favourable to the intervention.

Inclusion of fractures other than hip, vertebral, wrist and proximal humerus

The fractures that were considered osteoporotic were taken from Kanis and colleagues,[24] and were pelvis, other femoral fractures, humeral shaft, rib, scapula, clavicle, sternum, tibia and fibula.

In order to use the metamodel developed for the original assessment report,[23,25,26] which only considered hip, vertebral, wrist and proximal humerus fractures, the additional fracture types were approximated to those of the existing model. As described in the section 'Cost-effectiveness of interventions at different levels of absolute risk' (p. 31), the disutilities associated with pelvis and other femoral fractures resulted in their being grouped with hip fracture. Tibia, fibula and humeral shaft were grouped with proximal humerus, while rib, scapula, clavicle and sternum were grouped with wrist fractures.

Incidence of fractures other than hip, vertebral, wrist and proximal humerus

Data on the incidence of hip, wrist, proximal humerus, humeral shaft and other femoral fractures in women were taken from a large-scale Scottish study by Singer and colleagues.[21]

An exponential relationship was assumed between hip fracture and age,[2] and the curve that best fitted the data was calculated. This mainly had the effect of decreasing the risk at 70–74 and 80–84 years of age (*Figure 2*). This differs from the approach taken in the previous assessment report,[23,27,28] where the hip fracture rate was taken directly from the data.

In a similar manner, an exponential relationship was assumed between the incidence of other femoral fractures seen in Singer[21] and age. This was used in preference to the observed incidence by age band as the incidence appeared to be affected by the small number of fractures within each age band.

Data on the incidence of pelvis fractures were derived from a Welsh study.[29] However, this study includes fractures in children aged 0–14 years, and often does not give data broken down by age band. It was assumed that the ratio of pelvis fracture to hip fracture (12%) seen in Johansen[29] could be used to impute pelvis fracture incidence from the Singer data.[21] The ratio of pelvis fracture to hip fracture was assumed to apply at all age bands.

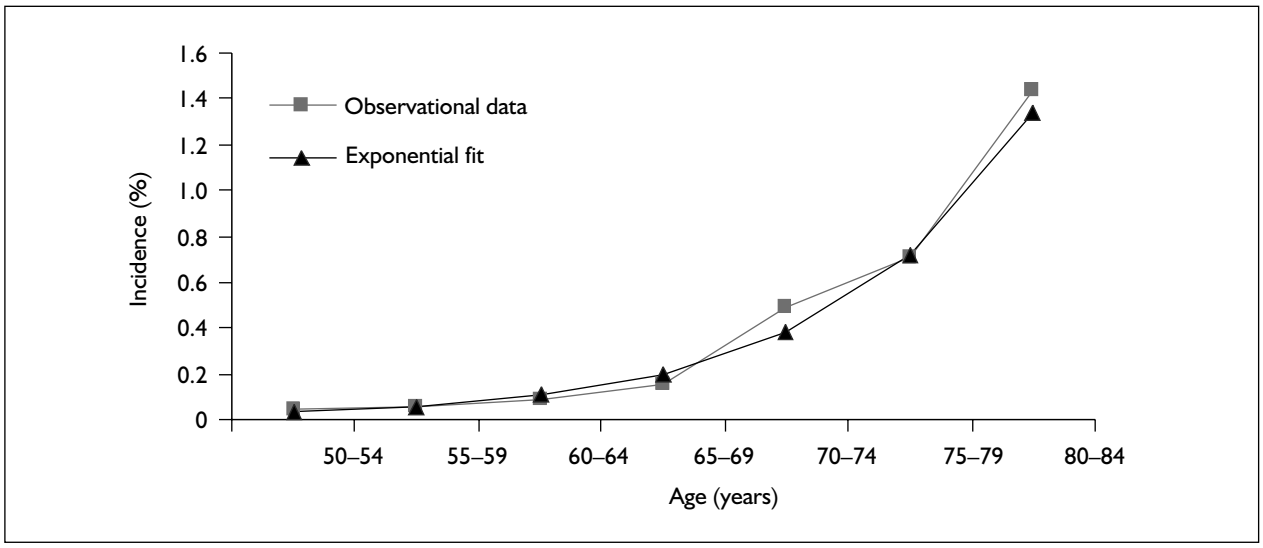

FIGURE 2 *Annual incidence of osteoporotic hip fracture in UK women*

TABLE 6 *Increase in incidence of hip, wrist and proximal humerus fractures to incorporate fractures at other sites*

Age (years)	Increase in hip fracture incidence to incorporate pelvis and other femoral fractures (%)	Increase in proximal humerus fracture incidence to incorporate tibia and fibula fractures (%)	Increase in wrist fracture incidence to incorporate rib, sternum, clavicle and scapula fractures (%)
50–54	27	112	79
55–59	25	69	38
60–64	23	37	21
65–69	21	44	34
70–74	20	41	47
75–79	19	35	76
≥ 80	18	21	104

To calculate the incidence of rib, sternum, scapula, clavicle, tibia and fibula fractures, it was assumed that the ratio seen between hip fracture and each fracture in Malmö, Sweden,[22] was applicable to the UK.

Given the grouping of additional fractures, the estimated increases in the incidence of the original fracture types are shown in *Table 6*.

Increased risk of fracture following a previous fracture

There is a breadth of published literature, meta-analysed by Klotzbeucher and colleagues,[30] that indicates that an initial fracture greatly increases the risk of subsequent fractures independently of BMD.

Prior fracture is one of the clinical risk factors assessed in the WHO algorithm, and therefore the fracture risk for individuals entering the model with a prior fracture will be taken from the WHO study. However, a woman can sustain more than one fracture within the time-horizon of the model, which may affect the individual's risk of fracture. As data from the WHO study were not available when the individual patient model, which forms the foundation for all of the cost-effectiveness analyses, was originally developed, the increase in fracture risk experienced by individuals who sustain a fracture during the time-frame of the model was taken from Klotzbeucher and colleagues[30] and is summarised in *Table 7*. The relative risk (RR) point estimates, for perimenopausal and postmenopausal women, were used in the model to increase the risk of subsequent fractures following an initial fracture.

It was assumed that the risk of secondary fractures at the proximal humerus is equivalent to the pooled non-spinal fractures category reported by Klotzbeucher and colleagues.[30] It was also

TABLE 7 *Relative risk of subsequent fracture following an initial fracture*

	Location of subsequent fractures			
Prior fracture site	**Hip**	**Vertebral**	**Wrist**	**Proximal humerus**
Hip	2.3	2.5	1.4	1.9
Vertebral	2.3	4.4	1.4	1.8
Wrist	1.9	1.7	3.3	2.4
Proximal humerus[a]	2.0	1.9	1.8	1.9

[a] Assumed equal to the value for all non-spinal fractures in Klotzbeucher *et al.*[30]

assumed that the proximal humerus had the predictive power equal to that of the 'other' category reported by Klotzbeucher and colleagues.[30] There have been no prior studies on the future effect that hip fractures have on wrist fractures. As a conservative estimate this risk was set at 1.4, equivalent to the lowest relative risk of all other fracture sites.

It is assumed that for women who have suffered fractures in two different sites only the greater risk adjustment will be applied in calculating the risks of subsequent fractures. For example, were a woman to have both a prior hip and wrist fracture, the relative risk adjustment for a subsequent vertebral fracture would be 2.5 (from the hip fracture), rather than 1.9 (from the wrist fracture). The relative risk adjustment for a subsequent wrist fracture would be 3.3 (from the wrist fracture), rather than 1.4 (from the hip fracture).

These values were not adjusted for BMD since most of the studies did not adjust for it. However, those studies that controlled for baseline BMD reported that adjusting for BMD reduced the magnitude of the association only slightly. Thus, any errors due to double-counting the effects of BMD are likely to be small. It is assumed that the same is true for all clinical risk factors; however, this assumption will be favourable to the intervention.

The change in methodology to incorporate the WHO algorithm necessitated that a bias be entered into the modelling. Previous work by this group specified the fracture status of women entering the model. For example, women entering the model with a prior vertebral fracture would start with an elevated fracture risk and this would not be increased further were another vertebral fracture to be sustained. In the WHO algorithm there is no differentiation between previous fracture types. All previous fractures are grouped as one and thus were a second fracture of the same type to be sustained, the risks would be further elevated. This will be favourable towards the interventions, particularly those with an impact on vertebral fractures.

Mortality following osteoporotic fractures

Mortality following a hip fracture

Excess mortality is well described after hip fracture. In the first year following hip fracture, relative mortality risk varies in women from 2.0 to greater than 10 depending on age.[31] However, case–control studies that adjust for prefracture morbidity indicate that a substantial component can be attributed to co-morbidity.[32,33]

The data used in the cost-effectiveness model are taken from unpublished data from the Second Anglian Audit of Hip Fracture,[34] which recorded deaths up to 90 days following hip fracture.

To account for mortality that was not related to the hip fracture, data were taken from Parker and Anand.[35] It was estimated that 33% of deaths 1 year after hip fracture were totally unrelated to the hip fracture, 42% were possibly related and 25% directly related. These figures were not available stratified by age, gender or residential status; but have been assumed to be constant for all population subsets.

It is likely that there was further mortality between 91 and 365 days that was not recorded by the audit.[34] An estimate of this can be inferred from the graph in Parker and Anand,[35] with the further mortality between 91 and 365 days estimated to be 40% of the mortality up to 91 days.

It was further assumed that attributing all of the deaths possibly due to hip fractures as directly to hip fracture and including only the data to 90 days would provide a reasonably accurate estimation of the true mortality rate. The mortality rates that were assumed attributable to

TABLE 8 *Percentage of hip fractures that result directly in mortality*

Residential status	Age band (years)	Percentage of hip fractures that result directly in mortality
Community	50–59	2
Community	60–69	6
Community	70–79	6
Community	80–89	11
Community	≥ 90	16
Nursing home	50–59	0
Nursing home	60–69	0
Nursing home	70–79	13
Nursing home	80–89	22
Nursing home	≥ 90	23

hip fracture are given in *Table 8*. No data were available for the age band 50–59 years and it was assumed that, as suggested by Swedish data,[31] this value was 33% that of the rate between 60 and 69 years.

Mortality following vertebral fracture

Several studies have shown an increase in mortality following vertebral fracture.[3,36–38] In one study, women with one or more vertebral fractures had a 1.23-fold greater age-adjusted mortality rate [95% confidence interval (CI) 1.10 to 1.37].[3] This study used morphometric rather than clinical definitions of vertebral fracture. In contrast, other studies that examine mortality after vertebral fracture using clinical criteria have shown more marked increases in mortality. In one study from Australia, vertebral fractures in women were associated with an age-standardised risk of 1.92 (95% CI 1.70 to 2.14),[36] and in another study the risk was more than eight-fold higher.[38] A study on clinical fractures from the UK compared mortality in women with osteoporosis (and no fracture) with mortality in women with osteoporosis and a previous vertebral fracture.[37] The hazard ratio was 4.4 (95% CI 1.85 to 10.6) and was used for the present model.

The pattern of mortality after clinical vertebral fracture is non-linear, suggesting, as is the case for hip fracture, that a fraction of deaths would not have occurred in the absence of a fracture. Using the patient register for hospital admissions in Sweden, 28% of all deaths associated with vertebral fracture were judged to be causally related.[39] This value for causality was used for all ages.

Death due to other fractures

This study assumed no increase in mortality from forearm fractures, consistent with published surveys.[3,38,40] For humeral fractures, the study conservatively assumed a two-fold increase in mortality and that 28% of deaths associated with humeral fractures are causally related.[39]

For pelvis and other femoral fractures, a mortality rate the same as that for hip was assumed. For tibia, fibula and humeral shaft fractures a mortality rate equal to that of proximal humerus fractures was assumed. For rib, sternum, scapula and clavicle fracture, no excess mortality was assumed.

Entry into a nursing home following an osteoporotic fracture

Entry into a nursing home following a hip fracture

Data were sought to estimate what percentage of women who suffer a hip fracture move from living in the community into nursing home accommodation. Global assumptions on this percentage, as used in some models,[41] were not used as this allows nursing home costs to be incorrectly allocated to women already residing in such care.

Unpublished data from the Second Anglian Audit of Hip Fracture[34] were used in the model. These data are shown in *Table 9*. It is assumed that women who enter a nursing home will remain there for the rest of their lives.

A recent estimate of the costs associated with osteoporotic fractures assumed that 10% of all women with a hip fracture would reside in a nursing home for the rest of their lives.[6] This figure looks plausible within the age range of 70 years and above, but appears to not be applicable within the range 50–69 years.

It is likely that the values assumed for entering a nursing home are underestimates as women who were initially discharged to the community, but

TABLE 9 *Percentage of women who move from the community to a nursing home following a hip fracture*

Age (years)	Percentage of women who move from the community to a nursing home following a hip fracture
50–59	0
60–69	4
70–79	4
80–89	12
≥ 90	17

TABLE 10 *Mortality due to other causes in the general female population and in women at the threshold for osteoporosis*

	Mortality rate due to other causes	
Age (years)	General population (%)	Population at the threshold for osteoporosis (%)
50–54	0.237	0.342
55–59	0.392	0.536
60–64	0.649	0.845
65–69	1.129	1.397
70–74	1.864	2.190
75–79	3.065	3.426
80–84	5.279	5.604
85–89	9.177	9.268

subsequently have to reside in a nursing home, are unlikely to be included in the audit.

Entry into a nursing home following fractures at sites other than the hip

It was assumed that other femoral fractures and pelvis fractures would have the same probability of entering a nursing home as hip fracture. It was assumed that fractures at sites other than the hip, pelvis and other femoral sites would not cause a woman to move from community living into nursing home accommodation.

Death due to other causes

These data were taken from interim life tables.[42] Several studies have shown an increased mortality associated with low BMD of similar magnitude derived from measurements at the radius or heel.[43,44] At the radius, the increase in relative risk was 1.22 per standard deviation decrease in BMD adjusted for age,[43] and this factor was used in the model, although it is unsure how much excess mortality may be related to co-morbidities. Ideally, a factor for BMD at the femoral neck would be used, but these data were not found when the model was constructed.

The data for the mortality rate of the general female population and for those women at the threshold of osteoporosis are shown in *Table 10*. The general population mortality rates were not adjusted to take into account the osteoporotic population, meaning that these death rates are likely to be slight overestimates. As these apply to all interventions it is unlikely that this will bias results between interventions, but will be slightly unfavourable to all interventions.

The Rotterdam Study[45] suggested that there may be no link between BMD value and excess mortality. This effect was examined in a previous assessment report and was shown to make little difference to the results, with a marginally unfavourable effect towards intervention.[23] As such, this review retained an increase in mortality associated with osteoporosis, in addition to that attributed to fracture, as this was fundamentally within the individual patient model.

Current service provision

Data taken from the company submission for Etidronate[17] state that approximately 275,000 women are being prescribed bisphosphonates, and that bisphosphonates represent 57% of all osteoporosis prescribing.

The total number of women receiving medication for osteoporosis is approximately 480,000. Assuming that all of these prescriptions are for women with osteoporosis, this would equate to 42% of the female osteoporotic population being prescribed medication.

Description of interventions

Identification of women and criteria for treatment

All postmenopausal women are potentially at risk of osteoporosis, and therefore of osteoporotic fracture. Therapy may be offered to those who already have osteoporosis, and to those who are perceived to be at risk of osteoporotic fracture as a result of the presence of CRFs.

Interventions

This report focuses on strontium ranelate which is licensed for use in postmenopausal women who have, or are at risk of, osteoporosis.

Summary of product characteristics

Strontium ranelate

Strontium is a bone-seeking element closely related to calcium. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption. Strontium ranelate (S12911) is composed of two atoms of stable strontium and one molecule of ranelic acid.[46]

Strontium ranelate was licensed in the UK in November 2004 at a dose of 2 g per day for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.[47] The UK licence for strontium ranelate is held by Servier Laboratories Ltd.

Strontium ranelate is marketed in the UK as Protelos, a sachet containing 2 g of strontium ranelate granules intended to be taken as a suspension in a glass of water. The product has a shelf-life of 3 years and does not require special storage conditions. However, the suspension should be drunk immediately after being prepared, even though it has been shown that it is stable for 24 hours after preparation.[48]

Protelos is available in packs of 28 sachets, at a cost of £25.60.[49]

Because the absorption of strontium ranelate is reduced by food, milk and products derived from milk, and by medicinal products containing calcium, it should be taken between meals. It is recommended that it is taken at bedtime, preferably at least 2 hours after eating.[48]

Patients taking strontium ranelate should receive calcium and vitamin D supplements if their dietary intake of these substances is inadequate. However, as noted above, administration of calcium and of strontium ranelate should be separated by at least 2 hours.[48]

Ideally, antacids should be taken at least 2 hours after strontium ranelate. However, if this is impractical, concomitant intake is acceptable.[48]

Administration of strontium ranelate should be suspended during treatment with oral tetracycline or quinolone antibiotics as it may reduce their effectiveness.[48]

Strontium ranelate is only intended for use in postmenopausal women. It should not be used in pregnancy or lactation.[48] It is not recommended in patients with severe renal impairment (creatinine clearance <30 ml per minute). No dosage reduction is required in patients with mild to moderate renal impairment (creatinine clearance 30–70 ml per minute), but periodic assessment of renal function is recommended in patients with chronic renal impairment.[48]

Strontium ranelate should be used with caution in patients at increased risk of venous thromboembolism (VTE).[48]

The use of Protelos is contraindicated in patients with hypersensitivity to strontium ranelate or to any of its excipients (aspartame, maltodextrin and mannitol). As aspartame is a source of phenylalanine, Protelos may be harmful to people with phenylketonuria.[48]

Personnel involved

Strontium ranelate can be prescribed by GPs as well as in specialist osteoporosis clinics.

Equipment required

No special equipment is required to deliver any of the interventions under review. However, special equipment is required to undertake the single- or dual-energy X-ray absorptiometry (DXA) necessary to determine BMD and thus ascertain the appropriateness of therapy with these or other antiosteoporotic agents.

Length of treatment

The length of treatment with strontium ranelate has not been specified. However, low BMD is not so much an illness that can be cured as a condition that, once developed, will continue, and may deteriorate further, without the use of some intervention. There is no evidence that any antiosteoporotic intervention, if given for a set period, will reduce the risk of fracture for the remainder of the patient's life, and the implication

therefore is that treatment is long term and open ended. However, few randomised controlled trials (RCTs) have been conducted with a duration of longer than 5 years, and to keep the results comparable with previous assessment reports, this study assumed a 5-year treatment period and a 10-year-time horizon.

Degree of diffusion

As strontium ranelate can be prescribed by GPs as well as by specialist osteoporosis clinics, the degree of diffusion is potentially substantial, were a major change in policy recommended.

Chapter 3

Clinical effectiveness

Methods for reviewing effectiveness

Search strategy

Initial clinical effectiveness searches were conducted in September 2004 and updated in March 2005. The utilities searches were performed in October and November 2002.

Sources searched

Fourteen electronic bibliographic databases were included in the clinical effectiveness searches; these are listed in Appendix 2. In addition, the reference lists of relevant articles and sponsor submissions were handsearched.

Search terms

The clinical effectiveness search strategy used terms specific to strontium ranelate. A copy of the MEDLINE search strategy is included in Appendix 3. Search strategies for the other databases are available on request.

Search restrictions

No language, date or study-type restrictions were applied to the clinical effectiveness searches.

Inclusion and exclusion criteria

Inclusion criteria

- Participants: postmenopausal women with osteoporosis, with or without previous fracture
- intervention: strontium ranelate
- comparator: the bisphosphonate alendronate
- outcome measures: survival, incident vertebral fracture, incident non-vertebral fracture, adverse effects, continuance, compliance, cost and health-related quality of life.
- study design: RCTs and economic evaluations.

Discussion of outcome measures

Vertebral fractures Vertebral fractures may be symptomatic or asymptomatic. Symptomatic, or clinical, vertebral fractures cause sufficient discomfort for the patient to bring them to the attention of a health professional, or cause a measurable loss of height. Their presence can be confirmed by radiography. However, radiographs can also identify asymptomatic fractures. Studies generally report vertebral fractures that are identified radiographically; such fractures, which are termed radiographic or morphometric, will include both symptomatic and asymptomatic fractures. However, some studies also report clinical fractures. Data from the Fracture Intervention Trial, a large study of alendronate which reported both clinical and radiographic fractures, suggest that, in postmenopausal osteoporosis, the relative risk of the two types of fracture is very similar.[50]

Various definitions of radiographic fractures have been developed. Definitions that require a 20% reduction in vertebral height are generally recognised as producing fewer false negatives and false positives than those that require only a 15% reduction. In this report, therefore, data based on a 20% fracture definition have been preferred, as the reduction in specificity associated with the use of a 15% definition would reduce the perceived efficacy of the intervention in question. The use of a semiquantitative method also results in greater specificity than the use of a 15% definition alone.

Adverse events RCTs generally cannot provide definitive information about drug toxicity. They may underestimate the incidence of drug-related adverse events, both because their populations may not be wholly typical of the target population (as they tend to exclude older participants and those with co-morbidities), and because they are not powered to identify rare, although potentially serious, adverse events; moreover, they do not always measure all potential side-effects.[51] For this reason, although studies reporting survival and adverse effects were only included in the systematic review if they also reported either fracture outcomes or health-related quality of life, the use of relevant evidence from other sources was not excluded in relation to adverse events.

Continuance and compliance The extent to which patients take a therapy in the intended manner will clearly affect the actual efficacy of that therapy. There are two aspects to this issue:

- continuance: the length of time for which the patient continues to take the medication (also referred to as adherence or persistence)

- compliance: the extent to which the medication is taken each day in accordance with the prescribed dosage regimen.

Thus, some patients may demonstrate good continuance, in that they persist with the medication for a long period, but poor compliance. Other patients may demonstrate perfect compliance for a relatively short period, but then completely cease taking the medication. Yet other patients may demonstrate partial compliance in the form of occasional missed doses or occasional extra doses: such partial compliance may be erratic, or may be consistent, but different from what the physician prescribed.[52] It has been suggested that partial compliance (defined as taking as taking 20–79% of the prescribed medication) is associated with inconsistent dosing, whereby the patient takes the drug in an erratic pattern of near-perfect compliance interspersed with multiple omission of single doses or of two or more consecutive days' doses.[53]

Compliance and continuance can be assessed by a number of methods, including:

- patient recall (e.g. self-reported questionnaire)
- pill counts
- self-recorded diaries
- electronic devices that record the date and time of opening of the drug containers
- direct measurements of therapeutic response, such as blood tests (these may be confounded by an unknown degree of variation in therapeutic response)
- repeat prescriptions.

However, none of these methods is ideal in terms of determining whether or when the patients actually took the medication. For example, it has been estimated that careful questioning will detect over 50% of non-compliant patients, but even patients who admit to missing medication during the previous day or week tend to overestimate their actual rate of compliance.[54] Moreover, a study of the proportion of medication taken would not necessarily identify partial compliance if this took the form of either extra doses or deviations from the prescribed time of dose. Electronic monitoring was used in a random sample of patients participating in a controlled trial of fluvastatin versus placebo and, although mean compliance as measured by the number of doses taken was found to be 94% (range 54–110%), mean compliance as measured by the number of days on which the correct number of doses was taken was only 81% (range 36–100%), and mean compliances to the prescribed morning and evening dosing schedules (i.e. within ± 6 hours) were only 71% (range 23–100%).[53] Thus, compliance measured by pill counts is likely to overestimate the actual degree of compliance with the study regimen.

Unsurprisingly, it has been found that continuance and compliance with a medication are related to a number of properties of that medication, including its tolerability, convenience of administration, the patient's perception of its safety, and quality of life while on treatment.[55] Thus, compliance decreases as the complexity, cost and duration of the regimen increase. Although compliance has little relation to sociodemographic factors, patients with psychological problems are less likely to comply with treatment, while those with physical disabilities caused by the disease are more likely to do so.[56] The risk of non-continuance or non-compliance with prescribed medication is particularly high in patients with asymptomatic chronic diseases or risk factors that require long-term preventive medication.[55] Because such treatments bring no immediately apparent benefits, patients are less well motivated to comply long term, and find any minor side-effects less acceptable.[57]

Adherence to, and compliance with, medication are clearly important in relation to the actual, rather than theoretical, efficacy of the interventions under study and therefore, as with adverse effects, data drawn from the studies under review will be supplemented with data from other sources when relevant.

Exclusion criteria

- Studies in which patients were not vitamin D replete and/or had insufficient calcium intake
- studies considered methodologically unsound in terms of either study design or method used to assess fractures, or that did not report results in the necessary detail.

Sifting

The references identified by the literature searches were sifted in three stages, being screened for relevance first by title and then by abstract. Those papers that seemed from their abstracts to be relevant were then read in full. Studies for which abstracts were not available were also read in full.

Data extraction strategy

Data were extracted by one reviewer, using customised data extraction forms.

Where available, data relating to the following outcomes were extracted:

- survival
- incident vertebral fractures
- incident non-vertebral fractures
- incident hip fractures
- incident wrist fractures
- incident humeral fractures
- adverse effects
- continuance and compliance.

Quality assessment strategy

The methodological quality of all trials that met the inclusion criteria was assessed using the tool developed by Gillespie and colleagues.[58] This tool was selected because it was intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis.

The quality assessment tool included the following items:

- adequacy of randomisation, and masking of randomisation
- blinded assessment of outcomes: whether outcome assessors were blind to subjects' treatment allocation
- withdrawals: whether the outcomes of people who withdrew were described and included in the analysis
- comparability of groups at baseline
- confirmation of diagnosis of hip or other appendicular skeleton fracture
- method of diagnosis of vertebral fracture.

Definitions of the various levels of randomisation and concealment of randomisation derived from Prendiville and colleagues[59] were incorporated in the tool (see Appendix 4).

It is recognised that the quality assessment tool assesses reporting quality, and not necessarily the true methodological quality of each study. However, where trials were reported in more than one publication, the quality score was calculated on the basis of the combined data from all relevant publications.

The quality assessment of studies included in the review of clinical effectiveness was carried out by one researcher. Blinding of the quality assessor to author, institution or journal was not considered necessary.[60,61]

Meta-analysis strategy

Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses, if this was appropriate (i.e. if the study populations, dose and outcomes were comparable), and provided that they reported fracture incidence in terms of the number of subjects sustaining fractures to enable calculation of the relative risk of subjects in the intervention group developing a new fracture or fractures, compared with subjects in the control group. Studies that reported only the number of fractures, or the proportion of subjects in each group who suffered fractures, could not be included in the meta-analyses unless it was possible to obtain from the authors unpublished information on the actual number of subjects in each group who were known to have either suffered or not suffered fractures.

Meta-analysis was carried out using Review Manager (Revman; The Cochrane Collaboration, Oxford; 2000). A random effects model was used, as this both allows generalisation beyond the sample of patients represented by the studies included in the meta-analysis and provides wider, more conservative confidence intervals than a fixed effects model.[51] Where possible, relative risks for individual studies were also calculated in Review Manager using the random-effects model. Where this was not possible, but relative risks were calculated by the study investigators, these are reported, and the fact that they are the investigators' calculations is noted.

Results

Quantity and quality of research available

Number of studies of clinical efficacy identified

The electronic literature searches identified 174 potentially relevant articles. Of these, 24 articles related to three trials that compared strontium ranelate with a relevant comparator in postmenopausal women with osteoporosis (*Figure 3*). An additional reference[62] relating to one of the included studies was identified only from a citation.

Number and type of studies included

A total of three individual RCTs, the Spinal Osteoporosis Therapeutic Intervention study (SOTI), Strontium Administration for Treatment of Osteoporosis Study (STRATOS) and Treatment of Peripheral Osteoporosis Study (TROPOS), met the review inclusion criteria. The various publications relating to these studies are listed in Appendix 5.

Number and type of studies excluded, with reasons

A substantial number of the references identified by the electronic searches did not relate to studies

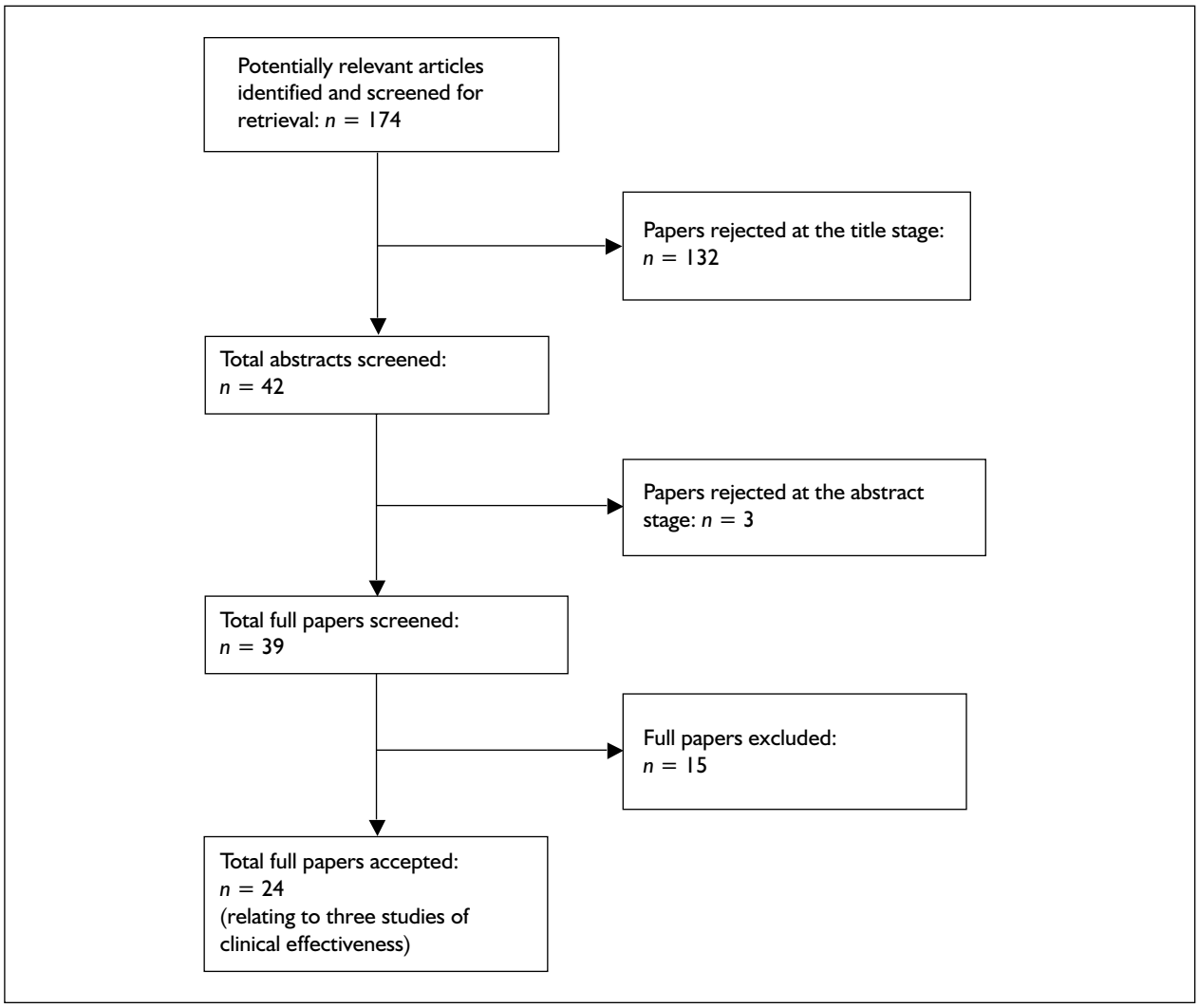

FIGURE 3 *Summary of study selection and exclusion: electronic literature searches*

that met the inclusion criteria; these were excluded as part of the sifting process. Details are therefore given only of those references that were excluded at the full paper stage, and then only if the reason for exclusion was not immediately apparent from the full text. These references, and the reasons for their exclusion, are listed in Appendix 6.

No studies that would otherwise have been included were excluded for either of the reasons listed above as exclusion criterion.

Tabulation of quality of studies

Tabulation and discussion of results: assessment of effectiveness

As noted above, evidence from other studies will be used where appropriate to supplement data from the studies under review in relation to the non-skeletal adverse effects of strontium ranelate, and in relation to continuance and compliance with treatment.

Unless stated otherwise, all relative risks have been calculated by the review team in Review Manager using the random effects model.

Quantity and quality of research available

Three studies met the review's inclusion criteria; they all compared strontium ranelate with placebo. They included one randomised, multicentre, double-blind, 2-year Phase II dose-ranging study (STRATOS[63]) and two randomised, multicentre, double-blind, 3-year Phase III studies, SOTI[64] and TROPOS[65] (for further details of study design and reporting quality, see Appendix 7).

The aim of STRATOS was to identify the smallest dose of strontium ranelate that was effective in treating postmenopausal vertebral osteoporosis,

using BMD of the lumbar spine adjusted for bone strontium content as the primary end-point. Participants were randomised to strontium ranelate at doses of 0.5, 1 and 2 g per day, or to placebo. In addition, all participants received 500 mg calcium and 800 IU vitamin D_3 daily.[63] Recruitment for STRATOS began in 1992, and the 2-year follow-up of the last patient ended in 1995 (Meunier PJ, Professor of Medicine, Faculty Laennec, INSERM, Lyon, France: personal communication; 4 April 2005).

Potential participants in SOTI and TROPOS were recruited into the Fracture International Run-in for Strontium ranelate Trial (FIRST), an open run-in study that had several aims:

- to start normalising calcium and vitamin D status
- to select participants for inclusion in either SOTI or TROPOS according to the inclusion criteria of each study[66]
- to exclude patients most likely to discontinue the trial prematurely.[67]

To allow supplementation to be adjusted as necessary, participants recruited to FIRST had their vitamin D status and calcium status assessed by blood assay and completion of a calcium questionnaire, respectively. They were subsequently advised to take daily calcium and vitamin D supplements, both at lunchtime, as follows:

- calcium supplements:
  - daily dietary calcium >1000 mg: no calcium supplement
  - daily dietary calcium intake 500–1000 mg: 500 mg supplement
  - daily dietary calcium intake <500 mg: 1000 mg supplement
- vitamin D supplementation initially 400 IU per day, subsequently increased to 800 IU per day if the serum concentration of 25-hydroxyvitamin D, as measured at the first selection visit, was found to be <45 nmol l.

This supplementation with calcium and vitamin D was continued during the SOTI and TROPOS intervention trials.[66]

The maximum expected duration of FIRST was 6 months, and the minimum expected duration was 15 days for women without any calcium and vitamin D deficiencies. Women with a severe vitamin D deficiency were to receive at least 3 months of supplementation before randomisation to either SOTI or TROPOS.[66]

In total, 9196 women who were considered to be suitable candidates for SOTI or TROPOS were recruited to the FIRST. However, only 6740 (73.3%) were in fact eligible for inclusion in those studies. Of the remainder, 1173 failed to meet the inclusion/exclusion criteria and 338 had a concomitant medical condition that precluded their inclusion. Despite the short duration of FIRST (mean 101 days), 215 patients had to be withdrawn because of adverse events. A further 56 were lost to follow-up and 594 were withdrawn for non-medical reasons.[67]

The aim of the SOTI study was to evaluate the efficacy of strontium ranelate against vertebral fracture in postmenopausal women with osteoporosis and a history of vertebral fracture.[64] However, in the event only 86.9% of the study population actually had prevalent vertebral fractures.[68] The aim of TROPOS was to assess the efficacy of strontium ranelate in reducing the incidence of non-vertebral fractures in postmenopausal women with osteoporosis with or without fracture.[65]

Assessment of effectiveness of strontium ranelate

Vertebral fracture All three studies only reported fractures that occurred in previously intact vertebrae. In TROPOS, vertebral radiographs were not mandatory, and although they were taken in as many patients as possible, baseline and follow-up radiographs were only available for 71% of the study population.[65]

STRATOS demonstrated a dose-dependent increase in lumbar BMD, adjusted for bone strontium content, as a result of which the investigators recommended the use of the 2 g daily dose. However, it was not powered to demonstrate a difference in vertebral fracture incidence between treatment groups, and the effects of treatment on vertebral fracture at 2 years were not statistically significant. The investigators suggested that this was because the effects of treatment were not fully realised in the first year, and certainly in months 12–24 treatment with strontium ranelate at doses of 0.5 and 2 g per day was associated with statistically significant reductions in the incidence of vertebral fractures, relative to placebo, although the 1-g dose was not associated with such a reduction. However, in both SOTI and TROPOS the point estimates suggest that the antifracture efficacy of strontium ranelate was at least as great in the first year of treatment as over the whole 3-year period (*Table 11*).

TABLE 11 *Strontium ranelate: vertebral fracture data*

Study	Dose (g per day)	Fracture definition	Number in each group suffering vertebral fracture (95% CI)	NNT for a given period to avoid an event (95% CI)
STRATOS[63]	0.5, 1 and 2	A decrease of at least 20% in one of the ratios of vertebral height	The numbers of women suffering fracture were neither published nor available from the study investigator. It was therefore not possible to calculate the relative risks in Review Manager, and those given below were calculated by the study investigators Months 1–12: 0.5 g: 36.6%, RR 1.09 (0.71 to 1.67) 1 g: 39.7%, RR 1.18 (0.78 to 1.78) 2 g: 29.7%, RR 0.88 (0.56 to 1.40) Placebo: 33.7% Months 12–24: 0.5 g: 24.2%, RR 0.51 (0.31 to 0.84) 1 g: 40.9%, RR 0.87 (0.59 to 1.26) 2 g: 26.5%, RR 0.56 (0.35 to 0.89) Placebo: 33.7% Months 1–24: 0.5 g: 38.8%, RR 0.71 (0.49 to 1.02) 1 g: 56.7%, RR 1.04 (0.77 to 1.39) 2 g: 42.0%, RR 0.77 (0.54 to 1.09) Placebo: 54.7%	Not calculable
SOTI[64]	2	Semi-quantitative (method of Genant)	Months 1–12: SR: 44/686 Placebo: 85/699[a] RR 0.53 (0.37 to 0.75), $p = 0.003$ Months 1–36: SR: 139/719 Placebo: 222/723[a] RR 0.63 (0.52 to 0.67), $p < 0.0001$ Months 25–36:[69] RR 0.49 (0.33 to 0.74), $p < 0.001$ (investigators' calculations) Clinical fracture, months 1–12: SR: 22/686 Placebo: 46/699[a] RR 0.49 (0.30 to 0.80), $p = 0.005$ Clinical fracture, months 1–36: SR: 75/719 Placebo: 117/723[a] RR 0.64 (0.49 to 0.85), 0.001	Radiographic fracture 1 year: 18 (11 to 37) 3 years: 9 (6 to 14) Clinical fracture 1 year: 30 (18 to 90) 3 years: 18 (11 to 44)
TROPOS[65]	2	Semi-quantitative (method of Genant)	The numbers of women suffering fracture were neither published nor available from the study investigator. It was therefore not possible to calculate the relative risks in Review Manager, and those given below were calculated by the study investigators	Not calculable

continued

TABLE 11 *Strontium ranelate: vertebral fracture data (cont'd)*

Study	Dose	Fracture definition	Number in each group suffering vertebral fracture (95% CI)	NNT for a given period to avoid an event (95% CI)
			Months 1–12: SR: ?/1817 Placebo: ?/1823 RR 0.55 (0.39 to 0.77), $p < 0.001$	
			Months 1–36: SR: ?/1817 Placebo: ?/1823 RR 0.61 (0.51 to 0.73), $p < 0.001$	
			Months 1–36, subgroup without baseline vertebral fracture: SR ($n = 1230$): 7.7% Placebo ($n = 1186$): 14.0% RR 0.55 (0.42-0.72), $p < 0.001$	
			Months 1–36, subgroup with at least one baseline fracture: SR ($n = 587$): 22.7% Placebo ($n = 637$): 31.5% RR 0.68 (0.53 to 0.85), $p < 0.001$	
Pooled SOTI and TROPOS[47]			Months 1–36: data and RR presented by Topol:[47] SR: 15.0% Placebo: 23.7% RR 0.60 (0.53 to 0.69), $p < 0.001$	NNT calculated by Topol: 11[47]

[a] Meunier PJ (personal communication; 11 March 2005).
NNT, number needed to treat; SR, strontium ranelate.

It was not possible to combine the results of the SOTI, STRATOS and TROPOS studies by meta-analysis as SOTI and TROPOS did not publish the actual numbers of participants who sustained incident vertebral fracture, and vertebral fracture data relating to TROPOS were not available from the investigators. However, a meta-analysis undertaken by another investigator with access to data from Servier Laboratories which were not available to the review team found a relative risk of radiographic fracture over 3 years of 0.60 (95% CI 0.53 to 0.69).[47]

The investigators carried out a number of preplanned subgroup analyses pooling data from SOTI and TROPOS. However, although they published the relative risks relating to these analyses, they did not always publish the underlying figures, and in these cases the relative risks could not be recalculated in Review Manager. Moreover, the study publications did not describe the method of randomisation; as there is therefore no reason to believe that randomisation was stratified taking any of the characteristics into account, none of the subgroup data are known to represent true randomised comparisons. The results of the subgroup analyses are presented in *Table 12*.

Non-vertebral fracture All three studies reported non-vertebral fractures, although they did not all present the data in such a way as to enable them to be included in a meta-analysis (*Table 13*).

In TROPOS, the incidence over time of patients with at least one incident of osteoporosis-related peripheral fracture was lower in the strontium ranelate group than in the placebo group from the first months of treatment onwards.[68]

[Confidential information removed.]

Again, the investigators carried out a preplanned subgroup analysis pooling non-vertebral fracture data from SOTI and TROPOS relating to women aged 80 years and over (*Table 14*). However, the same caveats apply as to the subgroup analyses of vertebral fracture data discussed above. The

TABLE 12 *SOTI and TROPOS subgroup analyses: incident vertebral fractures over 3 years*

Subgroup	No. of patients with fracture	RR (95% CI)	NNT for 3 years to avoid an event (95% CI)
Women aged >80 years (n = 895)[62]	SR: 19.1% Placebo: 26.5%48	0.68 (0.50 to 0.92),[46] p = 0.013[62]	13[47]
Postmenopausal women with osteoporosis but without prevalent vertebral fracture (n = 2605)[70]	SR: 87/1285 Placebo: 161/1320	0.56 (0.43 to 0.71), p < 0.00001	19 (13 to 31)
Postmenopausal women with lumbar and/or femoral neck osteopenia with or without prevalent fractures (n = 409)[71]	SR: 8.1% Placebo: 18.6%[47]	Investigators' calculations: 0.38 (0.21 to 0.70), p = 0.00174	10[47]
Postmenopausal women with lumbar and/or femoral neck osteopenia without prevalent fractures (n = 176)[47]	SR: 3.6% Placebo: 12.0%[47]	Investigators' calculations: 0.28 (0.07 to 0.99), p = 0.045[71]	12[47]
Postmenopausal women with lumbar osteopenia with or without prevalent vertebral fracture (n = 1170)[72]	SR: 11.1% Placebo: 17.8%[47]	Investigators' calculations: 0.60 (0.43 to 0.83), p = 0.002[72]	15[47]
Postmenopausal women with lumbar osteopenia with prevalent vertebral fracture (n = 722)[72]	SR: 15.5% Placebo: 23.6%[47]	Investigators' calculations: 0.63 (0.44 to 0.89), p = 0.008[72]	12[47]
Postmenopausal women with lumbar osteopenia without prevalent vertebral fracture (n = 448)[72]	SR: 3.5% Placebo: 8.6%[47]	Investigators' calculations: 0.41 (0.17 to 0.99), p = 0.038[72]	20[47]

results were presented in a form that did not permit the calculation of the relative risk and confidence intervals, and those reported here were calculated by another investigator.[47]

Hip, wrist and other non-vertebral fractures None of the studies was powered to identify a statistically significant difference in the incidence of fracture at any specific peripheral fracture site, and none reported a significant reduction in hip, wrist or humerus fracture in relation to its full intention-to-treat population (*Tables 15–17*). Although in TROPOS a significant reduction in hip fracture was seen in the subgroup of women who were aged over 74 years and were osteoporotic at study entry (*Table 15*), it should again be borne in mind that this is not a true randomised comparison.

Adverse effects

Pooled data from SOTI and TROPOS indicated that, in general, strontium ranelate therapy was not associated with an increased risk of adverse events. For the most part, adverse events were mild and transient. The most common adverse events (i.e. those that occurred in more than 1% of the treatment or placebo group) are set out in *Table 18*. Nausea and diarrhoea were the most commonly reported clinical adverse events; they were generally reported at the beginning of therapy, with no noticeable difference between groups thereafter. Creatine kinase elevations were seen in many patients, but in most cases these appeared to revert spontaneously to normal without changes in therapy.[48] The smaller STRATOS study did not identify any differences between groups in the incidence of emergent adverse events.[63]

The most serious adverse event associated with strontium ranelate therapy, an increased incidence of VTE, including pulmonary embolism, was less common, and was only identified when data from SOTI and TROPOS were pooled. The relative risk of VTE in patients receiving strontium ranelate

TABLE 13 *Strontium ranelate: all non-vertebral fractures*

Study	Dose (g per day)	No. in each group suffering non-vertebral fracture (95% CI)	NNT for 3 years to avoid an event (95% CI)
STRATOS[63]	0.5, 1 and 2	SR 0.5 g: 7.1% SR 1 g: 8.9% SR 2 g: 9.2% Placebo: 7.7% As the number of women in each group was not stated, it was not possible to calculate the RR, nor was this reported by the study investigators	Not calculable
SOTI[64]	2	All non-vertebral fractures: SR: 112/826 Placebo: 122/814 RR 0.90 (0.71 to 1.15), $p = 0.41$	71[a]
TROPOS[65]	2	Patients with at least one incident osteoporosis-related peripheral fracture at 3 years:[66] SR: 233/2479 Placebo: 276/2453 RR 0.86 (0.73 to 1.02)	54 (28 to 647)
SOTI + TROPOS[46]	2	Peripheral osteoporosis-related fractures: SR: 331/3295 Placebo: 389/3256 RR 0.84 (0.73 to 0.97), $p = 0.01$ Because of the form in which the data were available, it was only possible to calculate the RR as though the data were drawn from one study rather than to perform a meta-analysis of the data as coming from two studies	53 (29 to 259)

[a] 95% CI not calculated because the 95% CI for the absolute risk reduction extends from a negative number (indicating that treatment may be harmful) to a positive number (indicating that treatment may be beneficial).

TABLE 14 *Subgroup analyses: incident non-vertebral fractures*

Subgroup	No. of patients with fracture	RR (95% CI)	NNT for 3 years to avoid an event (95% CI)
Women aged >80 years ($n = 1488$)[62]	SR: 14.2% Placebo: 19.7%[47]	0.69 (0.52 to 0.92), $p = 0.011$[47]	18[47]

compared with placebo was 1.42 (95% CI 1.02 to 1.98, $p = 0.036$).[48] There were six fatal pulmonary embolisms in the strontium ranelate group compared with three in the placebo group, and 25 patients in the strontium ranelate group reported pulmonary embolism as an SAE compared with 14 in the placebo group.[46] In addition, some nervous system disorders were more common in patients randomised to strontium ranelate. These included mental impairment, disturbed consciousness, memory loss and seizures. No explanation of the increased incidence of VTE and nervous system disorders has been identified, and both are being addressed in the ongoing extension of SOTI and TROPOS and by postmarketing surveillance. This surveillance will also focus on the evidence of an effect on skeletal muscle cell integrity, as indicated by circulating levels of creatine kinase.[46]

Meta-analysis of data from SOTI and TROPOS did not indicate an increase in all-cause mortality in patients receiving strontium ranelate (RR 1.02, 95% CI 0.69 to 1.50) (*Figure 4*). However, there was an increased death rate due to cardiac disorders in patients receiving active treatment

TABLE 15 *Strontium ranelate in postmenopausal osteoporosis or osteopenia: hip fracture data*

Study	Dose (g per day)	No. of women in each group suffering hip fracture (95% CI)	NNT for 3 years to avoid an event (95% CI)
STRATOS	0.5, 1 and 2	NR	–
SOTI	2	NR	–
TROPOS	2	All participants:[68] SR: [C]/2479 Placebo: [C]/2453 RR [C]	[C]
		Participants aged >74 years and osteoporotic at baseline:[68] SR: 32/982 Placebo: 51/995 RR 0.64 (0.41 to 0.98), $p = 0.04$	Aged >74 and osteoporotic at baseline: 54 (28 to 968)

NR, not reported; [C], confidential information removed.

TABLE 16 *Strontium ranelate in postmenopausal osteoporosis or osteopenia: wrist fracture data*

Study	Dose (g per day)	No. of women in each group suffering wrist fracture	NNT for 3 years to avoid an event (95% CI)
STRATOS	0.5, 1 and 2	NR	–
SOTI	2	NR	–
TROPOS	2	SR: [C]/2479 Placebo: [C]/2453[70] RR [C]	[C]

TABLE 17 *Strontium ranelate in postmenopausal osteoporosis or osteopenia: humerus fracture data*

Study	Dose (g per day)	No. of women in each group suffering humerus fracture	NNT for 3 years to avoid an event (95% CI)
STRATOS	0.5, 1 and 2	NR	–
SOTI	2	NR	–
TROPOS	2	SR: [C]/2479 Placebo: [C]/2453[68] RR [C]	[C]

during the first year of therapy, but not thereafter. Deaths that could be related to thrombosis/embolism (including pulmonary embolism, cerebrovascular accident and intestinal infarction), were also nominally more common in patients receiving active treatment.[46]

Patients who discontinued study therapy because of adverse events did so mainly because of nausea. Diarrhoea was also associated with a statistically significant increase in the likelihood of discontinuing therapy (*Table 19*).

Quality of life

Both SOTI and TROPOS recorded health-related quality of life every 6 months using the Short Form 36 (SF-36); SOTI also used the Quality of Life in Osteoporosis (QUALIOST) questionnaire.[66]

In the SOTI study, strontium ranelate therapy was said to benefit quality of life as assessed by the QUALIOST specific scale and the general health perception score of the SF-36 general scale compared with placebo.[68]

TABLE 18 *Number of patients with common emergent adverse events: pooled data from SOTI and TROPOS*

Adverse event	SR (*n* = 3352)	Placebo (*n* = 3317)	RR (95% CI)	*p*
Nervous system disorders				
Headache[46]	101 (3.0%)	79 (2.4%)	1.27 (0.95 to 1.69)	0.11
Disturbances in consciousness[48]	2.5%	2.0%	Not calculable	
Memory loss[48]	2.4%	1.9%	Not calculable	
Gastrointestinal disorders				
Nausea[46]	222 (6.6%)	142 (4.3%)	1.55 (1.26 to 1.90)	>0.0001
Diarrhoea[46]	219 (6.5%)	154 (4.6%)	1.41 (1.15 to 1.72)	0.0008
Loose stools[46]	36 (1.1%)	6 (0.2%)	5.94 (2.51 to 14.07)	<0.0001
Skin and subcutaneous tissue disorders				
Dermatitis[46]	69 (2.1%)	54 (1.6%)	1.26 (0.89 to 1.80)	0.19
Eczema[46]	50 (1.5%)	40 (1.2%)	1.24 (0.82 to 1.87)	0.31
Allergic dermatitis[46]	33 (1.0%)	18 (0.5%)	1.81 (1.02 to 3.22)	0.04
Vascular disorders				
Thrombosis[46]	3.3%	2.2%	Not calculable	
VTE including pulmonary embolism[48]	Data not available	Data not available	1.42 (1.02 to 1.98)	0.036[48]
Pulmonary embolism as SAE[46]	25	14	1.77 (0.92 to 3.39)	0.09
Fatal pulmonary embolism[46]	6	3	1.98 (0.50 to 7.91)	0.33
Laboratory test findings				
Creatine kinase >upper limit of normal on at least one occasion[46]	789/2680 (29.4%)	475/2705 (17.6%)	1.68 (1.52 to 1.85)	<0.00001
Creatine kinase >3 times upper limit of normal[48]	1.0%	0.4%	Not calculable	

SAE, serious adverse event.

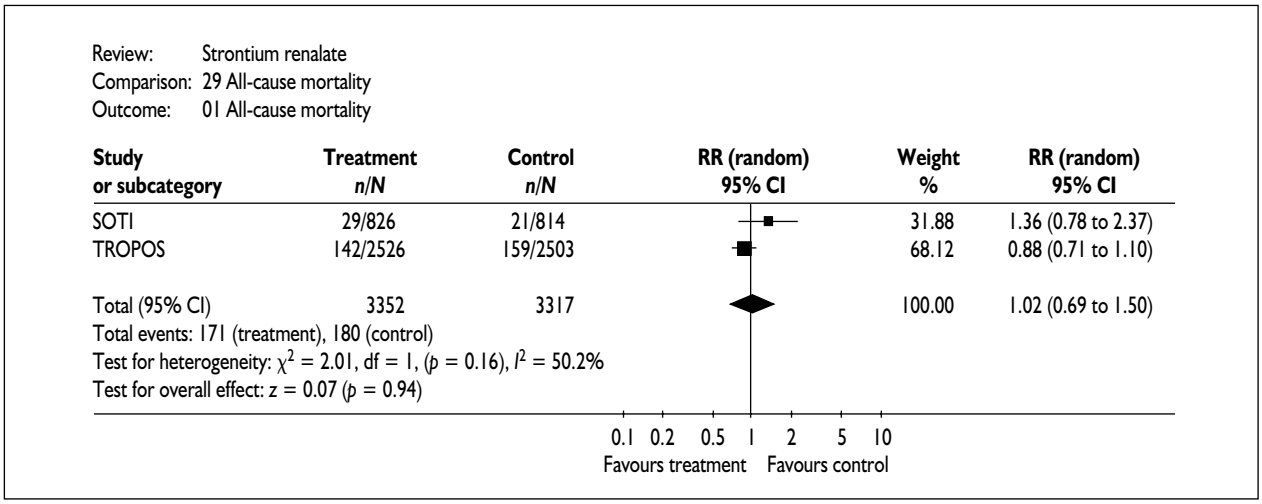

FIGURE 4 *All-cause mortality.*

[Confidential information removed]

No quality of life results were presented for TROPOS.

Continuance and compliance

Both STRATOS and SOTI presented data relating to compliance, but neither gave a definition of compliance and only STRATOS indicated how it had been measured (*Table 20*).

All three studies provided information on the proportion of participants who completed follow-up for the planned length of the study (*Table 21*). However, while it is clear that, in STRATOS, this figure represents the proportion who continued to

TABLE 19 *Number of patients discontinuing because of emergent adverse events considered possibly related to study therapy: pooled data from SOTI and TROPOS*[46]

Adverse event	SR (*n* = 3352)	Placebo (*n* = 3317)	RR (95% CI)	*p*
Nervous system disorders				
Headache	17 (0.5%)	8 (0.2%)	2.10 (0.91 to 4.67)	0.08
Gastrointestinal disorders				
Nausea	82 (2.4%)	47 (1.4%)	1.73 (1.21 to 2.46)	0.003
Diarrhoea	61 (1.8%)	28 (0.8%)	2.16 (1.38 to 3.36)	0.0007
Loose stools	6 (0.2%)	2 (0.1%)	2.97 (0.60 to 14.70)	0.18
Skin and subcutaneous tissue disorders				
Dermatitis	3 (0.1%)	3 (0.1%)	0.99 (0.20 to 4.90)	0.99
Eczema	1 (<0.1%)	1 (<0.1%)	0.99 (0.06 to 15.81)	0.99
Allergic dermatitis	5 (0.1%)	2 (0.1%)	2.47 (0.48 to 12.74)	0.28

TABLE 20 *Compliance with study treatment*

Study	Definition of compliance	How measured	Compliance
STRATOS[63]	Not given	Unused tablets returned at study visits; drug concentrations	Mean global compliance 93±13%; said to be no relevant differences between groups
SOTI[64]	Not given	NR	Number compliant in each group: SR: 83% Placebo: 85%
TROPOS[65]	No data	No data	No data

TABLE 21 *Proportion of participants completing study*

Study	Proportion of participants completing study protocol
STRATOS[63]	Proportion of participants completing study protocol (2 years): SR 0.5 g: 77% SR 1 g: 73% SR 2 g: 77% Placebo: 81%
SOTI[64]	Proportion of participants completing follow-up at 3 years: SR 2 g: 76% Placebo: 77%
TROPOS[65]	Proportion of participants completing follow-up at 3 years: SR 2 g: 66% Placebo: 64%

take the study medication for the length of the study period, it is not clear whether all the participants who completed follow-up in SOTI and TROPOS were still taking the study medication at the end of the 3-year period.

It is generally accepted that continuance and compliance with medication are higher in RCTs than in general clinical practice. This is particularly likely to be true of SOTI and TROPOS, which sought to minimise non-continuance by randomising patients who had undergone an initial run-in phase (FIRST) designed not only to normalise calcium and vitamin D status and to exclude patients who were not eligible for either study, but also to exclude those who were most likely to discontinue study medication prematurely as a result of either

TABLE 22 *Real-life continuance with non-hormonal antiosteoporotic therapies*

Medication	Proportion of patients still taking medication		
	At 6 months	At 1 year	At 2 years
Alendronate[75]	70%	No data	No data
Bisphosphonates[73]	No data	24%	No data
Raloxifene[73]	No data	18%	No data
Raloxifene[74]	No data	No data	44%

adverse reactions or low compliance.[67] Unfortunately, no UK studies were identified that investigate compliance and continuance with non-hormonal therapies for osteoporosis outside clinical trials. However, a recent US study used paid claims data to investigate real-world compliance and continuance with drug therapies for the treatment and prevention of osteoporosis during the period from 1 January 1998 to 30 August 2001, a period during which strontium ranelate was not available. This found that only 24% of patients initiating therapy with bisphosphonates and only 18% of those initiating therapy with raloxifene continued to use this therapy uninterrupted for a year (*Table 22*), compared with 31% of those using two hormone replacement therapies (HRTs). Older patients were generally likely to continue therapy for slightly longer than those under 55 years of age.[73] Two other US studies looked at continuance with non-hormonal therapies for osteoporosis. A retrospective search of a pharmacy prescription database found that, of women who were members of the Kaiser Foundation Health Plan, a large health maintenance organisation, and who had been prescribed raloxifene, 56% had discontinued treatment by 24 months.[74] A survey of 813 women treated with alendronate found that, at 6 months, 29% stated that they had discontinued treatment, while prescription refill records suggested that, in fact, 30% had discontinued treatment.[75]

Discussion

The available evidence suggests that, in postmenopausal women with osteoporosis, strontium ranelate is associated with a statistically significant reduction in the relative risk of both vertebral and non-vertebral fracture. The numbers needed to treat for 3 years to avoid an event are nine for a radiographic vertebral fracture and 53 for a peripheral fracture. Although adverse events are usually mild and transient, strontium ranelate therapy is associated with an increased risk of venous thromboembolism and a possible increase in nervous system disorders.

Strontium ranelate and teriparatide are the only antifracture therapies that stimulate bone formation.[76] A recent small, prospective, non-randomised study indicated that the effectiveness of teriparatide in increasing BMD is substantially reduced in postmenopausal women who have previously been treated with alendronate compared with similar women who had previously received raloxifene.[77] There is as yet no evidence to indicate whether prior alendronate therapy also reduces the effectiveness of strontium ranelate.

Efficacy data used in the model

RCT results on women were pooled regardless of fracture history. This is based on the opinion of the NICEGDG, which believes that there is no plausible reason for fracture efficacy to be altered following a fracture and that in many RCTs the confidence intervals of efficacy in women with fracture and those without have similar midpoints and overlapping confidence intervals.

Based on similar evidence, the NICEGDG also believes that the efficacy of interventions for osteoporosis should be assumed to be the same for women with osteopenia and women with osteoporosis. Therefore, this study used a constant efficacy for all women regardless of their *T*-score, which was derived from trials including women with osteoporosis and women with osteopenia.

Since fractures of the tibia, fibula and humeral shaft fractures are now included with proximal humerus fractures, it was decided that the efficacy applicable to these fractures would be that taken from all non-vertebral fractures. Similarly, since fractures of the ribs, sternum, scapula and clavicle are now included with wrist fractures, it was decided that the efficacy for all non-vertebral fractures would also be used for these fractures. It was assumed that the efficacy in reducing hip,

TABLE 23 *RR (95% CI) of fracture for women with severe osteoporosis, osteoporosis or osteopenia (assumes efficacy seen in women with osteoporosis, severe osteoporosis and osteopenia)*

Drug	Vertebral	Hip[a]	All non-vertebral fractures[b]
SR	0.60 (0.53 to 0.69)[47]	**[Confidential information removed]**	0.84 (0.73 to 0.97)[46]

[a] Assumed applicable to other femoral and pelvis fractures.
[b] Assumed applicable to wrist, humerus, rib, sternum, scapula, clavicle, tibia and fibula fractures.

pelvis and other femoral fractures would be equivalent to that for hip fractures alone.

The meta-analysed fracture efficacy data are summarised in *Table 23*. The assessment group was unable to carry out an independent meta-analysis of SOTI and TROPOS for vertebral fracture and non-vertebral fracture owing to inadequate reporting of the data. Instead, the relative risks are taken from published meta-analyses.

The analysis used efficacy specifically at the hip, rather than using all non-vertebral fractures as a proxy. This will slightly favour the intervention, although there is greater uncertainty in the results.

Description of comparator treatments

Since the publication of the scope and protocol for this appraisal, NICE has issued guidance on the secondary prevention of osteoporotic fractures.[23] As a direct consequence of the recommendations in that guidance, the bisphosphonate alendronate was selected as the comparator in the economic model for the current appraisal.

Alendronate

Alendronate is an oral bisphosphonate that is licensed in the UK at 5 mg per day for the prevention of postmenopausal osteoporosis and the treatment of corticosteroid-induced osteoporosis, and at 10 mg per day for the treatment of postmenopausal osteoporosis, corticosteroid-induced osteoporosis in postmenopausal women not receiving HRT, and osteoporosis in men. It is also licensed at 70 mg per week for the treatment of postmenopausal osteoporosis.[78]

The UK licence for alendronate is held by Merck Sharp & Dohme. It is marketed as Fosamax®. Fosamax is available in 5-mg and 10-mg tablets, which respectively contain 6.53 and 13.05 mg of alendronate sodium (the molar equivalent of 5 and 10 mg of alendronic acid). These are available in blister packs of 28 tablets. Fosamax is also available in once-weekly 70-mg tablets, which contain 91.37 mg alendronate sodium trihydrate (the equivalent of 70 mg of alendronic acid). These are available in blister packs of four tablets.[14]

For adequate absorption, Fosamax must be taken with at least 200 ml (5 fluid ounces) of plain water, at least 30 minutes before the first food, beverage (including mineral water) or medication of the day.[14]

Because of the risk of oropharyngeal ulceration, patients should not chew the tablet or allow it to dissolve in the mouth. They should not lie down until after their first food of the day (at least 30 minutes after taking the tablet). Fosamax should not be taken at bedtime or before rising for the day.[14]

Fosamax is contraindicated in patients with:

- abnormalities of the oesophagus or other factors such as stricture or achalasia which delay oesophageal emptying
- inability to stand or sit upright for at least 30 minutes
- hypersensitivity to any component of the product
- hypocalcaemia[14]
- renal impairment.

Because of a lack of experience, Fosamax is not recommended for patients with renal impairment where the glomerular filtration rate is less than 35 ml per minute. It should not be given to pregnant or lactating women.[14]

Because Fosamax can cause local irritation of the upper gastrointestinal mucosa, caution should be used when it is given to patients with active upper gastrointestinal problems (e.g. dysphagia, oesophageal disease, gastritis, duodenitis or ulcers).[14]

Efficacy

The clinical effectiveness of alendronate in the treatment of postmenopausal osteoporosis has been recently reviewed and reported.[79] The results of the previous review, which are summarised in *Table 24*, will be used in the current analysis.

TABLE 24 *RR (95% CI) of fracture for women with osteoporosis or osteopenia but no prior fracture (assumes efficacy seen in women with osteoporosis, severe osteoporosis and osteopenia)*

Drug	Vertebral	Hip[a]	All non-vertebral fractures[b]
Alendronate	0.56 (0.46 to 0.68)	0.62 (0.40 to 0.98)	0.81 (0.68 to 0.97)

[a] Assumed applicable to other femoral and pelvis fractures.
[b] Assumed applicable to wrist, humerus, rib, sternum, scapula, clavicle, tibia and fibula fractures.

Chapter 4
Economic analysis

The assessment group reviewed the existing economic analysis evidence, taken to be the submission documents[19] using the quality assessment checklist presented by Drummond and Jefferson.[80] These are presented in Appendix 8. The remainder of this section relates to the economic model constructed by the assessment group.

This section is divided into the following two components:

- establishing the cost-effectiveness of strontium ranelate at different levels of absolute fracture risk in postmenopausal women with osteoporosis, who have and have not had a fracture
- estimating how alternative approaches for the identification of osteoporotic women impact on the cost-effectiveness of the interventions in women who have not had a fracture.

Cost-effectiveness of interventions at different levels of absolute risk

Methods for economic analyses

The assessment group constructed a peer-reviewed model to estimate the cost-effectiveness of osteoporosis interventions.[81,82] It is assumed that all women in the model have an adequate baseline intake of calcium and vitamin D as RCT data on the effectiveness of interventions have been compared against such a population.

The key inputs to this model are the efficacy data for each intervention in terms of reducing the incidence of hip, vertebral, wrist and proximal humerus fractures. As detailed in the following section, other fracture types are subsumed into these groups, but for reasons of brevity this section will refer to just the four main fracture sites.

The model calculates the number of fractures that occur, and provides as output data the costs associated with osteoporotic fractures and the quality-adjusted life-years (QALYs) accrued by a cohort of 100 osteoporotic women, with each fracture being detrimental to health and incurring a cost. When the costs of the intervention are included, the incremental cost compared with no treatment can be calculated and divided by the gain in QALYs to calculate cost-effectiveness measures.

Treatment with strontium ranelate was calculated against a no-treatment option to evaluate whether it can be given cost-effectively. An incremental analysis against alendronate was also conducted to estimate the cost-effectiveness of strontium ranelate relative to a current standard treatment.

This section is divided into the following subsections.

- the structure of the model, which will discuss the formulation of the appraisal model and the modelling assumptions made
- the health state values assumed for each event contained in the model
- the costs associated with each event contained in the model
- the cost-effectiveness ratios calculated for each intervention.

Structure of the cost-effectiveness model

The model used to calculate cost-effectiveness ratios is an updated version of Sheffield Health Economic Model for Osteoporosis (SHEMO), which has been previously reported.[81,82] This model deviates from approaches previously used, which have been based on cohort analyses using the standard techniques of decision analysis and state transition models.[83,84]

The basic design of SHEMO is similar, in many ways, to the conventional state transition models used in the area of osteoporosis, where women pass through states using a set of time-dependent transition probabilities, and each state has its associated costs, mortality rates and health state utility values. However, it differs in a crucial respect from the conventional cohort design since individual women pass through the model one at a time. The model simulates for each patient whether or not an event occurs in the forthcoming year and then a mean estimate is taken of costs and QALYs for each cohort.

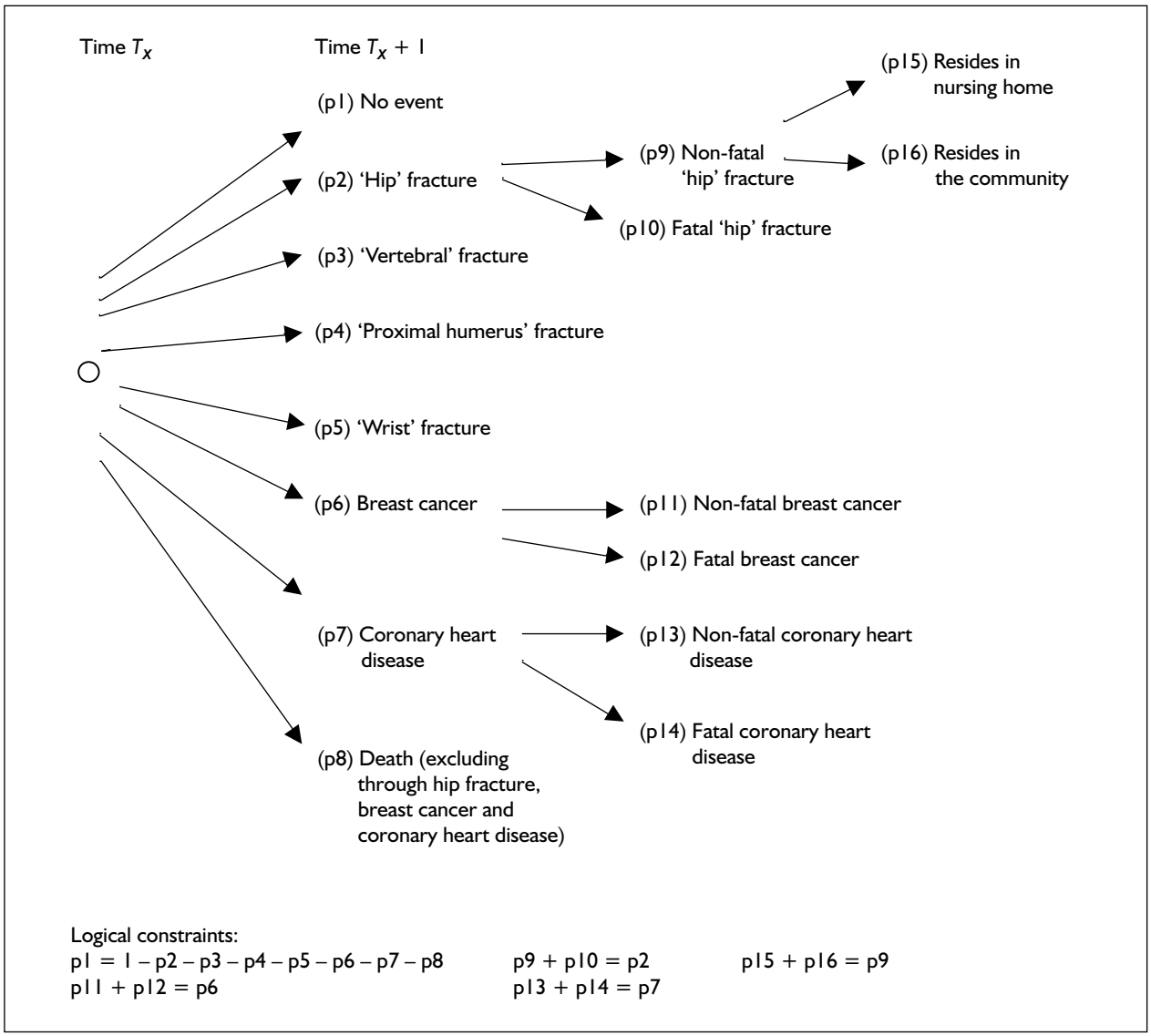

FIGURE 5 *Structure of the model*

The full patient history is recorded and factors such as prior fractures and current residential status can therefore be used to determine the likelihood of events in the next period. Following the simulated event, the quality of life of the patient and costs incurred in that period are calculated. These values have taken into account any residual costs or quality of life impacts from previous fractures. The model simulates at 1-year intervals until either the patient dies or a user-defined time-horizon, which was set to 10 years for the majority of the economic analyses, has been reached. This process is repeated until a selected number of women has been simulated. The rationale for using the individual patient approach is that it provides more accuracy and flexibility than a cohort approach, which is bounded by a limited number of transition states. Examples are given in Appendix 9.

The time-horizon of the model was constrained to a 10-year period, owing to the likely treatment effects being confined within this period, as well as uncertainty around future medical costs and technologies that may become available, and the gap in the evidence base concerning the effect of fractures on quality of life after a period of 10 years. The results presented, however, do take into account the expected number of future QALYs lost owing to mortality within the time-horizon. This methodology is explained in Appendix 10.

A diagram of the model structure is provided in *Figure 5*. The original fracture has been written

down, although the additional fractures are included. For example, 'hip' also includes pelvis and other femoral fracture.

The exact values of p2–p14 will be determined by the patient's age, her history regarding the presence of previous fracture at each site and her residential status. These probabilities are calculated for each individual at the beginning of each year.

The cycle is repeated for all non-absorbing states until the time-horizon is reached.

Modelling assumptions

For the purpose of this report, the transition states between which women can move were limited to fracture states, death due to hip fracture and death from other causes.

A separate variable was used to indicate the residential status of the patient, either community or nursing home. A 'no event' state, which signifies that the patient did not have an event that would be associated with a change of state, was also included. The transition probability for the no-event state was calculated as 1 minus the summation of the transition probabilities for the remaining states.

Diseases where possible links with osteoporosis treatments may exist, such as Alzheimer's disease, venous thrombolic events and cancer, were excluded from this cost-effectiveness analysis. Since strontium ranelate has been associated with an increased risk of venous thrombosis, it is noted that all cost-per-QALY results calculated in this report will be favourable to the intervention.

The basic probabilities for moving from transition state to transition state have been taken from the WHO algorithm, with the following exceptions. Once a fracture is sustained within the model the risk is increased in accordance with the data reported by Klotzbeucher and colleagues.[30] The increased risk of fracture as the woman ages has been taken from the underlying rise in fracture rates reported in Singer[21] as these were components of the individual patient model.

Having established the transition probabilities, the model simulates the experiences of each patient in the cohort under no treatment. The discount rate for costs was set to 6% per annum, in accordance with published guidelines.[85] The default discount rate for QALYs was set to 1.5% per annum.[86] No formal sensitivity analyses were conducted using different discount rates; however, had an analysis been undertaken using rates of 3.5% for both QALYs and costs, the cost per QALY ratios would have become more unfavourable to the intervention.

As a patient moves into a transition state, there is an initial one-off cost incurred and an ongoing cost incurred that is assumed to last until the end of the simulation. By using such a methodology, states with high ongoing costs can be distinguished from those where the costs incurred are all in the initial year. In circumstances where a patient has already been in this state, it was assumed that only the one-off costs will be incurred, with the ongoing costs from that state remaining constant. For example, if the consequences of a vertebral fracture comprised an initial cost of £600 and a recurrent cost of £300 per year, a further vertebral fracture in the same individual would cost a further £600, but the recurrent costs would not increase from £300 per year. This may underestimate the costs involved, but few data were found on the additional ongoing costs of second events. Following the introduction of additional fracture sites, the methodology of not duplicating the long-term fracture costs may be slightly unfavourable to the intervention. As a tibia fracture is now grouped with a proximal humerus fracture, if both fractures had been sustained then only one long-term cost would be included.

When a patient moves into a transition state this affects her quality of life. It was assumed that there will be a QALY multiplier effect within the first year and a QALY multiplier that will last for the remaining years of the simulation. Using this methodology, states from which the patient will recover but not to the level before the event can be modelled. It is assumed that when a patient suffers a transition state for a second or further time, only the initial year's reduction in quality of life will be taken into consideration. It is noted that in some cases this will underestimate the loss in QALYs, for example second hip or wrist fractures on a different side from the first, or a second vertebral fracture. However, owing to insufficient data the approach of assuming no extra residual QALY loss from a second incident was taken. Similarly to the explanation given when discussing costs, the inclusion of more than one fracture in some states may be slightly unfavourable to the intervention.

Having established a baseline no-treatment cost for the cohort, the incremental effects from pharmaceutical treatments were calculated. The

efficacy of each treatment is modelled by the use of relative risks in entering a transition state. It is expected that a cohort using a treatment with an RR of 0.5 for hip fracture would, in the next period, have half the number of hip fractures as the same cohort receiving no treatment (RR = 1), assuming an equal death rate. For an intervention the relative risks were sampled from the meta-analysis of efficacy undertaken.

The effect of treatment on fracture probability was assumed to be instantaneous and to persist unchanged throughout the treatment period. A 5-year treatment period was assumed, which corresponds to the duration of exposure in RCTs, particularly those undertaken in the past 10 years. In addition to the treatment relative risk, the model incorporates fall times, which were defined as the time from when the treatment is stopped to the time that the relative risk returns to 1 compared with no treatment. It is assumed that the relative risk returns to 1 in a linear manner during a fall period of 5 years. Sensitivity analyses were conducted using the assumption of lifetime treatment.

The cost savings and QALY gains associated with a set of relative risks are dependent on the underlying fracture probability, with the beneficial effects of an intervention that reduced all fractures by 30% being greater in women with an absolute fracture risk of 5% per annum than in women with a 1% risk of fracture. In the model, the absolute risks of fracture are calculated from age, *T*-score and the presence of CRFs. As the simulation progresses, the presence of prior fragility fractures impacts on the risk of fracture as described in the next section.

Each treatment option has also been assigned GP costs in addition to drug acquisition. Following NICEGDG advice, and considering that elderly women have their complete medication (for all diseases) reviewed annually, it was assumed that, following initiation, osteoporosis treatment would result in no additional costs for women aged 75 years or over, and would result in one-third of women below 75 years of age requiring an additional GP appointment per annum. It was also decided that no follow-up BMD scans would be required.

Lack of compliance is modelled in sensitivity analyses assuming that the patient incurs 1 month of drug costs but receives no health benefits.

It was assumed that for a year in which death occurred, the QALYs gained are half those for the prior year, that costs are incurred equal to half of the ongoing annual costs, and that only one half of the drug acquisition cost is paid.

The results from the individual patient model were converted into a metamodel using Gaussian process techniques.[25,26] The advantage of the Gaussian process technique is that given the same starting assumptions, the results for a new drug with defined relative risks can be calculated instantly, while retaining the benefits associated with an individual patient methodology.

Formulating cost-effectiveness results

To compare interventions (pharmaceutical, surgical or diagnostic) across different disease areas, all cost-effectiveness measures must be expressed in a common denominator. Cost per life-year gained (the additional cost associated with an intervention compared with a no-treatment option) divided by the additional life-years gained compared with a no-treatment option, satisfies that criterion, but this measure is insensitive to the patient's quality of life, resulting in treatments that significantly impact on quality of life but do not prolong life having an infinite cost per life-year gained. NICE has thus recommended the use of cost per QALY. The QALY combines increased life expectancy and improvements in health status by assigning a utility ranging from 0 to 1, corresponding to the health-related quality during a set period, where a utility of 1 corresponds to optimal health and a weight of 0 corresponds to a health state judged to be equivalent to death.[87]

The QALY approach thus quality adjusts survival. A person expected to survive for 10 years at a quality of 0.8 has 8 QALYs. The benefits of a treatment that increases survival at a utility of 0.8 (from 10 to 20 years), or improves the quality of the 10 years (from 0.8 to 0.9), can be valued in terms of the QALY gain (i.e. gains of 8 and 1, respectively).

Recent NICE guidance[88] suggests that cost per QALY values of less than £20,000 will be deemed cost-effective, while those between £20,000 and £30,000 will need additional factors beyond the cost per QALY ratio to be deemed cost-effective. Above £30,000 the additional factors must be very strong for the intervention to be considered cost-effective.

Potential problems in interpreting cost per QALY ratios

Cost per QALY values can be difficult to interpret, as the smallest cost per QALY value is not always

associated with the most optimal treatment. Thus, a treatment with a small increase in health (0.01 QALY) at a low cost (£1) would not necessarily be preferred to an intervention with higher health gains and costs (1 QALY and £10,000), despite the relative cost per QALY of the interventions being £100 and £10,000 respectively. The optimal hierarchy of interventions is calculated by ranking all interventions in order of ascending health gain and initially comparing the two least effective treatments. If the incremental cost per QALY between the more effective treatment and the lesser is below the cost per QALY threshold, the more effective treatment is selected as optimal. Similar comparisons are then iteratively conducted between the current optimal treatment and the next most efficacious treatment, until the list is exhausted and the optimal treatment found. In the above example, the incremental cost per QALY would be £10,100 (£9999/0.99) and if this is below the assumed threshold, the more efficacious intervention would be selected. More complex issues regarding estimating the confidence intervals of cost per QALY values exist, as the variable is not continuous. When the intervention is more costly than the comparator, but the incremental health gain is zero, the cost per QALY is infinite. A minimal health gain would provide large positive cost per QALY values, while conversely a minimal health loss would provide a large negative cost per QALY value.

Net benefit

Owing to potential difficulties in interpreting cost per QALY values, the use of net benefit (NB) is becoming more widespread. While these results are analogous to those presented in the more traditional cost per QALY format, there is less scope for mistakes when interpreting the data, as net benefit values can be compared directly across interventions and net benefit is a continuous variable.

Net benefit is calculated from the formula:

$$NB = \lambda Q - C$$

where λ is the maximum cost per QALY that society is prepared to pay (in the following example this is assumed to be £30,000), Q denotes the incremental QALY gain of the intervention, and C denotes the incremental cost of the intervention.

Where net benefit is positive, the treatment is cost-effective, where net benefit is negative, the treatment is not cost-effective, where net benefit is zero the cost per QALY is equal to the maximum cost per QALY that society is prepared to pay.

In this example, the net benefit of the first intervention would be equal to:

$$(£30{,}000 \times 0.01) - £1 = £299$$

The second intervention would have a net benefit of

$$(£30{,}000 \times 1) - £10{,}000 = £20{,}000$$

As both net benefits are positive, both treatments are cost-effective. However, the more cost-effective intervention is the second one, as it has a higher net benefit.

Review of health state values associated with osteoporosis

A review of the health state values associated with osteoporosis carried out by the authors has been reported previously.[23] Recent searches have identified only one additional study. This study, by Kanis and colleagues.[89] estimates utility multipliers for hip, vertebral, wrist and humerus fractures in both the first and second years following fracture. This comprehensive study provides a recent and coherent source of health state utility values for all the fracture types that are used in the model. The values provided are not too dissimilar to those reported by other studies and the data from this new source were therefore used in the model.

The utilities reported by Kanis[89] suggested that fractures of the pelvis and femoral shaft should be allocated to hip, fractures at the tibia and fibula should be allocated to proximal humerus, and fractures of the scapula, ribs and sternum should be allocated to wrist. These are shown in *Table 25*. The only case where the utility data did not match closely was for tibia and fibula fractures (multiplier of 0.926) compared with proximal humerus fractures (multiplier of 0.973) in the second year. To prevent the disutility of tibia and fibula fractures being underestimated, a weighted mean was calculated using the incidences of these fractures relative to proximal humerus fractures at each age. This varies the utility multiplier for proximal humerus, tibia and fibula fractures from 0.949 at 50–54 years of age to 0.966 at 80 years and over.

One alteration was that the fractures grouped as similar to wrist were not assumed to affect utility in the second year. This is likely to be very slightly unfavourable to the intervention.

TABLE 25 *Health state utility values according to site of fracture for women*[89]

Fracture type	Utility in 1st year following fracture	Utility in 2nd year following fracture
Spine (clinical)	0.626	0.909
Hip	0.792	0.813
Forearm	0.977	0.999
Humerus	0.794	0.973
Pelvis	0.794	0.815
Other femoral	0.792	0.813
Tibia	0.794	0.926
Clavicle, scapula and sternum	0.977	0.999
Ribs	0.977	0.999

Women entering the model with a previous fracture should have a health state utility that reflects their previous fracture. Instead, they enter the model with the same health state utility as women without a previous fracture. This will favour the intervention when treating women with a history of prior fracture since they enter the model with better health and therefore have more to gain from treatment to prevent further fractures. The error is greatest in women with a history of prior hip fracture as the health state utility multiplier in the second and subsequent years following fracture is 0.813 for hip fracture but greater than 0.9 for all other fractures. A sensitivity analysis was carried out to assess the extent to which this error favours intervention in women with a previous fracture; it was seen that the costs per QALY are underestimated by approximately 5%, by assuming no long-term disutility for women with a prior fracture (see Appendix 11). Thus, the model favours interventions in women with prior fractures, particularly in the hip or vertebrae, where the residual effect is greatest.

Cost data used in the treatment model

This report uses the costs reported in a systematic review by Kanis and colleagues,[90] having inflated, where applicable, to 2003/04 prices.[91] The costs presented were divided, where possible, into first year costs and costs that are assumed to be paid for the remainder of a patient's lifetime. The costs were weighted by patient age, based on data regarding the length of stay in hospital and patient age. The full methodology is presented in detail in Kanis,[90] with the updated costs given in *Table 26*. These costs were used as the input to the cost-effectiveness model.

A more recent estimate of the cost of nursing home care is provided in the assessment report for the NICE appraisal of treatments for Alzheimer's disease.[92] The impact of using this alternative estimate of £18,471 per annum is examined in a sensitivity analysis in Appendix 11.

The cost of a GP visit was estimated at £18.00[91] and the cost of a BMD scan at £35, as previously used in a NICE assessment.[23]

The costs of the interventions

Women receiving strontium ranelate or alendronate should also be prescribed calcium plus vitamin D supplements if their dietary intake is insufficient. As an assumption of the model is that all women have adequate vitamin and calcium D intakes, it is assumed that only the intervention is prescribed. The costs per annum are shown in *Table 27* and came from the British National Formulary (BNF).[93]

Calculation of the cost-effectiveness of each intervention

In previous analyses of treatments for the prevention of osteoporosis[94] an extensive analysis of the uncertainty relating to the efficacy of each intervention was undertaken. For each treatment, 1000 values for efficacy of each type of fracture were selected by Monte Carlo methods, from the meta-analysed efficacy data, assuming independence in the relationship between the selected relative risks. From these samples the Gaussian model generated 1000 cost and QALY estimates. These formed the basis for the estimated mean cost per QALY compared with no treatment and the 95% confidence intervals.

However, when assessing the cost-effectiveness at given absolute risk levels, based on *T*-score and CRF, it was not possible to generate 1000 cost and QALY estimates for each age and combination of CRF within the time available. Formal probabilistic sensitivity analyses were conducted for some selected analyses and cost-effectiveness acceptability curves (CEACs) produced.

TABLE 26 *Costs of each event, by age and by initial and subsequent years*

State	Age 50–54 costs (£)		Age 60–64 costs (£)		Age 70–74 costs (£)		Age 80–84 costs (£)	
	1st year costs	Subsequent annual costs	1st year costs	Subsequent annual costs	1st year costs	Subsequent annual costs	1st year costs	Subsequent annual costs
Hip fracture[a]	5,157	–	5,157	–	6,487	–	8,538	–
Hip fracture leading to nursing home entry[a]	31,299	23,562	31,299	23,562	32,606	24,240	34,654	25,357
Death due to hip fracture	8,666	–	8,666	–	8,666	–	8,666	–
Vertebral fracture	477	222	477	222	539	222	581	222
Wrist fracture[b]	359	–	359	–	359	–	585	–
Proximal humerus fracture[c]	1,024	–	1,024	–	1,024	–	1,674	–

[a] Assumed applicable for pelvis and other femoral fracture.
[b] Assumed applicable for tibia, fibula and humeral shaft fractures.
[c] Assumed applicable for rib, sternum, clavicle and scapula fractures.
Costs at 55–59, 65–69 and 75–79 years of age have been interpolated from the above data.
The report from Kanis *et al.*[90] did not age-weight proximal humerus fracture, nor make a distinction between the costs of wrist fracture between 50 and 70 years. If such a weighting does exist the model is expected to favour slightly treatment in the young at the expense of the old.
Note that the costs due to hip fracture were not adjusted when formulising the Gaussian process model and remain at 1999/2000 prices.

TABLE 27 *Cost for each intervention per annum*

Intervention	Assumed dosage	Cost per annum (£)
SR	2 g per day	334
Alendronate	10 mg per day	301

For the majority of combinations of age and CRF, single point efficacies were calculated from the log-normal efficacy distributions. A characteristic of the log-normal distribution is that the mean of the log-normal distribution is not equal to the log of the mean. The true midpoint of a log-normal distribution can be calculated from the mean, μ, and standard deviation, *s*, of the normal distribution to which it relates, according to the formula:

$$\mu = 10^{[(2m + s^2)/2]}$$

Using this formula, the point estimates in *Table 28* were used for the modelling exercise.

The reduction of the distribution to a single point estimate has the disadvantage of removing the ability to draw CEACs as only a midpoint estimate is generated. However, as the efficacy data typically do not have highly skewed upper limits, the loss in accuracy is not expected to be large.

To provide some indication of the uncertainty surrounding the cost-effectiveness results, the full uncertainty analysis using 1000 efficacy estimates was carried out for women with a prior fracture for the age bands 50–54, 60–64, 70–74 and 80–84 years.

The cost-effectiveness analysis stopped after a time horizon of 10 years. So that the loss of life due to fractures was taken into consideration, the expected QALY of an average woman from the end of the model until death was calculated. This was then multiplied by the number of hip mortalities that were expected to be saved by the intervention. A similar methodology was also applied to the expected mortalities from vertebral fractures and from proximal humerus fractures (see Appendix 10 for the full methodology).

Results of cost-effectiveness analyses

The results of the cost-effectiveness analyses will be presented as follows:

- cost-effectiveness for different levels of absolute risk
- results for patients with a prior fracture
- results for patients without a prior fracture.

Cost-effectiveness for different levels of absolute risk

This section establishes the cost-effectiveness of strontium ranelate compared with no treatment at different levels of absolute fracture risk. The cost-effectiveness presented in this section includes drug acquisition costs and the cost of GP consultations to initiate and monitor treatment, but does not include the cost of assessing the woman's risk of fracture.

The absolute risk of fracture is the annual risk of fracture at any site and provides a single measure for a woman's risk. However, absolute risk of fracture does not provide a single measure of cost-effectiveness as might be expected. This is because the absolute risk of fracture is the total for all fracture sites included in the analysis, but different fracture sites have different impacts on quality of life, costs and mortality. Hip fracture in particular has a much greater impact on costs and mortality than fractures at other sites. Therefore, the cost-effectiveness is dependent on the contribution from each fracture site to the total risk of fracture and, in particular, on the ratio of hip fracture risk to non-hip fracture risk at any given absolute fracture risk.

The absolute fracture risk is a result of both the woman's CRF and her BMD. So, any given absolute fracture risk will be reached at different *T*-scores for individuals with different CRFs. This ratio or hip fracture risk to non-hip fracture risk at any given absolute fracture risk is therefore fairly complex and is derived from two main factors, the relative risk associated with the risk factors and

TABLE 28 *Assumed RR of fracture for each intervention in women with osteoporosis*

Intervention	Hip	Spine	Wrist	All non-vertebral fractures
SR	**[Confidential information removed]**	0.60	0.84	0.84
Alendronate	0.63	0.56	0.81	0.81

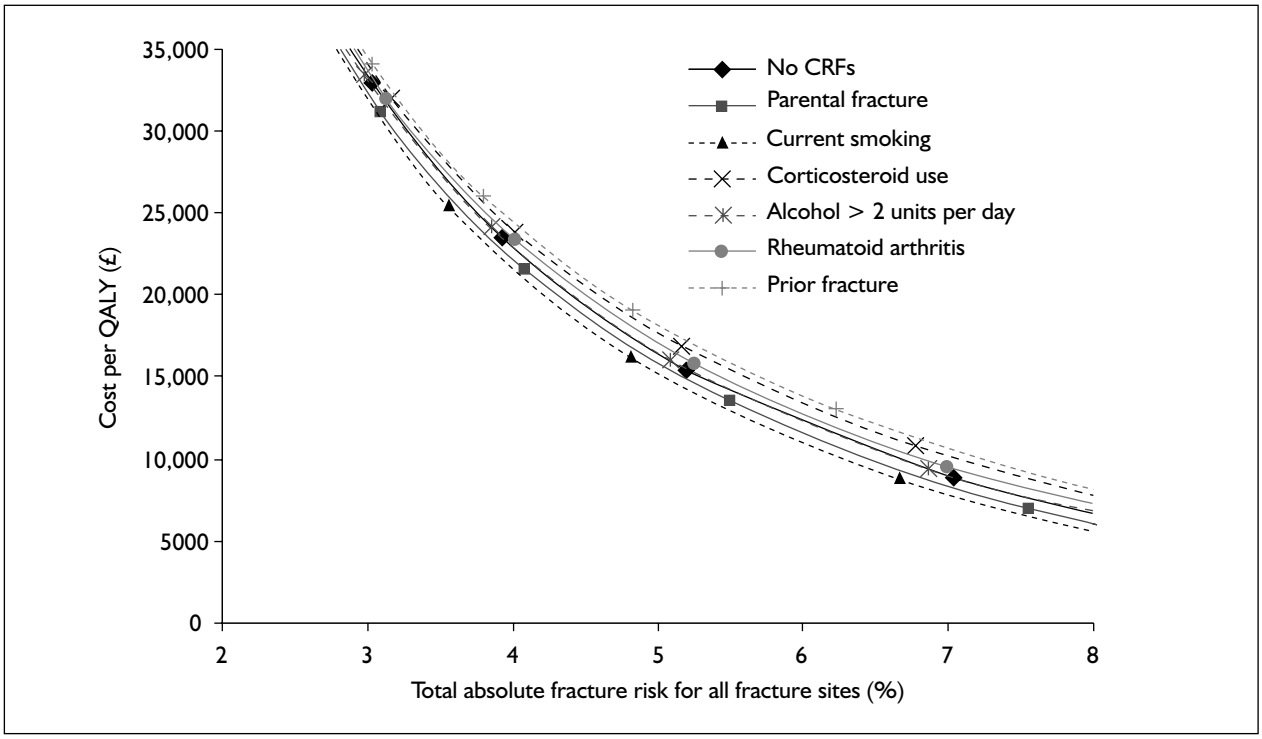

FIGURE 6 *Cost-effectiveness of strontium ranelate compared with no treatment at 70–74 years of age for women with different CRFs*

the relative risk associated with the *T*-score. If the contribution of the *T*-score to absolute risk is large, it is possible that, at a given absolute risk of fracture, treating women without CRFs will be more cost-effective than treating women with CRFs. It is therefore not possible to define a single absolute fracture risk threshold at which treatment is cost-effective for all women, as it will depend on the individual's risk factors. This is shown in *Figure 6*, where the cost-effectiveness is shown by absolute fracture risk thresholds for women aged 70–74 years with different CRFs. However, despite this complex relationship, the cost-effectiveness is broadly similar at a given absolute risk for individuals with different risk factors, and for any given *T*-score, women with risk factors will have a higher cost-effectiveness than women without risk factors. Smoking has a low cost per QALY ratio as it is assumed to increase the risk of hip fracture, but decrease the risk of non-hip fracture.

Figure 7 gives the cost-effectiveness of strontium ranelate for women, at different ages, with no CRFs. The results are broadly comparable across age. Differences in the values are accounted for by the ratio of the increases in hip to non-hip fracture risk as a women ages and other factors such as the mortality hazard, the baseline utility values and the probability of entering a nursing home following a fracture, which vary with age. For comparison, the same graph is shown for alendronate, which is seen to be more cost-effective at given risks than strontium ranelate (*Figure 8*).

Tables giving the absolute fracture risk at different *T*-scores according to age and clinical risk factors are provided in Appendix 12.

Results for patients with prior fracture

The results provided in *Tables 29–42* give the *T*-score and absolute risk thresholds for treatment with strontium ranelate and alendronate relative to no treatment when assuming a maximum acceptable incremental cost-effectiveness ratio (MAICER) of £20,000 and £30,000 per QALY. These thresholds are for women with a prior fracture. Where treatment was cost-effective in women with a *T*-score greater than +1 SD, the absolute risk threshold was not calculated. Although the calculations of the cost-effectiveness ratios presented in this report are based on absolute fracture risk of hip and non-hip fractures, it is acknowledged that clinicians would need practical advice that is related to the *T*-score of the woman, and thus this information has been provided. Based on the results, alendronate appears to be more cost-effective than strontium ranelate. One caveat is that strontium ranelate has

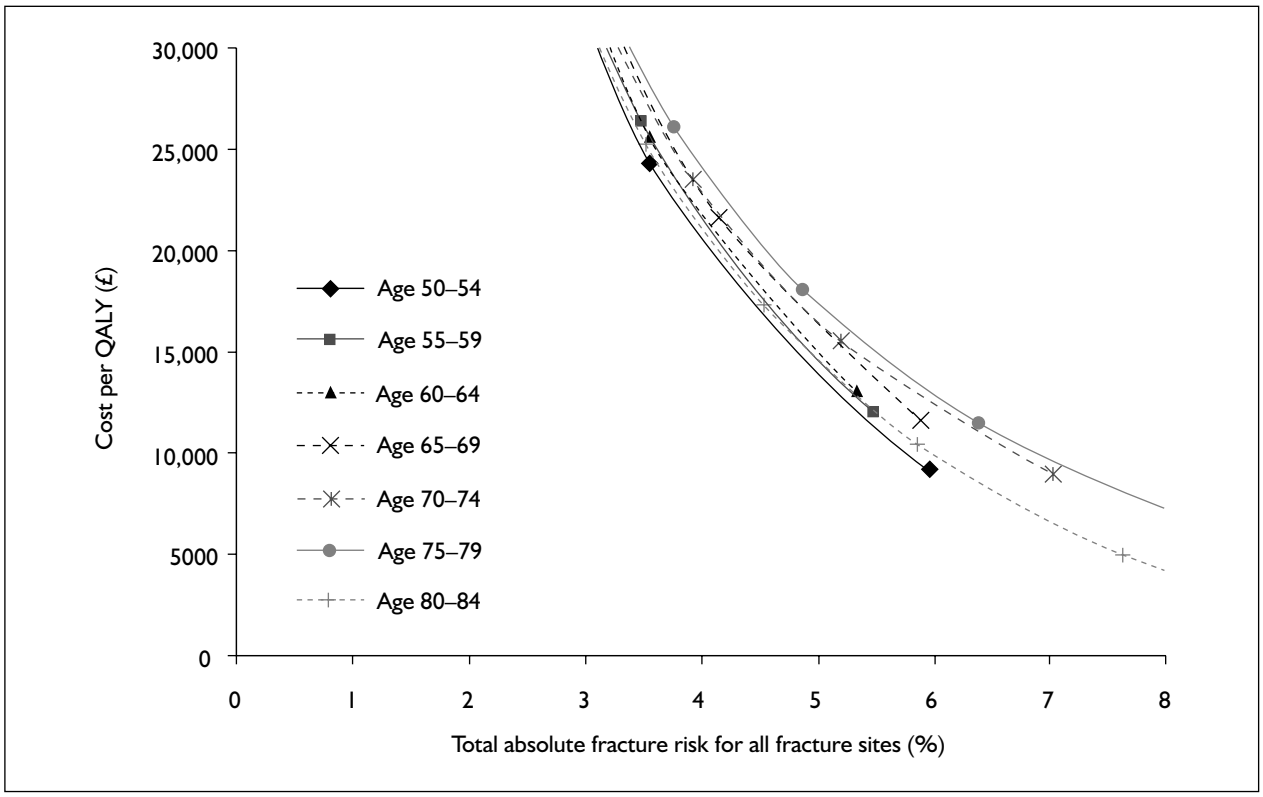

FIGURE 7 *Cost-effectiveness of strontium ranelate compared with no treatment for women with no CRFs according to age*

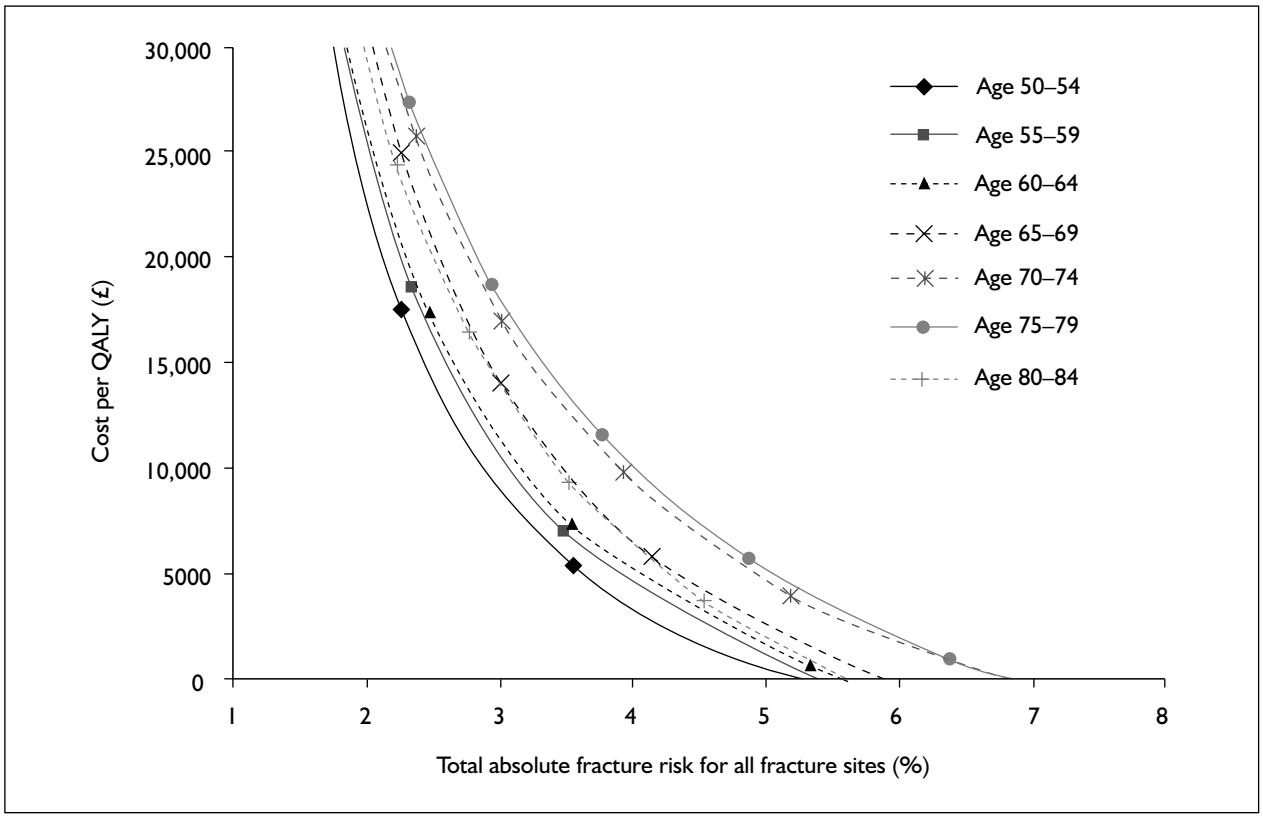

FIGURE 8 *Cost-effectiveness of alendronate compared with no treatment for women with no CRFs according to age*

TABLE 29 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 50 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–4.1	4.84	–3.8	3.75
Prior fracture and parental fracture	–3.8	5.92	–3.4	4.72
Prior fracture and current smoking	–3.7	4.66	–3.4	3.57
Prior fracture and corticosteroid use	–3.5	5.23	–3.2	4.23
Prior fracture and alcohol > 2 units per day	–3.7	4.68	–3.4	3.68
Prior fracture and rheumatoid arthritis	–3.8	5.10	–3.4	3.75
3 risk factors including prior fracture but excluding parental fracture	–3.2	4.89	–2.9	3.94
3 risk factors including prior fracture and parental fracture	–3.3	6.57	–2.8	5.23

TABLE 30 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 55 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–4.1	4.64	–3.8	3.71
Prior fracture and parental fracture	–3.7	5.77	–3.1	4.33
Prior fracture and current smoking	–3.7	4.51	–3.4	3.56
Prior fracture and corticosteroid use	–3.4	4.94	–3	3.87
Prior fracture and alcohol > 2 units per day	–3.7	4.61	–3.4	3.72
Prior fracture and rheumatoid arthritis	–3.8	5.02	–3.4	3.82
3 risk factors including prior fracture but excluding parental fracture	–3.2	4.97	–2.8	3.83
3 risk factors including prior fracture and parental fracture	–3	6.04	–2.3	4.60

TABLE 31 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 60 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–4.1	4.60	–3.7	3.51
Prior fracture and parental fracture	–3.6	5.66	–3	4.30
Prior fracture and current smoking	–3.7	4.51	–3.3	3.38
Prior fracture and corticosteroid use	–3.4	5.06	–3	4.01
Prior fracture and alcohol > 2 units per day	–3.7	4.64	–3.3	3.57
Prior fracture and rheumatoid arthritis	–3.8	5.06	–3.3	3.69
3 risk factors including prior fracture but excluding parental fracture	–3.2	5.11	–2.7	3.75
3 risk factors including prior fracture and parental fracture	–3	6.26	–2.2	4.55

TABLE 32 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 65 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual Absolute risk threshold (%)**	***T*-score threshold (SD)**	**Absolute risk threshold (%)**
Prior fracture	–4	4.99	–3.5	3.75
Prior fracture and parental fracture	–3.1	5.31	–2.5	4.05
Prior fracture and current smoking	–3.5	4.53	–3.1	3.54
Prior fracture and corticosteroid use	–3.1	5.19	–2.5	3.86
Prior fracture and alcohol > 2 units per day	–3.5	4.83	–3	3.66
Prior fracture and rheumatoid arthritis	–3.5	5.00	–3	3.84
3 risk factors including prior fracture but excluding parental fracture	–2.9	5.14	–2.3	3.75
3 risk factors including prior fracture and parental fracture	–2.5	5.74	–1.7	4.11

TABLE 33 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 70 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Absolute risk threshold (%)**	***T*-score threshold (SD)**	**Absolute risk threshold (%)**
Prior fracture	–3.5	4.82	–2.8	3.46
Prior fracture and parental fracture	–2.4	4.66	–1.7	3.30
Prior fracture and current smoking	–3.1	4.49	–2.5	3.29
Prior fracture and corticosteroid use	–2.4	4.87	–1.6	3.50
Prior fracture and alcohol > 2 units per day	–3	4.74	–2.3	3.41
Prior fracture and rheumatoid arthritis	–2.9	4.78	–2.2	3.49
3 risk factors including prior fracture but excluding parental fracture	–2.2	4.69	–1.4	3.41
3 risk factors including prior fracture and parental fracture	–1.6	4.51	–0.8	3.42

TABLE 34 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 75 years of age*

CFRs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
Prior fracture	–3.2	4.97	–2.5	3.58
Prior fracture and parental fracture	–1.9	4.46	–1.1	3.24
Prior fracture and current smoking	–2.8	4.61	–2.2	3.41
Prior fracture and corticosteroid use	–2.1	5.03	–1	3.57
Prior fracture and alcohol > 2 units per day	–2.7	4.90	–2	3.53
Prior fracture and rheumatoid arthritis	–2.6	4.94	–1.8	3.51
3 risk factors including prior fracture but excluding parental fracture	–1.9	4.88	–0.9	3.57
3 risk factors including prior fracture and parental fracture	–0.8	4.34	–0.1	3.27

TABLE 35 *T-scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 80 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–2.6	4.33	–1.9	3.25
Prior fracture and parental fracture	–1	3.96	–0.3	3.02
Prior fracture and current smoking	–2.2	4.06	–1.5	3.14
Prior fracture and corticosteroid use	–1.2	4.39	–0.2	3.25
Prior fracture and alcohol > 2 units per day	–2	4.20	–1.2	3.22
Prior fracture and rheumatoid arthritis	–1.9	4.29	–1	3.23
3 risk factors including prior fracture but excluding parental fracture	–0.9	4.20	0	3.16
3 risk factors including prior fracture and parental fracture	0.2	3.79	0.8	2.99

TABLE 36 *T-scores and risk thresholds by CRF for alendronate at 50 years of age*

CRFs	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–3.4	2.79	–3.1	2.30
Prior fracture and parental fracture	–3.1	4.09	–2.7	3.46
Prior fracture and current smoking	–3	2.61	–2.7	2.12
Prior fracture and corticosteroid use	–2.8	3.31	–2.5	2.83
Prior fracture and alcohol > 2 units per day	–3	2.78	–2.7	2.33
Prior fracture and rheumatoid arthritis	–3.1	3.07	–2.7	2.44
3 risk factors including prior fracture but excluding parental fracture	–2.5	3.07	–2.2	2.61
3 risk factors including prior fracture and parental fracture	–2.6	4.83	–2.1	4.05

TABLE 37 *T-scores and risk thresholds by CRF for alendronate at 55 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–3.4	2.85	–3	2.26
Prior fracture and parental fracture	–2.9	3.98	–2.3	3.17
Prior fracture and current smoking	–3	2.67	–2.6	2.08
Prior fracture and corticosteroid use	–2.7	3.30	–2.3	2.72
Prior fracture and alcohol > 2 units per day	–3	2.89	–2.6	2.32
Prior fracture and rheumatoid arthritis	–3	3.01	–2.6	2.44
3 risk factors including prior fracture but excluding parental fracture	–2.4	3.05	–2	2.51
3 risk factors including prior fracture and parental fracture	–2.3	4.60	–1.5	3.53

TABLE 38 *T-scores and risk thresholds by CRF for alendronate at 60 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–3.3	2.76	–2.9	2.22
Prior fracture and parental fracture	–2.8	3.96	–2.2	3.14
Prior fracture and current smoking	–2.9	2.60	–2.5	2.05
Prior fracture and corticosteroid use	–2.6	3.25	–2.2	2.69
Prior fracture and alcohol > 2 units per day	–2.9	2.82	–2.5	2.29
Prior fracture and rheumatoid arthritis	–3	3.11	–2.5	2.42
3 risk factors including prior fracture but excluding parental fracture	–2.4	3.18	–1.9	2.48
3 risk factors including prior fracture and parental fracture	–2.2	4.55	–1.4	3.44

TABLE 39 *T-scores and risk thresholds by CRF for alendronate at 65 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–3.1	3.04	–2.6	2.40
Prior fracture and parental fracture	–2.3	3.72	–1.7	2.93
Prior fracture and current smoking	–2.7	2.82	–2.2	2.17
Prior fracture and corticosteroid use	–2.3	3.53	–1.7	2.73
Prior fracture and alcohol > 2 units per day	–2.7	3.14	–2.2	2.47
Prior fracture and rheumatoid arthritis	–2.7	3.31	–2.2	2.64
3 risk factors including prior fracture but excluding parental fracture	–2	3.25	–1.5	2.59
3 risk factors including prior fracture and parental fracture	–1.7	4.11	–0.7	3.15

TABLE 40 *T-scores and risk thresholds by CRF for alendronate at 70 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
Prior fracture	–2.6	3.17	–2	2.45
Prior fracture and parental fracture	–1.5	3.08	–0.7	2.44
Prior fracture and current smoking	–2.2	2.85	–1.7	2.26
Prior fracture and corticosteroid use	–1.6	3.50	–0.5	2.68
Prior fracture and alcohol > 2 units per day	–2.2	3.26	–1.4	2.42
Prior fracture and rheumatoid arthritis	–2.1	3.34	–1.3	2.54
3 risk factors including prior fracture but excluding parental fracture	–1.3	3.32	–0.3	2.57
3 risk factors including prior fracture and parental fracture	–0.6	3.22	0.3	2.51

TABLE 41 *T-scores and risk thresholds by CRF for alendronate at 75 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
Prior fracture	–2.3	3.27	–1.5	2.46
Prior fracture and parental fracture	–0.7	2.80	0	2.21
Prior fracture and current smoking	–1.8	2.87	–1.1	2.29
Prior fracture and corticosteroid use	–1	3.57	0.1	2.68
Prior fracture and alcohol > 2 units per day	–1.7	3.19	–0.9	2.53
Prior fracture and rheumatoid arthritis	–1.6	3.31	–0.7	2.59
3 risk factors including prior fracture but excluding parental fracture	–0.7	3.37	0.2	2.64
3 risk factors including prior fracture and parental fracture	0.4	2.73	>1	NA

TABLE 42 *T-scores and risk thresholds by CRF for alendronate at 80 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
Prior fracture	–1.5	2.87	–0.7	2.25
Prior fracture and parental fracture	0.3	2.42	0.9	1.97
Prior fracture and current smoking	–0.9	2.55	–0.2	2.03
Prior fracture and corticosteroid use	0	3.06	0.9	2.38
Prior fracture and alcohol > 2 units per day	–0.8	2.84	0	2.23
Prior fracture and rheumatoid arthritis	–0.7	2.95	0.1	2.33
3 risk factors including prior fracture but excluding parental fracture	0.2	2.97	>1	NA
3 risk factors including prior fracture and parental fracture	>1	N/A	>1	NA

efficacy data in the elderly (those aged 80 years and above), whereas bisphosphonates have relatively few data in this age group. As an example in interpreting the results, a woman aged 50 years, with prior fracture and who had used corticosteroids, would need an absolute risk of fracture of 5.23% per annum, which is achieved at a *T*-score of –3.5 SD, to be cost-effective assuming a MAICER of £20,000. This is given in *Table 29*.

Probabilistic sensitivity analysis

The results provided in *Tables 29–42* have assumed that the midpoint efficacy is correct. To provide an indication of the spread in the cost per QALY due to uncertainty in the efficacy values, probabilistic sensitivity analyses have been conducted for both strontium ranelate and alendronate assuming the average *T*-score of all the women who are osteoporotic at 50, 60, 70 and 80 years of age. These values are –2.8, –2.8, –3.0 and –3.1 SD, respectively, and have been taken from the Holt data.[12]

Figures 9 and *10* show the CEACs for strontium ranelate and alendronate, respectively. The wider spread of the curves in *Figure 9*, particularly at the ages of 70 and 80 years, is due to the wider uncertainty in hip fracture efficacy with strontium ranelate.

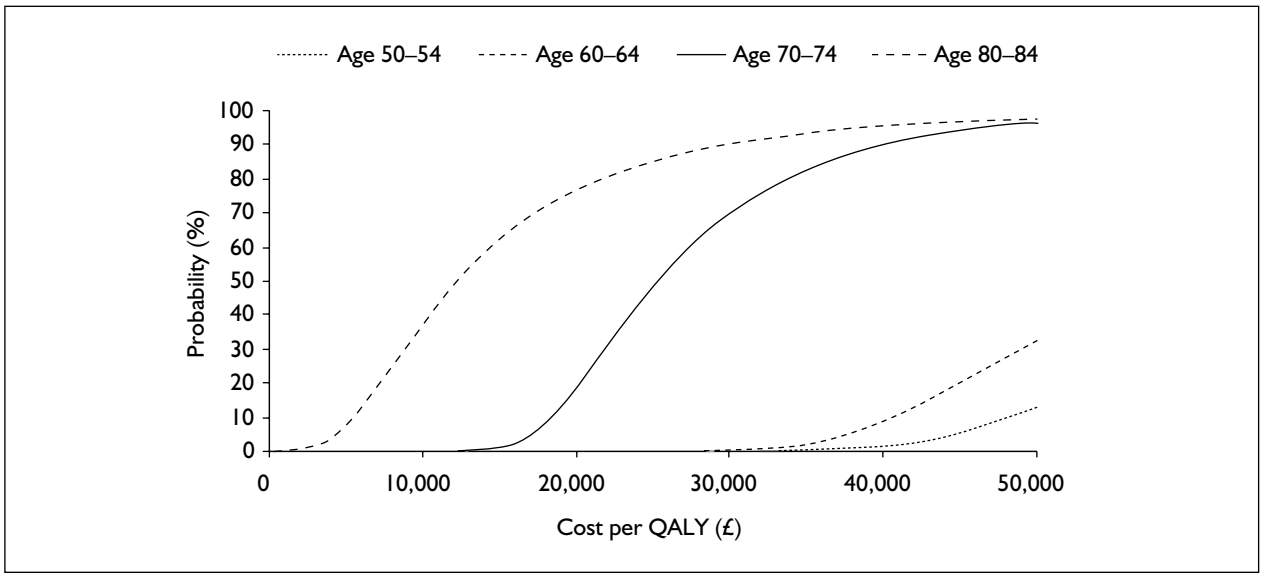

FIGURE 9 *CEAC for strontium ranelate for women with a prior fracture but no other CRFs and at average BMD for women who are osteoporotic*

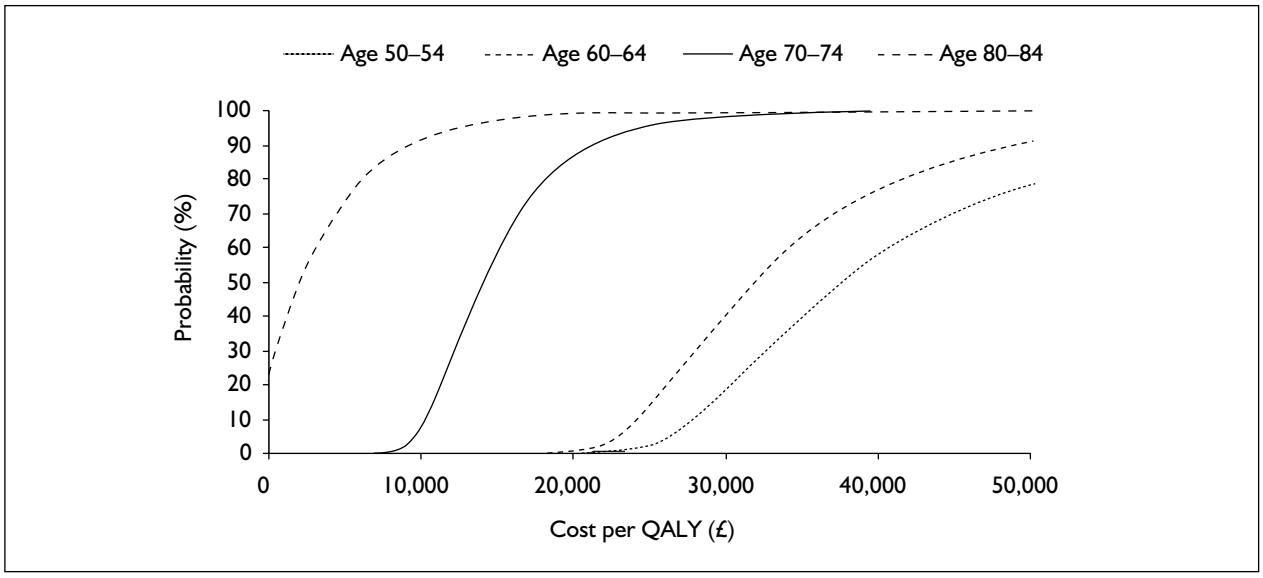

FIGURE 10 *CEAC for alendronate for women with a prior fracture but no other CRFs and at average BMD for women who are osteoporotic*

Formal probabilistic sensitivity analysis regarding the optimal intervention was undertaken for women with a prior fracture, with a BMD equal to that of the average of osteoporotic women, at the ages of 50, 60, 70 and 80 years. The multi-interventional CEACs are shown in *Figures 11–14*. As expected, since alendronate has better midpoint efficacy at all sites, and has a lower acquisition price, it is optimal on substantially more occasions than strontium ranelate.

Results for women without a prior fracture

The results provided in *Tables 43–56* give the *T*-score and absolute risk thresholds for treatment with strontium ranelate and alendronate relative to no treatment when assuming a MAICER of £20,000 and £30,000 per QALY. These thresholds are for women without a prior fracture. Where treatment was cost-effective in women with a *T*-score greater than +1 SD, the absolute risk threshold was not calculated. Although the calculations of the cost-effectiveness ratios

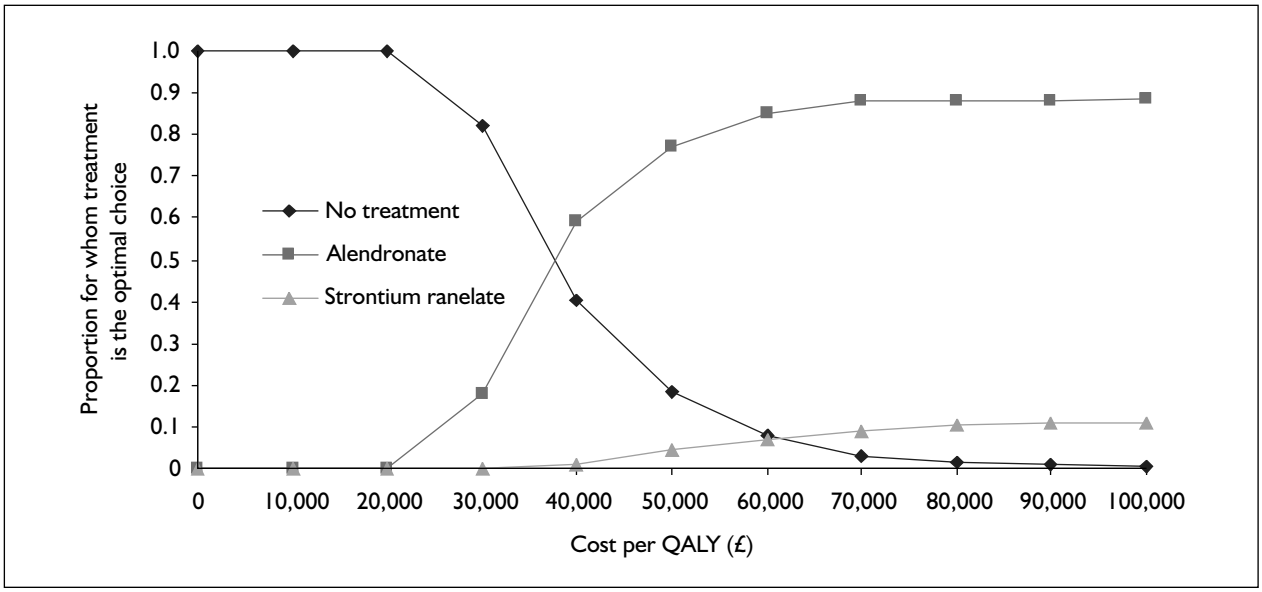

FIGURE 11 *Multi-interventional CEAC for women with a* T*-score equal to that of all osteoporotic women at 50 years of age (women aged 50–54 with average BMD and BMI), with a prior fracture but no other CRFs*

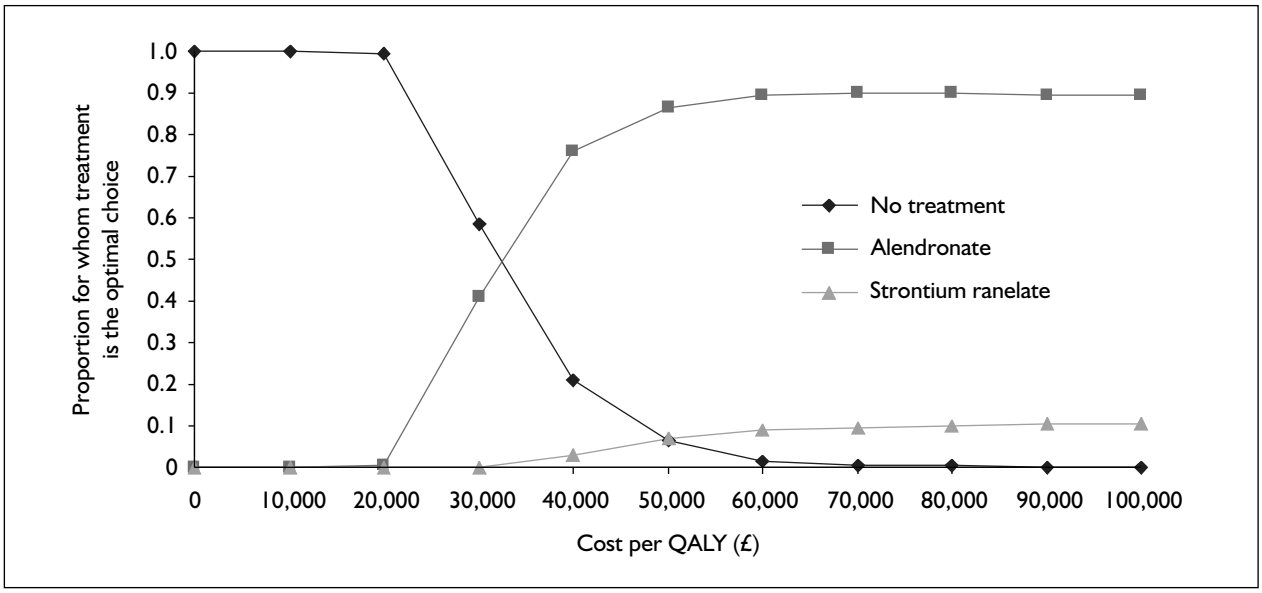

FIGURE 12 *Multi-interventional CEAC for women with a* T*-score equal to that of all osteoporotic women at 60 years of age (women aged 60–64 with average BMD and BMI), with a prior fracture but no other CRFs*

presented in this report are based on absolute fracture risk of hip and non-hip fractures, it is acknowledged that clinicians would need practical advice related to the *T*-score of the woman, and thus this information has been provided.

However, in contrast to the situation where a woman has sustained a prior fracture, the cost-effectiveness ratio estimated for treating an individual woman is not the only criterion, as this ratio does not include the costs associated with finding the woman, which may be prohibitive if only a small proportion of women can be treated cost-effectively. The methodology used to evaluate the impact of identification strategies on the cost-effectiveness of treating women without a prior fracture but at risk of osteoporotic fracture is discussed in the next section.

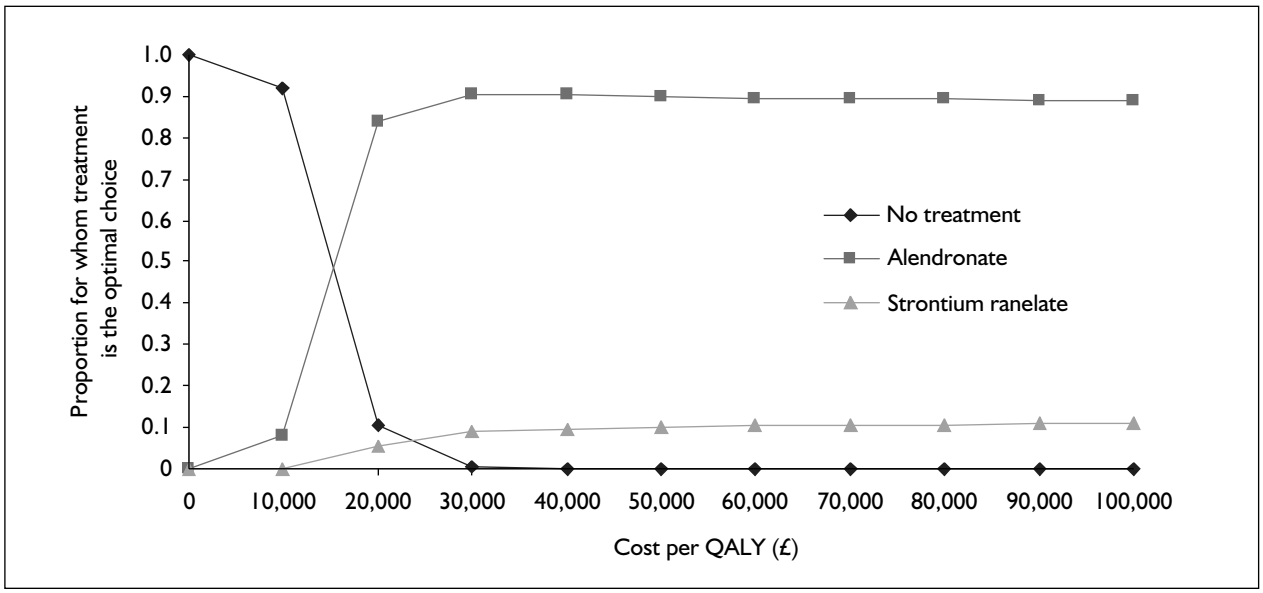

FIGURE 13 *Multi-interventional CEAC for women with a* T*-score equal to that of all osteoporotic women at 70 years of age (women aged 70–74 with average BMD and BMI), with a prior fracture but no other CRFs*

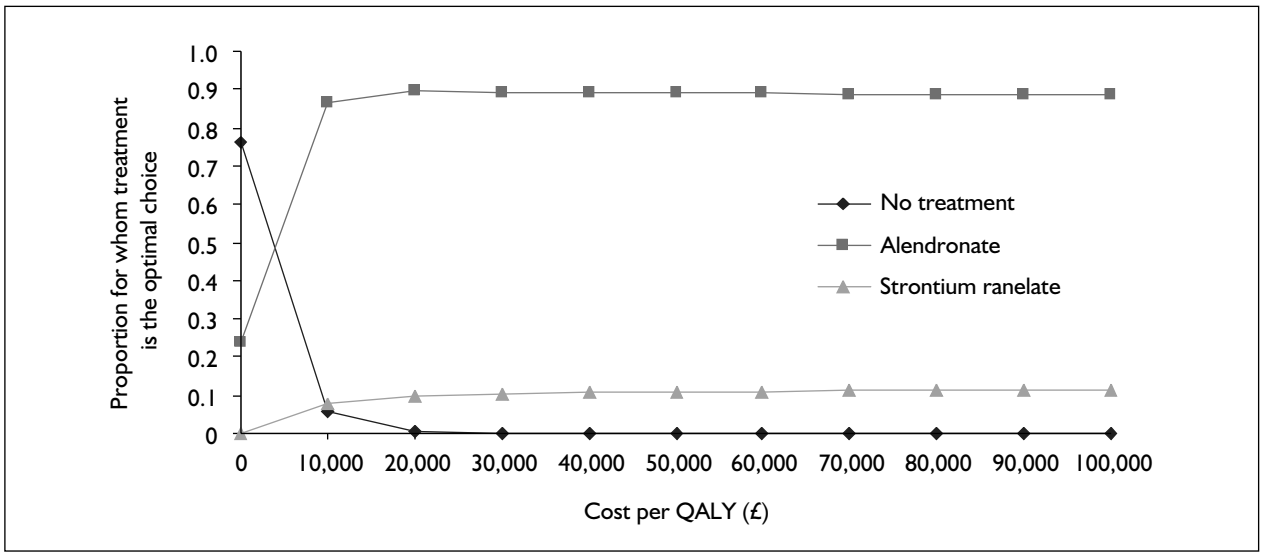

FIGURE 14 *Multi-interventional CEAC for women with a* T*-score equal to that of all osteoporotic women at 80 years of age (women aged 80–84 with average BMD and BMI), with a prior fracture but no other CRFs*

The impact of alternative identification approaches on the cost-effectiveness of the interventions

This section of the report evaluates the cost-effectiveness of strategies for identifying and treating women without a prior fracture. The total costs of each strategy (those from the osteoporosis model plus those from identifying potentially cost-effective women), in combination with the QALYs gained from women who could be treated cost-effectively, are used to ascertain whether the overall strategy is cost-effective. Women with a prior fracture are assumed to be identified at the time of fracture diagnosis with no additional costs incurred and are therefore not included in this analysis.

The current standard practice in the UK for identifying women at risk of osteoporotic fracture is the selective case-finding approach of the Royal College of Physicians (RCP). The aim of selective case finding approaches is to identify those women who will benefit the most from treatment without

TABLE 43 *T–scores and risk thresholds by CRF for strontium ranelate at 50 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–4.7	4.34	–4.4	3.23
Parental fracture	–4.5	5.00	–4.2	4.00
Current smoking	–4.3	4.26	–4	3.14
Corticosteroid use	–4.1	4.39	–3.9	3.69
Alcohol > 2 units per day	–4.3	4.10	–4.1	3.39
Rheumatoid arthritis	–4.4	4.44	–4.1	3.36
Parental fracture and smoking	–4.1	4.75	–3.8	3.75
Parental fracture and corticosteroid use	–3.9	5.67	–3.5	4.46
Parental fracture and alcohol > 2 units per day	–4.2	5.30	–3.8	3.99
Parental fracture and rheumatoid arthritis	–4.2	5.39	–3.8	4.13
Current smoking and corticosteroid use	–3.7	4.24	–3.5	3.53
Current smoking and alcohol > 2 units per day	–3.9	4.01	–3.7	3.29
Current smoking and rheumatoid arthritis	–4	4.34	–3.7	3.24
Corticosteroid use and alcohol > 2 units per day	–3.8	4.62	–3.5	3.59
Corticosteroid use and rheumatoid arthritis	–3.8	4.62	–3.5	3.64
Alcohol > 2 units per day and rheumatoid arthritis	–4	4.24	–3.8	3.54
3 risk factors excluding parental fracture	–3.5	4.69	–3.2	3.63
3 risk factors including parental fracture	–3.7	5.65	–3.3	4.38

TABLE 44 *T-scores and risk thresholds by CRF for strontium ranelate at 55 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–4.7	4.14	–4.4	3.19
Parental fracture	–4.5	5.12	–4.1	3.96
Current smoking	–4.3	4.13	–4	3.14
Corticosteroid use	–4.1	4.45	–3.8	3.54
Alcohol > 2 units per day	–4.4	4.42	–4.1	3.41
Rheumatoid arthritis	–4.4	4.37	–4.1	3.42
Parental fracture and smoking	–4.1	4.88	–3.7	3.70
Parental fracture and corticosteroid use	–3.7	5.41	–3.2	4.21
Parental fracture and alcohol > 2 units per day	–4.1	5.15	–3.7	4.03
Parental fracture and rheumatoid arthritis	–4.1	5.30	–3.6	3.99
Current smoking and corticosteroid use	–3.7	4.35	–3.4	3.40
Current smoking and alcohol > 2 units per day	–4	4.40	–3.7	3.36
Current smoking and rheumatoid arthritis	–4	4.33	–3.7	3.33
Corticosteroid use and alcohol > 2 units per day	–3.8	4.76	–3.4	3.54
Corticosteroid use and rheumatoid arthritis	–3.8	4.80	–3.4	3.62
Alcohol > 2 units per day and rheumatoid arthritis	–4.1	4.67	–3.7	3.39
3 risk factors excluding parental fracture	–3.4	4.51	–3.1	3.60
3 risk factors including parental fracture	–3.5	5.33	–3	4.08

TABLE 45 *T-scores and risk thresholds by CRF for strontium ranelate at 60 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
No CRFs	–4.8	4.50	–4.4	3.28
Parental fracture	–4.4	5.04	–4	4.00
Current smoking	–4.3	4.21	–4	3.27
Corticosteroid use	–4.1	4.65	–3.7	3.51
Alcohol > 2 units per day	–4.4	4.50	–4	3.30
Rheumatoid arthritis	–4.4	4.48	–4	3.33
Parental fracture and smoking	–4	4.80	–3.6	3.73
Parental fracture and corticosteroid use	–3.6	5.52	–3.1	4.34
Parental fracture and alcohol > 2 units per day	–4	5.13	–3.5	3.89
Parental fracture and rheumatoid arthritis	–4	5.33	–3.5	4.09
Current smoking and corticosteroid use	–3.7	4.61	–3.3	3.41
Current smoking and alcohol > 2 units per day	–3.9	4.19	–3.6	3.28
Current smoking and rheumatoid arthritis	–4	4.50	–3.6	3.27
Corticosteroid use and alcohol > 2 units per day	–3.7	4.69	–3.3	3.56
Corticosteroid use and rheumatoid arthritis	–3.7	4.75	–3.3	3.66
Alcohol > 2 units per day and rheumatoid arthritis	–4	4.50	–3.6	3.36
3 risk factors excluding parental fracture	–3.3	4.51	–3	3.65
3 risk factors including parental fracture	–3.4	5.43	–2.9	4.19

TABLE 46 *T-scores and risk thresholds by CRF for strontium ranelate at 65 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
No CRFs	–4.6	4.43	–4.2	3.41
Parental fracture	–4	5.10	–3.4	3.69
Current smoking	–4.2	4.46	–3.8	3.35
Corticosteroid use	–3.8	4.63	–3.4	3.67
Alcohol > 2 units per day	–4.2	4.54	–3.8	3.49
Rheumatoid arthritis	–4.2	4.60	–3.8	3.58
Parental fracture and smoking	–3.5	4.60	–3.1	3.63
Parental fracture and corticosteroid use	–3.1	5.40	–2.4	3.89
Parental fracture and alcohol > 2 units per day	–3.5	4.96	–3	3.80
Parental fracture and rheumatoid arthritis	–3.5	5.17	–2.9	3.82
Current smoking and corticosteroid use	–3.4	4.51	–3	3.49
Current smoking and alcohol > 2 units per day	–3.7	4.24	–3.3	3.21
Current smoking and rheumatoid arthritis	–3.8	4.56	–3.4	3.47
Corticosteroid use and alcohol > 2 units per day	–3.4	4.76	–2.9	3.57
Corticosteroid use and rheumatoid arthritis	–3.4	4.91	–2.9	3.73
Alcohol > 2 units per day and rheumatoid arthritis	–3.8	4.72	–3.3	3.47
3 risk factors excluding parental fracture	–3	4.60	–2.6	3.62
3 risk factors including parental fracture	–2.8	5.03	–2.3	3.92

TABLE 47 *T-scores and risk thresholds by CRF for strontium ranelate at 70 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–4.3	4.64	–3.7	3.35
Parental fracture	–3.1	4.32	–2.6	3.26
Current smoking	–3.8	4.25	–3.3	3.17
Corticosteroid use	–3.3	4.66	–2.7	3.48
Alcohol > 2 units per day	–3.8	4.54	–3.2	3.29
Rheumatoid arthritis	–3.8	4.71	–3.2	3.45
Parental fracture and smoking	–2.7	4.26	–2.2	3.13
Parental fracture and corticosteroid use	–2.2	4.52	–1.6	3.37
Parental fracture and alcohol > 2 units per day	–2.7	4.48	–2.1	3.19
Parental fracture and rheumatoid arthritis	–2.6	4.36	–2.1	3.33
Current smoking and corticosteroid use	–2.9	4.38	–2.4	3.35
Current smoking and alcohol > 2 units per day	–3.4	4.42	–2.9	3.29
Current smoking and rheumatoid arthritis	–3.4	4.51	–2.8	3.22
Corticosteroid use and alcohol > 2 units per day	–2.8	4.58	–2.2	3.42
Corticosteroid use and rheumatoid arthritis	–2.8	4.82	–2.1	3.48
Alcohol > 2 units per day and rheumatoid arthritis	–3.3	4.61	–2.7	3.39
3 risk factors excluding parental fracture	–2.5	4.63	–1.9	3.41
3 risk factors including parental fracture	–2	4.53	–1.3	3.27

TABLE 48 *T-scores and risk thresholds by CRF for strontium ranelate at 75 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–3.9	4.62	–3.3	3.41
Parental fracture	–2.5	4.22	–2	3.14
Current smoking	–3.5	4.48	–3	3.40
Corticosteroid use	–2.9	4.77	–2.2	3.41
Alcohol > 2 units per day	–3.4	4.57	–2.8	3.36
Rheumatoid arthritis	–3.4	4.76	–2.8	3.54
Parental fracture and smoking	–1.9	3.88	–1.4	3.00
Parental fracture and corticosteroid use	–1.5	4.36	–0.8	3.26
Parental fracture and alcohol > 2 units per day	–2	4.19	–1.4	3.14
Parental fracture and rheumatoid arthritis	–2	4.25	–1.4	3.23
Current smoking and corticosteroid use	–2.5	4.49	–1.9	3.30
Current smoking and alcohol > 2 units per day	–3	4.44	–2.4	3.18
Current smoking and rheumatoid arthritis	–3	4.56	–2.4	3.30
Corticosteroid use and alcohol > 2 units per day	–2.4	4.70	–1.7	3.47
Corticosteroid use and rheumatoid arthritis	–2.4	4.95	–1.5	3.47
Alcohol > 2 units per day and rheumatoid arthritis	–2.9	4.70	–2.3	3.49
3 risk factors excluding parental fracture	–2	4.54	–1.2	3.37
3 risk factors including parental fracture	–1.1	4.21	–0.5	3.23

TABLE 49 *T-scores and risk thresholds by CRF for strontium ranelate at 80 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
No CRFs	–3.4	4.30	–2.8	3.19
Parental fracture	–1.7	3.68	–1.1	2.83
Current smoking	–2.9	3.99	–2.4	3.06
Corticosteroid use	–2.3	4.27	–1.5	3.20
Alcohol > 2 units per day	–2.8	4.08	–2.3	3.17
Rheumatoid arthritis	–2.8	4.25	–2.2	3.16
Parental fracture and smoking	–1	3.53	–0.5	2.79
Parental fracture and corticosteroid use	–0.5	3.84	0.1	3.02
Parental fracture and alcohol > 2 units per day	–1.1	3.78	–0.5	2.90
Parental fracture and rheumatoid arthritis	–1.1	3.83	–0.5	2.97
Current smoking and corticosteroid use	–1.7	3.91	–1	3.00
Current smoking and alcohol > 2 units per day	–2.4	4.02	–1.7	2.93
Current smoking and rheumatoid arthritis	–2.3	3.89	–1.7	3.03
Corticosteroid use and alcohol > 2 units per day	–1.6	4.15	–0.8	3.16
Corticosteroid use and rheumatoid arthritis	–1.5	4.22	–0.6	3.15
Alcohol > 2 units per day and rheumatoid arthritis	–2.3	4.22	–1.5	3.12
3 risk factors excluding parental fracture	–1.1	4.09	–0.3	3.07
3 risk factors including parental fracture	–0.1	3.76	0.5	2.92

TABLE 50 *T-scores and risk thresholds by CRF for alendronate at 50 years of age*

CRFs present	MAICER of £20K		MAICER of £30K	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
No CRFs	–4	2.26	–3.7	1.78
Parental fracture	–3.8	3.09	–3.5	2.62
Current smoking	–3.6	2.16	–3.3	1.68
Corticosteroid use	–3.4	2.51	–3.2	2.20
Alcohol > 2 units per day	–3.6	2.20	–3.4	1.90
Rheumatoid arthritis	–3.7	2.41	–3.4	1.94
Parental fracture and smoking	–3.4	2.85	–3.1	2.39
Parental fracture and corticosteroid use	–3.2	3.83	–2.8	3.21
Parental fracture and alcohol > 2 units per day	–3.5	3.32	–3.1	2.69
Parental fracture and rheumatoid arthritis	–3.5	3.47	–3.1	2.85
Current smoking and corticosteroid use	–3	2.35	–2.8	2.04
Current smoking and alcohol > 2 units per day	–3.2	2.09	–3	1.78
Current smoking and rheumatoid arthritis	–3.3	2.29	–3	1.81
Corticosteroid use and alcohol > 2 units per day	–3.1	2.68	–2.8	2.21
Corticosteroid use and rheumatoid arthritis	–3.1	2.76	–2.8	2.31
Alcohol > 2 units per day and rheumatoid arthritis	–3.4	2.56	–3.1	2.07
3 risk factors excluding parental fracture	–2.8	2.69	–2.5	2.21
3 risk factors including parental fracture	–3	3.71	–2.6	3.08

TABLE 51 *T-scores and risk thresholds by CRF for alendronate at 55 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–4	2.33	–3.7	1.89
Parental fracture	–3.7	3.17	–3.3	2.61
Current smoking	–3.6	2.25	–3.3	1.79
Corticosteroid use	–3.4	2.69	–3	2.12
Alcohol > 2 units per day	–3.6	2.32	–3.3	1.90
Rheumatoid arthritis	–3.7	2.54	–3.4	2.09
Parental fracture and smoking	–3.3	2.91	–3	2.48
Parental fracture and corticosteroid use	–3	3.85	–2.4	3.03
Parental fracture and alcohol > 2 units per day	–3.3	3.25	–2.9	2.70
Parental fracture and rheumatoid arthritis	–3.3	3.44	–2.9	2.89
Current smoking and corticosteroid use	–3	2.54	–2.7	2.09
Current smoking and alcohol > 2 units per day	–3.2	2.23	–2.9	1.79
Current smoking and rheumatoid arthritis	–3.3	2.43	–2.9	1.83
Corticosteroid use and alcohol > 2 units per day	–3	2.72	–2.7	2.29
Corticosteroid use and rheumatoid arthritis	–3	2.83	–2.7	2.40
Alcohol > 2 units per day and rheumatoid arthritis	–3.3	2.55	–3	2.11
3 risk factors excluding parental fracture	–2.7	2.74	–2.3	2.17
3 risk factors including parental fracture	–2.8	3.71	–2.3	2.99

TABLE 52 *T-scores and risk thresholds by CRF for alendronate at 60 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–4	2.46	–3.6	1.89
Parental fracture	–3.6	3.25	–3.2	2.69
Current smoking	–3.5	2.23	–3.2	1.81
Corticosteroid use	–3.3	2.73	–2.9	2.18
Alcohol > 2 units per day	–3.6	2.49	–3.2	1.93
Rheumatoid arthritis	–3.6	2.54	–3.2	2.00
Parental fracture and smoking	–3.2	2.97	–2.8	2.43
Parental fracture and corticosteroid use	–2.8	3.81	–2.3	3.12
Parental fracture and alcohol > 2 units per day	–3.2	3.34	–2.7	2.67
Parental fracture and rheumatoid arthritis	–3.2	3.55	–2.7	2.86
Current smoking and corticosteroid use	–2.9	2.59	–2.5	2.02
Current smoking and alcohol > 2 units per day	–3.1	2.25	–2.8	1.83
Current smoking and rheumatoid arthritis	–3.1	2.28	–2.8	1.88
Corticosteroid use and alcohol > 2 units per day	–2.9	2.79	–2.5	2.23
Corticosteroid use and rheumatoid arthritis	–2.9	2.90	–2.5	2.35
Alcohol > 2 units per day and rheumatoid arthritis	–3.2	2.59	–2.8	2.04
3 risk factors excluding parental fracture	–2.5	2.66	–2.1	2.13
3 risk factors including parental fracture	–2.6	3.65	–2.1	2.95

TABLE 53 *T-scores and risk thresholds by CRF for alendronate at 65 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
No CRFs	–3.8	2.67	–3.4	2.13
Parental fracture	–3.1	3.18	–2.6	2.53
Current smoking	–3.3	2.41	–2.9	1.90
Corticosteroid use	–3	2.96	–2.5	2.31
Alcohol > 2 units per day	–3.3	2.59	–2.9	2.08
Rheumatoid arthritis	–3.4	2.85	–2.9	2.19
Parental fracture and smoking	–2.7	2.92	–2.2	2.27
Parental fracture and corticosteroid use	–2.2	3.57	–1.6	2.79
Parental fracture and alcohol > 2 units per day	–2.7	3.28	–2.2	2.61
Parental fracture and rheumatoid arthritis	–2.7	3.48	–2.1	2.68
Current smoking and corticosteroid use	–2.6	2.76	–2.1	2.11
Current smoking and alcohol > 2 units per day	–2.9	2.47	–2.5	1.95
Current smoking and rheumatoid arthritis	–2.9	2.54	–2.5	2.02
Corticosteroid use and alcohol > 2 units per day	–2.6	3.04	–2.1	2.38
Corticosteroid use and rheumatoid arthritis	–2.6	3.20	–2.1	2.53
Alcohol > 2 units per day and rheumatoid arthritis	–2.9	2.77	–2.5	2.25
3 risk factors excluding parental fracture	–2.2	2.91	–1.7	2.26
3 risk factors including parental fracture	–2	3.41	–1.5	2.75

TABLE 54 *T-scores and risk thresholds by CRF for alendronate at 70 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**	***T*-score threshold (SD)**	**Annual absolute risk threshold (%)**
No CRFs	–3.4	2.87	–2.8	2.15
Parental fracture	–2.2	2.64	–1.7	2.06
Current smoking	–2.9	2.54	–2.4	1.96
Corticosteroid use	–2.5	3.17	–1.8	2.33
Alcohol > 2 units per day	–2.9	2.82	–2.4	2.22
Rheumatoid arthritis	–2.9	2.98	–2.3	2.26
Parental fracture and smoking	–1.8	2.49	–1.2	1.92
Parental fracture and corticosteroid use	–1.2	2.94	–0.5	2.38
Parental fracture and alcohol > 2 units per day	–1.8	2.73	–1.1	2.09
Parental fracture and rheumatoid arthritis	–1.8	2.86	–1.1	2.23
Current smoking and corticosteroid use	–2.1	2.88	–1.5	2.22
Current smoking and alcohol > 2 units per day	–2.5	2.63	–2	2.03
Current smoking and rheumatoid arthritis	–2.5	2.74	–2	2.14
Corticosteroid use and alcohol > 2 units per day	–2	3.12	–1.2	2.36
Corticosteroid use and rheumatoid arthritis	–1.9	3.19	–1.1	2.48
Alcohol > 2 units per day and rheumatoid arthritis	–2.4	2.93	–1.8	2.23
3 risk factors excluding parental fracture	–1.6	2.99	–0.8	2.34
3 risk factors including parental fracture	–0.9	2.83	–0.2	2.27

TABLE 55 *T-scores and risk thresholds by CRF for alendronate at 75 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–3	2.94	–2.4	2.22
Parental fracture	–1.4	2.41	–0.8	1.90
Current smoking	–2.5	2.61	–2	2.02
Corticosteroid use	–2	3.11	–1.2	2.42
Alcohol > 2 units per day	–2.5	2.90	–1.9	2.19
Rheumatoid arthritis	–2.4	2.92	–1.8	2.26
Parental fracture and smoking	–0.7	2.17	–0.2	1.75
Parental fracture and corticosteroid use	–0.3	2.70	0.4	2.13
Parental fracture and alcohol > 2 units per day	–0.8	2.43	–0.2	1.93
Parental fracture and rheumatoid arthritis	–0.8	2.53	–0.2	2.03
Current smoking and corticosteroid use	–1.5	2.86	–0.8	2.27
Current smoking and alcohol > 2 units per day	–2	2.57	–1.4	2.04
Current smoking and rheumatoid arthritis	–2	2.69	–1.3	2.08
Corticosteroid use and alcohol > 2 units per day	–1.4	3.15	–0.5	2.42
Corticosteroid use and rheumatoid arthritis	–1.3	3.27	–0.4	2.53
Alcohol > 2 units per day and rheumatoid arthritis	–1.9	2.90	–1.2	2.32
3 risk factors excluding parental fracture	–0.9	3.05	–0.1	2.39
3 risk factors including parental fracture	0.1	2.55	0.7	2.05

TABLE 56 *T-scores and risk thresholds by CRF for alendronate at 80 years of age*

CRFs present	MAICER of £20,000		MAICER of £30,000	
	T-score threshold (SD)	Annual absolute risk threshold (%)	*T*-score threshold (SD)	Annual absolute risk threshold (%)
No CRFs	–2.3	2.50	–1.7	2.02
Parental fracture	–0.4	2.13	0.1	1.75
Current smoking	–1.7	2.27	–1.1	1.82
Corticosteroid use	–1	2.72	–0.3	2.19
Alcohol > 2 units per day	–1.7	2.52	–1	1.99
Rheumatoid arthritis	–1.6	2.58	–0.9	2.06
Parental fracture and smoking	0.3	1.96	0.8	1.59
Parental fracture and corticosteroid use	0.8	2.32	>1	NA
Parental fracture and alcohol > 2 units per day	0.3	2.09	0.8	1.73
Parental fracture and rheumatoid arthritis	0.2	2.25	0.8	1.80
Current smoking and corticosteroid use	–0.5	2.52	0.2	1.99
Current smoking and alcohol > 2 units per day	–1	2.24	–0.5	1.86
Current smoking and rheumatoid arthritis	–1	2.34	–0.4	1.89
Corticosteroid use and alcohol > 2 units per day	–0.4	2.77	0.4	2.17
Corticosteroid use and rheumatoid arthritis	–0.3	2.87	0.5	2.26
Alcohol > 2 units per day and rheumatoid arthritis	–1	2.63	–0.3	2.10
3 risk factors excluding parental fracture	0.2	2.60	0.9	2.08
3 risk factors including parental fracture	>1	NA	>1	NA

incurring large costs in assessing a large number of women who will not benefit from treatment. As BMD is a significant risk factor for fracture, DXA scans are often used when assessing an individual's fracture risk and therefore whether she will benefit from treatment. It is important that any selective case-finding approach makes efficient use of the resources available for DXA scanning. An initial assessment of risk is needed to select women who are at high risk of fracture to be offered DXA scanning, and this is usually based on risk factors for osteoporotic fracture. For example, in the RCP selective case-finding approach, women without a prior fracture receive a DXA scan if they have at least one risk factor for osteoporotic fracture and receive treatment if their *T*-score is below –2.5 SD. The NICEGDG advised the assessment group that it is appropriate for clinicians to treat women at a high risk of fracture without performing a DXA scan if it is unlikely that the DXA scan results would change the estimation of fracture risk enough to alter the decision to treat. This evaluation, therefore, considers identification strategies that allow fracture risk assessment both with and without DXA scanning.

Methodology for finding the optimum identification strategy

To assess the percentage of the population that would be identified by a selective case-finding approach, data were needed on the prevalence of CRFs in UK women. The CRFs were those identified in the WHO study: age, gender, BMI, BMD, parental hip fracture, current smoking, corticosteroid use, alcohol consumption and rheumatoid arthritis. Although a low BMI is shown to be predictive of fracture risk, when BMD is not known, it was omitted from the analyses for a number of reasons. First, the correlation of BMI with BMD seen in the Holt study[12] is low (an r^2 of 0.1). If both BMI and BMD were incorporated, the computational time required would be significantly increased as combinations of BMD and BMI would need to be simulated. Secondly, since BMI is not a predictive factor once BMD is known, the omission only has an influence on those women who do not receive BMD scans. From analyses of the results presented later, the effect of this simplification is likely to be small; however, it is acknowledged that some younger women with CRFs, and a very low BMI may incorrectly not receive a DXA scan.

The following set of groups was defined:

- no CRFs
- smoking only
- steroid use only
- alcohol consumption only
- parental history of hip fracture only
- rheumatoid arthritis osteoporosis only
- smoking and steroid use only
- smoking and alcohol consumption only
- smoking and parental history of hip fracture only
- smoking and rheumatoid arthritis osteoporosis only
- steroid use and alcohol consumption only
- steroid use and parental history of hip fracture only
- steroid use and rheumatoid arthritis osteoporosis only
- alcohol and parental history of hip fracture only
- alcohol and rheumatoid arthritis osteoporosis only
- parental history of hip fracture and rheumatoid arthritis osteoporosis only
- three risk factors including parental history of hip fracture
- three risk factors excluding parental history of hip fracture.

The distinction between the last two groups was made owing to the relatively large risk conferred by parental history of hip fracture at advanced ages.

The investigators wished to correlate BMD with the combinations of CRFs. However, the data from the WHO study were not sufficient to find robust correlations between BMD with single, and particularly, multiple CRFs. The correlation between age and BMD was taken from the Holt data.[12] As such, it had to be assumed that BMD was equal in all age groups. This is likely to be incorrect, in that patients with more risk factors are suspected to have lower BMD values than patients with fewer risk factors. This would have the effect of overestimating the risk in patients with relatively few risk factors and underestimating the risk in patients with a relatively large number of risk factors. In younger patients this may restrict the number of women treated without BMD scans, or who receive BMD scans. In older women this may result in some women incorrectly receiving treatment without BMD scanning, and some incorrectly receiving a BMD scan. Establishing how the CRFs are correlated with BMD is an area in which future research should be undertaken.

The expected *T*-score distribution at the femoral neck for women in each age band was calculated from the Holt database.[12] A linear relationship

between *T*-score and age was assumed. The formula was: *T*-score = 2.0251 – (0.0512 × Age). This formula relates to all women in the database, rather than only those women without a prior fracture. As women with a prior fracture are likely to have a lower BMD than women without a prior fracture, this method will overestimate the risk of women without a prior fracture, with the effect being largest in the higher ages where a higher proportion of women has a prior fracture. A normal distribution around the average *T*-score was assumed, with a mean of 0 and variance of 1. The proportion of women at each age falling within each 0.1 SD step between a *T*-score of –5 and +1 was calculated. An example distribution for 70–74 years of age with a mean *T*-score of –1.69 SD is shown in *Figure 15*. Any values below a *T*-score of –5 SD or above a *T*-score of +1 SD were truncated to –5 SD and +1 SD, respectively.

For each of the defined groups the total risk of fracture was assessed using the methods described in Chapter 2 of this report.

The risk of fracture was then used as an input to the cost-effectiveness model. The incremental net benefit, assuming a threshold of £20,000 per QALY (with £30,000 per QALY used in a sensitivity analysis) of treatment, was calculated for each 0.1 step in *T*-score from –5 to +1 and summated for each defined group.

As expected, the net benefits were highest in the groups with highest risk of fracture. This net benefit excludes the cost of identifying the patient. The resulting net benefit distribution for women aged 70–74 years with no CRFs and for those who have taken corticosteroids is shown in *Figure 16*. The threshold for cost-effective treatment of an individual is where the net benefit distribution crosses the *T*-score axis. Thus, it is anticipated that a woman aged between 70 and 74 years with no CRFs would require a *T*-score of approximately –3.3 SD or lower to be treated cost-effectively with alendronate, whereas a woman using corticosteroids would need a *T*-score of –2.4 or lower to be treated cost-effectively. These data are contained in *Table 54*.

Alendronate was chosen as the drug to be used in evaluating identification strategies since it has better midpoint efficacies than strontium ranelate and is also cheaper.

The *T*-score value for singular and combinations of risk factors for the cost-effective treatment of an individual was calculated; however, the costs of identifying these women were not incorporated into the model, and if these costs were higher than the net benefit accrued by the summation of all the women who can be cost-effectively treated, then the identification strategy as a whole would not be cost-effective.

The optimal identification strategy for women with different ages and CRFs was calculated. Three strategies were evaluated: (a) offer neither treatment nor a BMD scan; (b) offer treatment without a BMD scan; and (c) offer BMD scans to all and treatment to those whose *T*-score shows that they can be treated cost-effectively.

The net benefit for option (a) is assumed to be zero minus the costs of identification, which would

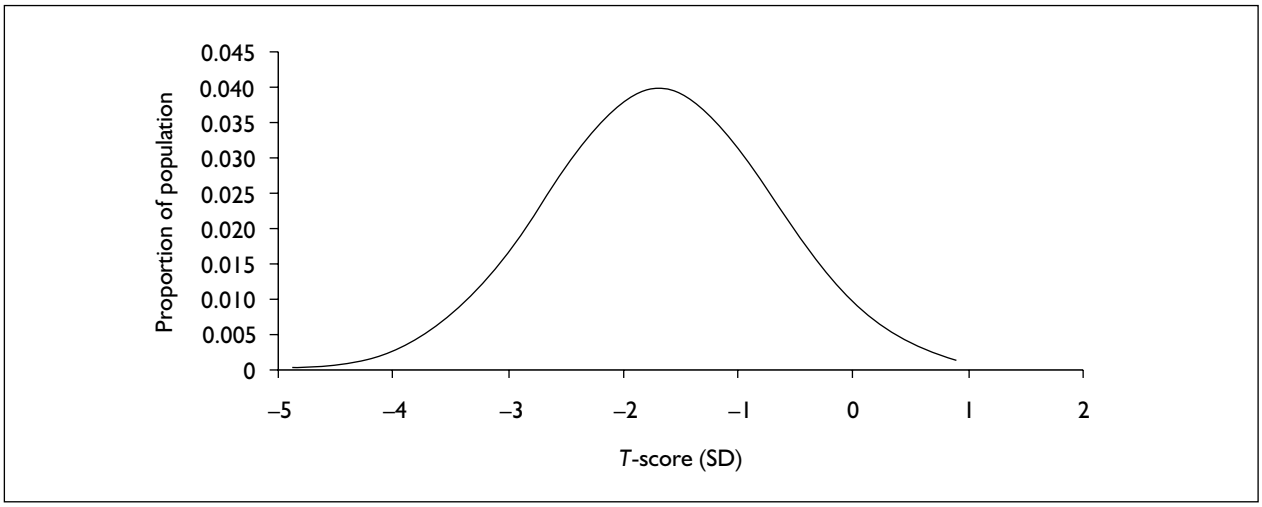

FIGURE 15 *T-score distribution at 70–74 years of age with a mean of –1.69 SD*

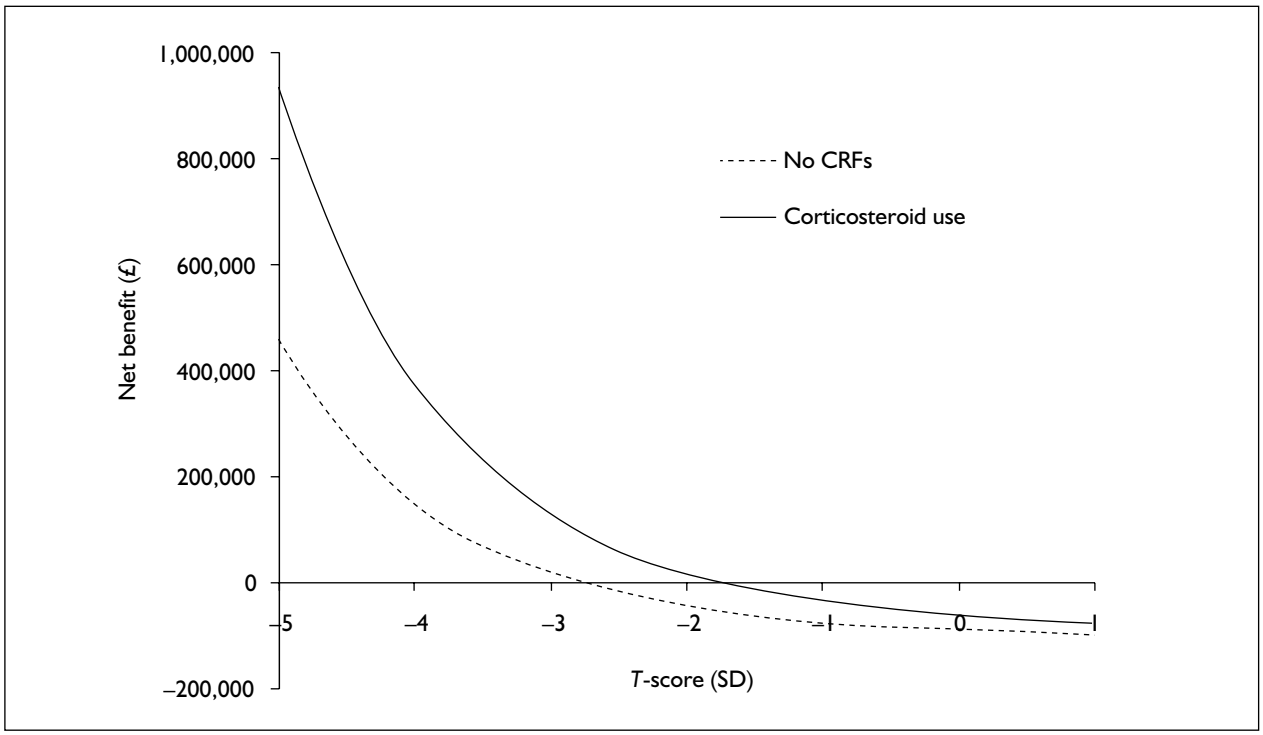

FIGURE 16 *Example net benefit distribution for an individual woman aged 70–74 years, assuming treatment with alendronate and a cost-effectiveness threshold of £20,000*

include the costs of asking the initial questions. The net benefit for option (b) is the number of women in each *T*-score band who can be treated cost-effectively multiplied by the appropriate net benefit from treatment, minus the costs of identification and BMD scanning. The net benefit for option (c) is the number of women multiplied by the appropriate net benefit of treatment minus the cost of identification. The optimal strategy for each defined group is the strategy with the highest net benefit. This does allow the possibility that some women are inappropriately treated; however, this inefficiency is less than that associated with the number of BMD scans that would be required to exclude these women from treatment.

The decision on whether an identification strategy should be initiated is dependent on the sum of the highest net benefit from each of the defined groups. If the sum of net benefits is positive then an identification strategy is cost-effective. Conversely, if the sum of net benefits is negative then an identification strategy is not cost-effective. In the latter example, it is acknowledged that some patients could have been treated cost-effectively, but the identification costs of finding these people were prohibitive. The net benefit of the identification strategy as a whole is relative to a strategy of no identification.

In addition to calculating the total net benefit of implementing the optimal identification strategy for each age band, this was compared with the total net benefit of current standard practice, which was taken to be the RCP selective case-finding approach for identifying women at risk of osteoporotic fracture. This was modelled as offering DXA scans to those with one or more CRF and treating those with a BMD of –2.5 SD or less. The total net benefit was calculated in the same manner with the same assumptions for the cost of identification.

Identification costs

It was assumed that the initial risk assessment, which takes the form of questions regarding a woman's CRF, would be opportunistic and occur while the woman was consulting the GP for a non-osteoporosis-related reason. This was assumed to incur an opportunity cost of 3 minutes of GP time. The average cost for 1 minute of GP surgery consultation time is costed at £1.92.[91] Following the initial risk assessment the GP would consult the algorithm, which provides the GP with the optimum strategy for further risk assessment and treatment. If treatment is to be initiated without a DXA scan then a 10-minute appointment is booked to discuss osteoporosis and initiate treatment. If a

DXA scan is required then this is booked and the costs are accumulated. After the DXA scan a 10-minute appointment is required to discuss the DXA results and reassure the patient that treatment is not required or to initiate treatment. A further 2 minutes of GP time is added to the initial appointment for those who require a DXA scan to discuss why they are being referred for a scan (*Figure 17*).

Following initiation of treatment, the NICEGDG assumed that as there are requirements to review all medications in the elderly, for women over the age of 75 years this would be done at the same GP consultation where other medications are reviewed, and a marginal cost of zero was applied. For women under 75 years of age, the GPs on the NICEGDG estimated that two-thirds of the population would already be on long-term medication, and that an additional one-third of the population would be reviewed annually, each incurring a cost of £18.[91]

It was assumed that all women without a prior fracture would be applicable for assessment.

The model allows the uptake of assessment by a GP and the uptake of BMD scans to be varied. In the base-case analysis it is assumed that the compliance rates for both GP assessment and BMD scanning are 100%, but this has been explored in sensitivity analyses.

The number of women in England and Wales is needed to estimate the full costs of identification strategies. These are given in *Table 57*.[95]

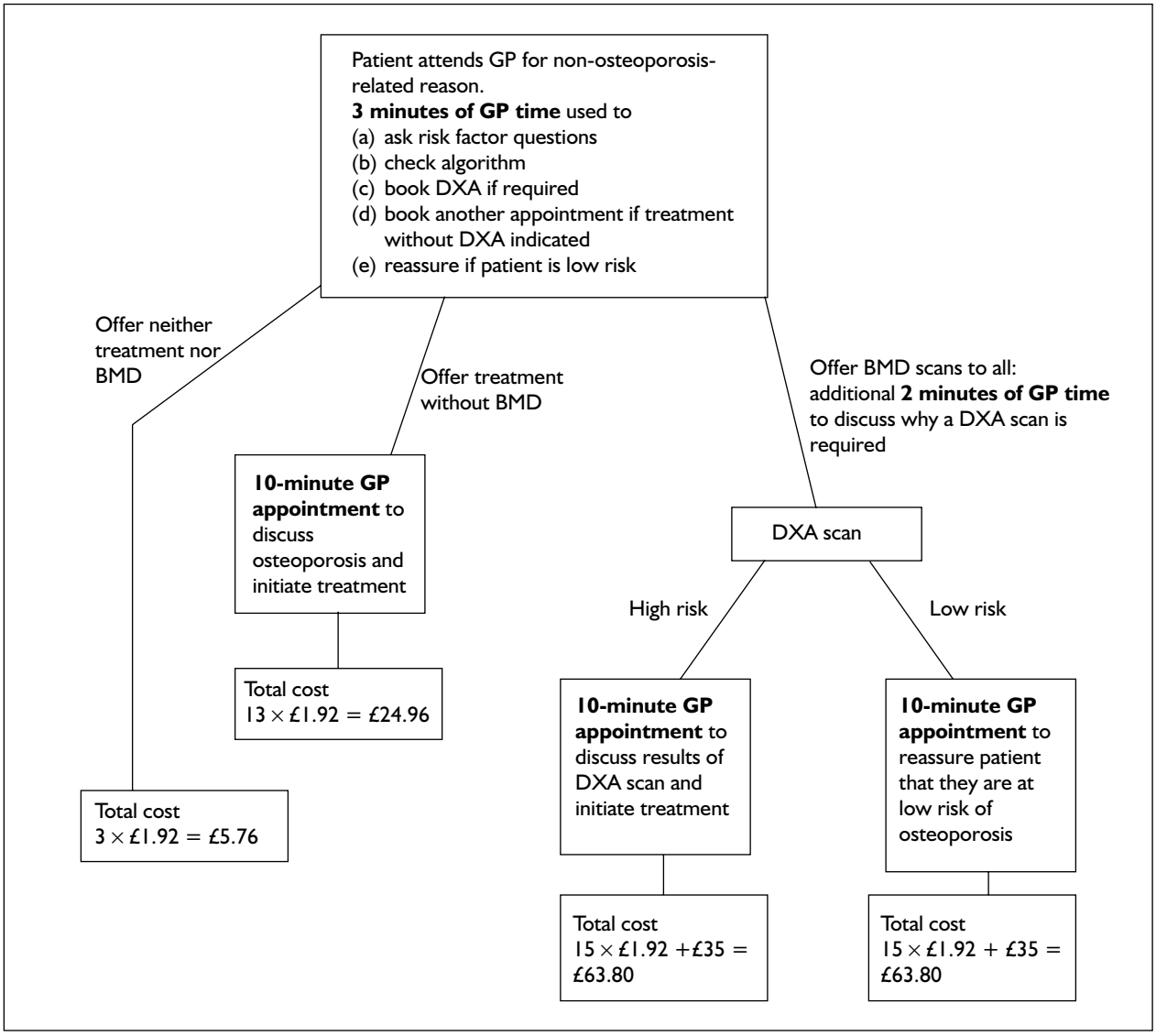

FIGURE 17 *Identification costs*

TABLE 57 *Number of women in England and Wales*

Age (years)	No. of women in England and Wales (thousands)
50–54	1242
55–59	1310
60–64	982
65–69	879
70–74	774
75–79	581
≥ 80	900

Results

The identification strategies that are cost-effective at a £30,000 cost per QALY threshold using the WHO algorithm are as follows.

- Between 50 and 64 years: no identification strategy is cost-effective.
- Between 65 and 69 years: offer BMD scans to all women except for those without CRFs, those who smoke only, those who consume alcohol only and those with rheumatoid arthritis only.
- Between 70 and 74 years: treat women with three or more CRFs or who have a parental history of hip fracture and who use corticosteroids. Offer BMD scans to all other women.
- Between 75 and 79 years: treat women with three or more CRFs or who use corticosteroids and smoke, or who use corticosteroids and consume alcohol, or who use corticosteroids and have rheumatoid arthritis, or who have a parental history of hip fracture. Offer BMD scans to all other women.
- Aged 80 years and over: treat all women with one or more CRF and offer BMD scans to those with no CRFs.

The identification strategies that are cost-effective at a £20,000 cost per QALY threshold using the WHO algorithm are as follows.

- Between 50 and 69 years: no identification strategy is cost-effective.
- Between 70 and 74 years: offer BMD scans to all women except for those without CRFs.
- Between 75 and 79 years: treat women with three or more CRFs or who have a parental history of hip fracture and another CRF. Offer BMD scans to all other women.
- Aged 80 years and over: treat all women with parental fracture alone, corticosteroid use alone or any two or more CRFs. Offer BMD scanning to all other women.

The expected net benefit of implementing an identification strategy assuming a MAICER of £30,000 for each age band is presented in *Table 58*. Although some women can be cost-effectively treated at ages below 65 years, the benefit of treating these women is outweighed by the identification costs. It is only at ages of 65 years and above that enough benefit is achieved from treating to make it worthwhile using an identification strategy. Since all women may be cost-effectively treated at 80 years and over, the identification costs at this age may be overestimated; however, these have not been adjusted.

The expected net benefit of implementing an identification strategy assuming a MAICER of £20,000 for each age band is presented in *Table 59*.

From these tables, it is seen that the likely net expenditure (cost of risk assessment and BMD scans plus net costs of treatment) over the 10-year time-horizon would be £0.84 billion using a

TABLE 58 *Optimum strategy results from the WHO algorithm when assuming treatment with alendronate and a MAICER of £30,000*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
50–64	0	0	0	0	0	0	0
65–69	879	156	13.6	27	24.6	21.8	8.2
70–74	774	770	46.0	171	154.7	136.0	90.0
75–79	581	535	30.3	257	185.9	293.4	263.1
≥ 80	900	716	37.0	692	346.8	924.0	887.0
Total	3134	2177	126.9	1147	712.0	1375.2	1248.3

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 59 *Optimum strategy results from the WHO algorithm when assuming treatment with alendronate and a MAICER of £20,000*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
50–69	0	0	0	0	0	0	0
70–74	774	234	17.1	51	34.5	45.8	28.7
75–79	581	566	33.7	145	73.9	155.9	122.2
≥ 80	900	809	44.3	502	177.3	536.3	492.0
Total	2255	1609	95.1	698	285.7	738.0	642.9

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 60 *Results from the RCP guidelines when assuming treatment with alendronate and a MAICER of £30,000*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who are treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treatment (£ million)	Total net benefit of identification strategy (£ million)
50–54	1242	287	23.6	11	11.8	–3.7	–27.3
55–59	1310	498	35.9	31	33.9	–3.6	–39.5
60–64	982	344	25.0	35	36.3	2.3	–22.7
65–69	879	310	22.2	48	44.6	26.1	3.9
70–74	774	234	17.0	52	37.0	80.2	63.2
75–79	581	150	11.2	46	5.4	143.0	131.8
≥ 80	900	184	14.5	74	–33.7	300.0	285.5
Total	6668	2007	149.4	297	135.3	544.3	394.9

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 61 *Results from the RCP guidelines when assuming treatment with alendronate and a MAICER of £20,000*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who are treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
50–54	1242	287	23.6	11	11.8	–6.4	–30
55–59	1310	498	35.9	32	33.9	–13.7	–49.6
60–64	982	344	25.0	35	36.3	–10.5	–35.5
65–69	879	310	22.2	48	44.6	2.5	–19.7
70–74	774	234	17.0	52	37.0	41.1	24.1
75–79	581	150	11.2	46	5.4	93.5	82.3
≥ 8	900	184	14.5	74	–33.7	211.2	196.8
Total	6668	2007	149.4	298	135.3	317.7	168.4

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

MAICER of £30,000 and £0.38 billion using a MAICER of £20,000, and assuming that capacity was available for this quantity of BMD scanning. After the initial introduction of identification strategies, it is likely that the annual costs will be approximately 20% of these figures, assuming that women are evaluated on their 65th, 70th, 75th and 80th birthdays, as appropriate. The majority of these costs is associated with the acquisition of the intervention.

So that the costs from the identification strategy can be compared with the current guidelines, the costs from the RCP approach (assuming that it is fully utilised) have also been estimated. These are detailed in *Tables 60* and *61*.

At both MAICERs the RCP guideline is, on average, treating patients who are not cost-effective below the age of 65 years. This approach only becomes cost-effective at the age of 70 years and over when a cost per QALY threshold of £20,000 is assumed.

The net cost of the RCP strategy is £285 million, regardless of the MAICER threshold used. The value does not change because the decision to treat is made not on cost-effectiveness grounds, but on whether the woman has a *T*-score below –2.5 SD.

While the identification strategies that are suggested by the WHO algorithm cost more than the RCP strategy, there is clearly a gain in the overall health of the population, which is shown by comparing the net benefits gained through the WHO algorithm approach and the RCP approach.

Cost implications of using strontium ranelate in women without a prior fracture

From the cost-effectiveness results presented previously, strontium ranelate appears to be less cost-effective than the bisphosphonate alendronate. The characteristics of women in whom strontium ranelate can be used cost-effectively were given in *Tables 43–49*. Given that the number of women who will be treated with strontium ranelate is expected to be low, the cost implications have not been evaluated; however, it is noted that the expected net benefit of the identification strategy is likely to decrease and the total costs of acquiring drugs for osteoporosis are likely to increase.

Sensitivity analyses

Several sensitivity analyses were run to explore the impact of changing variables on the cost-effectiveness for identification strategies. These are contained in detail in Appendix 11.

The inclusion of morphometric vertebral fractures in the model had little impact on the overall cost-effectiveness.

Doubling the time required for the GP to undertake the initial assessment and discuss a BMD scan did not alter the identification strategy assuming a MAICER of £20,000. However, when the baseline times for undertaking the assessment and discussing the BMD scan were halved, identification strategies could be implemented in the 65–69-year age band.

The addition of an extra £5 cost incurred by the NHS above that of a BMD scan, to cover the costs of administering the system, did not result in identification strategies in the 70–74-year age group becoming non-cost-effective.

Compliance with drug use was investigated. If an assumption was made that non-compliance was associated with 6 months' drug cost but no benefit accrued, the identification strategy aimed at 70–74-year-olds was no longer cost-effective at compliance levels of 25%. This level of compliance also resulted in the identification strategy becoming cost-ineffective when only 1 month of drug treatment was assumed to be prescribed.

When additional GP costs were incorporated to address the costs of women changing from one drug to another, the identification strategies selected were still cost-effective.

Simplified identification strategies for use in clinical practice

The optimum strategies for women without a prior fracture, as outlined in the section 'Results' (p. 59), require the treating physician to have access to the recommended course of action for each combination of CRFs. This detailed information cannot easily be presented in a quick reference form and is therefore not very practical for clinical use. To address this issue, a simplified strategy was developed which assigns a specific number of points to each CRF and recommends one course of action for each number of points. This was done by considering which risk factors had similar intervention thresholds and assigning them a similar number of points. The aim was to keep the strategy simple while trying to minimise the difference from the full strategy in terms of the number of patients receiving treatment and

TABLE 62 *CRF scores*

CRF	Score
Parental history of hip fracture	2
Alcohol consumption >2 units per day	1
Ever use of glucocorticoids	1
Rheumatoid arthritis	1
Current smoking	1

TABLE 63 *Simplified strategy for women with no prior fracture (assumes treatment with alendronate and a cost per QALY threshold of £20,000)*

	No. of 'CRF points' (see *Table 62*)			
Age (years)	**0**	**1**	**2**	**3 or more**
50–69	Reassure/lifestyle advice			
70–74	Reassure/lifestyle advice	DXA and treat at *T*-score ≤ –2.8	DXA and treat at *T*-score ≤ –2.3	DXA and treat at *T*-score ≤ –1.7
75–79	DXA and treat at *T*-score ≤ –3.0	DXA and treat at *T*-score ≤ –2.3	DXA and treat at *T*-score ≤ –1.5	Treat without DXA
≥ 80	DXA and treat at *T*-score ≤ –2.3	DXA and treat at *T*-score ≤ –1.5	Treat without DXA	Treat without DXA

the total net benefit. The resulting point-scoring system is shown in *Table 62*. The simplified strategy for women with no prior fracture is shown in *Table 63*. It assumes a cost per QALY threshold of £20,000 and treatment with alendronate. The result of using this simplified strategy as opposed to the full strategy described in the section 'Results' (p. 59) is to reduce the number of patients treated and the overall net benefit by less than 1%.

Chapter 5

Implications for other parties

The main increase in workload that could arise for the intervention strategies evaluated in this report is for GPs, and for the workforce that undertakes DXA scanning. The time implications for GPs may be quite considerable; however, a costing of this time has been undertaken. Similarly, the costs of DXA scanning have been incorporated, but no evaluation of whether there is capacity in the UK system to perform these scans has been undertaken. If there are substantial costs in establishing scanning centres to perform these tests, then the inferred decision may change.

There is however, expected to be a large net benefit gained from treating women (over £600 million, when using a MAICER of £20,000) and the decision would still be correct provided the costs of establishing sufficient BMD capacity did not exceed this figure.

Chapter 6
Discussion

The efficacy of strontium ranelate at the hip is uncertain, and for all women with osteoporosis is non-significant. Analyses were, however, carried out assuming a beneficial effect at the hip, taking the mean relative risk from the trials. Subgroup analyses undertaken by the manufacturer of the intervention showed a significant and more efficacious effect in older women (aged 74 years and upwards).

On the advice of the NICEGDG, all interventions for the prevention of osteoporotic fractures are assumed to have the same efficacy regardless of the *T*-score, prior fracture history or age of the woman. If strontium ranelate does have a differential effect based on the characteristics (and absolute fracture risk) of a woman, this needs to be proven.

Diseases where possible links with osteoporosis treatments may exist, such as Alzheimer's disease, venous thrombolic events and cancer, were excluded from this cost-effectiveness analysis. Since strontium ranelate has been associated with an increased risk of venous thrombosis, it is noted that all cost per QALY results calculated in this report will be favourable to the intervention.

The analyses presented used discount rates of 6% for benefits and 1.5% for costs, as these were the recommended rates at the initiation of the project. These rates have since been revised to 3.5% for both benefits and costs. No formal sensitivity analyses were undertaken; however, it can be stated that the cost per QALY values presented in the report will be more favourable towards the interventions than if the new rates had been used.

This report has not considered the recent introduction of generic alendronate and has based the acquisition cost of alendronate on the price of Fosamax, at the time of writing. If alendronate were to become widely available at a lower price then this would lower the cost per QALY threshold for treatment with alendronate.

The cost-effectiveness results in the current report differ somewhat from those published by Kanis and colleagues in 2005.[96] Although the two approaches used are difficult to compare directly, there are several differences in the assumptions made that may affect estimates of cost-effectiveness.

First, the costs of the hip fracture differ, not because of the unit costs themselves, since they are taken from the same source,[90] but owing to differences in the proportion of patients assumed to enter nursing homes. Kanis and colleagues assume that 25% of patients enter a nursing home after hip fracture, as given by Torgerson and Dolan,[5] an estimate similar to that for Sweden.[20] The admission rate is assumed to be constant with age. By contrast, the current analysis assumes, from data requested from the authors from an audit in the UK,[34] that no one enters a nursing home below the age of 60 years and that 12% are admitted to nursing homes between the ages of 80 and 89 years. Thus, the difference in overall hip fracture costs are most marked at younger ages, being £5157 at the age of 50 years in the present report and £12,488 in the report of Kanis and colleagues.[96] The differences are less marked at higher ages. The 25% is likely to be an overestimation as it will include women who were already residing in a nursing home; the figures from the audit are likely to be an underestimate since patients originally discharged to the community may subsequently reside in a nursing home following inability to live in the community.

A second difference is the manner in which costs for fractures other than those at the hip have been derived. Kanis and colleagues[96] estimate the costs of fractures other than at the hip as being proportional to their disutility, so-called hip fracture equivalents. The adequacy of this assumption was subsequently tested by Melton and co-workers[97] and found to be reasonably appropriate, at least in a US healthcare setting. Since then, utility losses, particularly for vertebral fracture, have been revised upwards[89] and used in both the present report and that of Kanis.[96] For example, using a utility value of 0.05 for vertebral fracture, vertebral fractures account for 15.1% of the total disutility of osteoporotic fractures at the age of 50–55 years and 17% between the ages of 80 and 85 years. With the revised utilities, the estimate is 48% and 15%, respectively. Since fracture costs are assumed to be proportional to

disutility, the costs of vertebral (and humeral) fractures are also revised upwards. Thus, the costs of fractures are proportionately increased. The present study used a more direct method to evaluate the cost of fractures, but is subject to as many uncertainties as that of Kanis and colleagues.[96]

A third way in which the two approaches differ relates to the efficacy assumed for treatment. Kanis and colleagues have assumed an overall relative risk reduction of 35%, whereas the present report used individual estimates for the relative risk reduction for hip, humeral and vertebral fracture. The site-specific values were 44% at the vertebrae, 37% at the hip and 19% at all other sites.

A further difference relates to the time-horizon used in the respective models. The present model limits the period of analysis to 10 years, but the mathematical model of Kanis[96] continues until the death of the patient. The present results will, therefore, underestimate the long-term disutility in younger women, and will be more unfavourable to the intervention, particularly in younger women. It should be acknowledged that the long-term disutility associated with a fracture (e.g. 10 years after fracture) is fairly poorly researched, and this may be an area for future research. Notwithstanding, Kanis and colleagues discount disutilities at 10% per annum,[96] so this is unlikely to give rise to major discrepancies in cost-effectiveness between the two approaches.

Finally, different mathematical models have been used to assess the cost-effectiveness of interventions. This will have some effect, but is likely to be small. When the present individual patient model and the modelling structure from Kanis[96] were both used with similar cost and epidemiological assumptions to evaluate the cost-effectiveness of risedronante in a previous assessment,[23] the results were broadly comparable.

These considerations suggest that the major reasons for differences between the two analyses reside in the assumptions made on the cost of fractures. It is clear that there is some debate over the true costs of hip fracture, and also costs at other sites, which will have a significant bearing on the estimation of cost-effectiveness. It is recommended that further research be undertaken in this area to produce a more robust value. The level of nursing home admission following a hip fracture in the UK is also uncertain and this should be incorporated into the research agenda so that the full costs of hip fracture are considered.

In general, the assumptions made by Kanis and colleagues[96] were more favourable to the intervention in younger patients than those used in this report, primarily because of the increased costs assumed for fracture.

Vertebral and proximal humerus fractures are proportionally more common in the young, and this is reflected in the results of Kanis,[96] with an increasing risk of hip fracture required for cost-effectiveness as a woman ages. This increase is not seen in the present results, mainly owing to the assumptions being less favourable to the intervention in the young. As such, the total absolute risk required to be cost-effective is greater, at all combinations of age and CRF. To reach the cost-effectiveness threshold, these women require a lower *T*-score at all combinations than in the Kanis paper.[96] Since worsening *Z*-scores have a much greater effect on the hip than at other sites,[10] particularly in the young,[98] the percentage risk of hip fracture to be cost-effective is more equivalent across the ages.

As noted, the thresholds for cost-effectiveness presented in this report and those in the Kanis paper[96] are different, although it was not possible to compare results directly. This is because the starting base for Kanis' analysis is the general population with average risk, onto which additional risks (e.g. prior fracture and low BMD) have been added. By contrast, the present analysis starts with a population with no risk factors on which additional risks are added. Even so, the results at the older ages are generally comparable. In broad terms, the results of Kanis and colleagues[96] suggest that women at average risk could be treated at the age of 75 years, assuming no identification costs and a MAICER of £30,000. Although the results are not directly comparable, as the present study did not evaluate the cost-effectiveness at the average population level of risk, the results relating to ages where interventions become cost-effective are not greatly different. Assuming no identification costs, it is estimated that the majority of women aged 75 years with at least one CRF could be treated cost-effectively, with *T*-score thresholds of –2.0 SD or lower needed for cost-effectiveness (*Tables 41* and *55*) compared with an expected *T*-score of –1.94 at this age. For women without CRFs (and thus with a risk of fracture below that of the general population) a *T*-score threshold of –2.4 SD is needed for cost-effective treatment.

For resource reasons, the present results were estimated for women without a prior fracture assuming that the midpoint efficacy estimation was correct. In future work the full uncertainty in the estimated cost-effectiveness should be explored; however, this is not expected to alter the mean results.

The foundation of this work was a Gaussian process model based on an individual patient model. The Gaussian model had to be adapted so that it could be used in conjunction with the WHO algorithm, and this introduced some bias that is likely to be favourable to the intervention, particularly in women with a prior hip or vertebral fracture. However, there was insufficient time between receiving the WHO algorithm and the project deadline to formulate a new model. Although the results from this model are still expected to be robust following the adaptations, for future work, where other parameters may become available, a new mathematical model structure would be recommended. The costs of fatality were inadvertently omitted from the parameters that were varied in the construction of the Gaussian process model, so these had to remain constant at the 1999/2000 value. This error is not expected to have a significant impact on the cost-effectiveness ratios, but will favour no treatment over interventions with beneficial effects on the incidences of hip fracture. In addition, the costs of death following a hip fracture were assumed not to vary with age and this assumption may be incorrect. However, this is not expected to have a significant impact on the cost-effectiveness results.

There is some evidence that strontium ranelate may make a contribution to and cause interference with DXA results. The exact effects and implications of this in clinical care need to be further quantified, and further research on this is recommended.

There is some evidence that strontium ranelate may affect the measurement of calcium levels in blood. This could have implications in routine patient management, and further research in this area is recommended.

Given that the modelling assumptions in this study are less favourable to the interventions than those of other models, it is expected that where scenarios are shown to be cost-effective in this analysis, these results are robust.

Chapter 7
Conclusions

Strontium ranelate has been shown to be clinically effective in the prevention of osteoporotic fractures. Scenarios have been found where strontium ranelate can be used cost-effectively; however, given the probabilistic sensitivity analyses conducted in this study, this intervention appears to be less cost-effective than the bisphosphonate alendronate.

Work has been presented on the cost-effectiveness of identifying asymptomatic women who could be treated cost-effectively. This work is part of an ongoing project undertaken with the NICEGDG and will be further reviewed and used as part of the guidelines issued for the management of women at high risk of osteoporotic fracture.

Chapter 8

Need for further research

A key research recommendation is that the evidence base for the efficacy of strontium ranelate be strengthened, in particular at the hip.

A second recommendation is that the evidence on *T*-scores by age is strengthened at older ages. The database used to produce these results contained only 40 women aged between 80 and 84 years, and it was assumed that there is a linear decrease in BMD with age from 50 years. Increasing the number of women in the database at older ages would strengthen the conclusions. If this data were to be collected anew, it is recommended that those factors shown to increase fracture incidence independently of BMD, BMI, parental history of hip fracture, current smoking, ever use of systemic corticosteroids, alcohol intake greater than 2 units daily, rheumatoid arthritis and prior fracture after 50 years, are also recorded. These data would allow the correlations between each CRF and *T*-score, as well as the prevalence in the community, to be estimated. The present analysis assumed no relationship between CRFs, except for age, and BMD. Gaining further evidence on these correlations would allow the identification strategies to become more sensitive and specific.

No head-to-head comparisons of strontium ranelate and bisphosphonates have been undertaken. Such comparisons may be of most benefit in the over-80 age group, where there are relatively few efficacy data for bisphosphonates. However, it is acknowledged that the number of patients needed to be recruited to prove statistical significance would be very large. As such, decision-makers have to base decisions on indirect evidence. Establishing a high-quality observational database detailing patient characteristics and fracture rates may be the most appropriate way of establishing efficacy differences between different interventions.

There is some debate on the actual costs of hip and other fractures, with the main UK costing paper being relatively old[5,6] and a range of costs being used in published cost-effectiveness models. Research is needed to establish more accurately the true level of costs of treating fracture. A component of this will be the requirement of women who have sustained a fracture to enter a nursing home. The proportion of fractures, by site and by age, that require women to enter a nursing home is also uncertain. This will have an impact on the cost-effectiveness results, and research is required to estimate these figures more accurately.

Although data have recently become available on the disutility of fractures in the initial and subsequent years, evidence is scarce on the residual effect of fracture after a longer period, for example 10 years. Finding the value of this figure may be an area for future research.

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The modelling structure and population were developed alongside work undertaken as part of the National Institute for Clinical Excellence Osteoporosis Guidelines Development Group (NICEGDG), of whom the lead author is a member, and all members from that committee contributed, in part, to the development. The NICEGDG consists of a number of eminent clinicians specialising in osteoporosis and also representatives from other healthcare bodies. Where there was debate on particular aspects of this work, this was discussed with NICEGDG members, with their advice generally being the deciding factor, and sensitivity analyses were undertaken to show the effects of alternative assumptions being made.

The cost-effectiveness analyses relied heavily on soon-to-be published work for WHO undertaken by Professor Kanis and colleagues. This was supplied in the strictest confidence.

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Contribution of authors

Matt Stevenson (Operational Research Analyst) led the project. He has led a number of studies investigating the cost-effectiveness of treatments for osteoporosis and this previous work formed the foundation for this work. Sarah Davis (Operational Research Analyst) updated the previous models and ran the new models to produce the cost-effectiveness results. Myfanwy Lloyd-Jones (Senior Research Fellow) carried out the review of the clinical effectiveness review. Catherine Beverley (Systematic Reviews Information Officer) undertook the electronic literature searches.

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Appendix 1

Detailing the WHO methodology

The WHO has commissioned a programme of work to identify and validate CRFs for use in fracture risk assessment on an international basis, either alone or in combination with BMD tests. A further aim was to develop algorithms for risk assessment that were sufficiently flexible to be used in the context of many primary care settings, including those where BMD testing was not readily available. The analysis underpinning this work is carried out by the WHO Collaborating Centre at Sheffield, with support from the International Osteoporosis Foundation (IOF), the National Osteoporosis Foundation (NOF), the International Society for Clinical Densitometry (ISCD) and the American Society for Bone and Mineral Research (ASBMR).

The WHO Collaborating Centre at Sheffield examined a series of candidate risk factors from 12 prospectively studied cohorts drawn from the general population, utilising the primary data from each study (*Table 64*).

Risk factors were selected on the basis of their availability and reasonable uniformity in the construct of the questionnaire used in each study. The following risk factors were selected on the likelihood that the risk identified would be amenable to pharmaceutical manipulation and the ease with which the risk factor could be utilised in clinical practice:

- age (all centres)
- BMD (all centres)
- BMI (all centres)
- prior fragility fracture (11 centres)
- ever use of systemic glucocorticoids (eight centres)
- parental history of fracture (seven centres)
- parental history of hip fracture (three centres)
- current smoking (ten centres)
- alcohol intake of greater than 2 units per day (three centres)
- rheumatoid arthritis (three centres).

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kilograms divided by height squared in metres. BMD tests were available in 70% of individuals. BMD was measured at the femoral neck by DXA, with the exception of the two Gothenburg cohorts, where BMD was assessed by DXA at the distal forearm or by dual-photon absorptiometry at the right heel. The BMD data were also analysed excluding these two cohorts. BMD was expressed as gender- and cohort-specific *Z*-scores.

A history of current or past smoking was obtained by self-report. There was inadequate information to assess possible dose–response effects. The assessment of alcohol intake differed between cohorts, and was converted into a daily intake

TABLE 64 *Details of cohorts studied by meta-analysis of risk factors (from WHO manuscript; full manuscript supplied academic in confidence)*

Cohort	*n*	% Female	Person-years	Mean age (years)
EVOS/EPOS	13,490	52	40,681	64
CaMos	9,101	69	25,834	62
Rochester	1,001	65	6,227	56
Rotterdam	6,851	59	39,593	69
DOES	2,089	61	15,994	70
Gothenburg II	1,970	59	15,201	78
Hiroshima	2,603	70	9,825	64
OFELY	430	100	2,144	64
Sheffield	2,170	100	6,894	80
Kuopio	11,691	100	56,091	52
Gothenburg I	7,065	100	29,603	59
EPIDOS	1,183	100	3,947	82
Total	59,644	75	252,034	63

expressed as units per day. A unit of alcohol is equivalent to 8 g in the UK, but this varies somewhat in different countries. A family history of any fracture was collected in first degree relatives. In addition, a family history of hip fracture was noted, but was available only in three of the cohorts. Prior fracture history of each individual was documented, although the construct of the question varied, particularly the age from which a fracture had occurred. Ever use of oral corticosteroids was used to characterise steroid exposure, because all but three cohorts did not distinguish between ever and current use. Neither the dose nor the duration of use was analysed. The presence or absence of rheumatoid arthritis was ascertained by self-report.

Fracture ascertainment was undertaken by self-report (Sheffield, EVOS/EPOS, Hiroshima, Kuopio, EPIDOS, OFELY) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Kuopio, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS, Hiroshima and Rotterdam studies also included sequential systematic radiography to define incident vertebral deformities, but these were not used in the analyses. In the analyses, information was used on any clinical fracture considered to be osteoporotic. An osteoporotic fracture was one considered to be due to osteoporosis by the investigator in the EVOS/EPOS study and in CaMos. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos study they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts, fractures at sites considered to be characteristic for osteoporosis were extracted. In addition, hip fracture alone was considered separately in the analysis.

The effect of the CRF, gender and age on the risk of any fracture, any osteoporotic fracture and hip fracture alone was examined using Poisson regression models in each cohort separately. A Poisson model was chosen since it has greater power than logistic regression and can accommodate all information with variable durations of follow-up. In addition, time can be accommodated as an interaction term, and for some risk factors, risk ratios may decrease with longer durations of observation. For each risk factor studied, covariates included current age and time since follow-up, with and without BMD. Where appropriate, interaction terms were included. Outcome variables comprised any fracture, any osteoporotic fracture and hip fracture alone. The results of different cohorts (men separately from women) were then merged using weighted coefficients. (Examples of results are illustrated in *Figures 18* and *19*.)

A fixed effects rather than a random effects model was used, since the latter weights the smaller cohorts disproportionately. In addition, the fixed effect model gives generally a more conservative point estimate for the risk ratio, albeit with wider confidence estimates. Heterogeneity between cohorts was tested by means of the I^2 statistic. Where more than moderate heterogeneity was found (>50%), risk ratios were computed using the random effects model to determine whether the significance of estimates had changed. It was judged that the heterogeneity between cohorts was sufficiently low.

FIGURE 18 **[Confidential information removed]**

FIGURE 19 **[Confidential information removed]**

From these data the WHO fracture assessment tool (algorithm) was developed.

Each of the risk factors was examined for interactions with gender, age, BMD and the variable itself. Before such risk factors can be used for fracture prediction their independent contribution needs to be assessed, but all risk factors with the exception of BMI were associated with fracture risk independently of BMD.

Four algorithms for each gender were constructed from the risk factor analysis to compute fracture probabilities. These comprised:

- the probability of hip fracture without knowledge of BMD
- the probability of hip fracture with knowledge of BMD
- the probability of spine, forearm and proximal humerus fractures without knowledge of BMD
- the probability of spine, forearm and proximal humerus with knowledge of BMD.

For each risk factor, all significant interactions terms that were identified by meta-analysis were entered (with age, time, gender and the risk factor) with and without BMD. Interactions that were significant for hip fracture risk were also entered into the model for spine, forearm and proximal humerus fractures, and also included in the model for death. It was also considered that some interactions noted in the mega-analyses were no longer significant.

Complete information from all cohorts used in the model was available for the continuous variables (BMI and BMD). Where information was missing from one cohort, the variable (e.g. smoking) was deleted from the model and, since this had a minor effect on the *B* coefficients for the other dichotomous risk factors, the original *B* coefficients were used.

In addition to rheumatoid arthritis, provision was made for the inclusion of other secondary causes of osteoporosis. Whereas there is strong evidence for the association of these disorders and fracture risk, the independence of these risk factors from BMD is uncertain. It was conservatively assumed, therefore, that the fracture risk was mediated via low BMD, but with a risk ratio similar to that noted in rheumatoid arthritis.

Algorithms were developed for regions of the world using epidemiological information for index countries, categorised into very high risk, high risk, moderate risk and low risk. The UK was in the high-risk region, and the data were adjusted so that they matched those reported by Singer and colleagues.[21]

Input parameters into the model were age, gender, weight (kg), and height (cm) and the dichotomised risk listed above. Femoral neck BMD can additionally be entered as either a *Z*-score or a *T*-score. The algorithm provides annual probabilities of fracture as defined above with and without the inclusion of BMD. These data are then combined with expected mortality to produce estimates of 10-year fracture risks.

Appendix 2

Electronic bibliographic databases searched

1. CENTRAL
2. CINAHL
3. CDSR (Cochrane Database of Systematic Reviews)
4. EMBASE
5. HEED (Health Economic Evaluations Database)
6. MEDLINE
7. NEAT
8. NHS DARE (Database of Assessments of Reviews of Effectiveness)
9. NHS EED (Economic Evaluations Database)
10. NHS HTA (Health Technology Assessment)
11. PREMEDLINE
12. Pubmed
13. Science Citation Index
14. TRIP

Other sources research

Google
EMC (www.medicines.org.uk)
EMEA

Appendix 3

MEDLINE clinical effectiveness search strategy

1 strontium ranelate.af.
2 osseor.af.
3 protelos.af.
4 s12911.af.
5 or/1-4

Appendix 4

Quality assessment tool

TABLE 65 *Quality assessment tool*[a]

	Score
Was randomisation to the study groups blinded?	
Not randomised	0
States random but no description or quasi-randomised (*e.g. allocation by date of birth, hospital record no., admission dates, alternately*)	1
Small but real chance of disclosure of assignment *(e.g. sealed envelopes)*	2
Method does not allow disclosure of assignment *(e.g. assigned by telephone communication, or by indistinguishable drug treatments randomly precoded by centralised pharmacy)*	3
Were assessors of outcome blinded to treatment status?	
Not mentioned	1
Moderate chance of unblinding of assessors	2
Action taken to blind assessors, or outcomes such that bias is unlikely	3
Were the outcomes of patients who withdrew described and included in the analysis?	
Not mentioned or states number of withdrawals only	1
States numbers and reasons for withdrawal, but analysis unmodified	2
Primary analysis based on all cases as randomised	3
Comparability of treatment and control groups at entry	
Large potential for confounding or not discussed	1
Confounding small; mentioned but not adjusted for	2
Unconfounded; good comparability of groups or confounding adjusted for	3
For hip or other appendicular skeleton fracture	
Not applicable	0
No confirmation of diagnosis	1
X-ray confirmation of diagnosis	3
For vertebral fracture	
Not applicable	0
Inadequately described method	1
Radiological method: uses anterior/posterior height ratio	2
Radiological method: uses anterior, middle and posterior height in criteria OR reports radiologically confirmed clinical events only	3
Total methodology score (actual score as a percentage of possible score)	

[a] Developed from Gillespie *et al*. (2001)[58] and Prendiville *et al*. (1988).[59]

Appendix 5

Publications relating to the trials that met the inclusion criteria for review

The major publication for the study is marked with an asterisk.

SOTI

Adami S, Meunier PJ, Devogelaer JP, Hoszowski K, Fardellone P, Benhamou V, *et al*. Strontium ranelate reduces the risk of vertebral and non-vertebral fractures in Caucasian women with postmenopausal osteoporosis. *Osteoporosis Int* 2004;**15**(Suppl 1):S93–4.

Marquis P, De la Loge C, Roux C, Meunier PJ, Reginster JY. Strontium ranelate treatment prevents health-related quality of life impairment in postmenopausal women with severe osteoporosis: results from the SOTI study. *Osteoporosis Int* 2002;**13**(Suppl 3):S11–15.

Meunier PJ. Postmenopausal osteoporosis and strontium ranelate. *N Engl J Med* 2004;**350**:2002–3.

Meunier PJ, Lorenc RS, Smith IG, Roces-Varela A, Passariello R, Bonidan O, *et al*. Strontium ranelate: new efficient anti-osteoporotic agent for treatment of vertebral osteoporosis in postmenopausal women. *Osteoporosis Int* 2002;**13**(Suppl 3):S34–P66.

Meunier PJ, Marquis P, Lemmel EM, Martin TJ, Sawicki A, Isaia G, *et al*. Early effect of strontium ranelate on clinical, vertebral fractures in women with postmenopausal osteoporosis. *Bone* 2003;**32**(5 Suppl 1):S222.

Meunier PJ, Reginster JY. Design and methodology of the phase 3 trials for the clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis. *Osteoporos Int* 2003; **14**(Suppl 3):S66–76.

Meunier PJ, Roux C, Ortolani S, Badurski J, Kaufman JM, Spector T, *et al*. Strontium ranelate reduces the vertebral fracture risk in women with postmenopausal osteoporosis. *Osteoporosis Int* 2002;**13**:521–2.

Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, *et al*. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *Obstet Gynecol Surv* 2004;**59**:526–7.

* Meunier PJ, Roux C, Seeman E, Sergio O, Badurski J, Spector T, *et al*. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;**350**:459–68.

Reginster JY, Sawicki A, Devogelaer JP, Padrino JM, Brandi MI, Fardellone P, *et al*. Rapid and sustained anti-fracture efficacy of strontium ranelate in postmenopausal osteoporosis. *Arthritis Rheuma* 2002;**46**:S584–5.

Reginster JY, Spector T, Badurski J, Ortolani S, Martin TJ, Diez-Perez A, *et al*. A short-term run-in study can significantly contribute to increasing the quality of long-term osteoporosis trials. The strontium ranelate phase 3 program. *Osteoporosis Int* 2002; **13**(Suppl 1):S30.

Rizzoli R. Vertebral and non-vertebral antifracture efficacy of strontium ranelate. *Osteoporosis Int* 2003;**14**(Suppl 7):S106.

STRATOS

Meunier PJ, Reginster JY. Dose-related bone effects of strontium ranelate in postmenopausal women. *Osteoporosis Int* 2002;**13**(Suppl 1):S153.

Meunier PJ, Slosman D, Delmas PD, Sebert JL, Albanese C, Brandi ML, *et al*. Strontium ranelate as a treatment of vertebral osteoporosis. *J Bone Miner Res* 1997;**12**:107.

* Meunier PJ, Slosman D, Delmas P, Sebert J, Brandi M, Albanese C, *et al*. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis – a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab* 2002;**87**:2060–6.

Reginster JY, Meunier PJ. Strontium ranelate phase 2 dose-ranging studies: PREVOS and STRATOS studies. *Osteoporosis Int* 2003;**14**(Suppl 3):S56–65.

TROPOS

Adami S, Meunier PJ, Devogelaer JP, Hoszowski K, Fardellone P, Benhamou V, *et al*. Strontium ranelate reduces the risk of vertebral and non-vertebral fractures in Caucasian women with postmenopausal osteoporosis. *Osteoporosis Int* 2004;**15**(Suppl 1):S93–4.

Meunier PJ, Reginster JY. Design and methodology of the phase 3 trials for the clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis. *Osteoporos Int* 2003; **14**(Suppl 3):S66–76.

Reginster JY, Hoszowski K, Varela AR, Balogh A, Clements M, Fiore C, *et al*. Strontium ranelate: a new effective antiosteoporotic treatment reducing the incidence of vertebral and non vertebral fractures in postmenopausal women with osteoporosis. *Bone* 2003; **32**(5 Suppl 1):S94.

Reginster JY, Lorenc RS, Spector TD, Benhamou C, Isaia G, Brixen K, *et al*. Strontium ranelate reduces the risk of non vertebral fractures in women with postmenopausal osteoporosis. *Osteoporosis Int* 2003; **14**(Suppl 7):S51–2.

Reginster JY, Sawicki A, Devogelaer JP, Padrino JM, Kaufma JM, Doyle DV, *et al*. Strontium ranelate reduces the risk of hip fracture in women with postmenopausal osteoporosis. *Osteoporosis Int* 2002;**13**(Suppl 3):S14.

* Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, *et al*. Strontium ranelate reduces the risk of nonvertebral fractures in post-menopausal women with osteoporosis: TROPOS study. *J Clin Endocrinol Metab* 2005;**90**:2816–22.

Reginster JY, Spector T, Badurski J, Ortolani S, Martin TJ, Diez-Perez A, *et al*. A short-term run-in study can significantly contribute to increasing the quality of long-term osteoporosis trials. The strontium ranelate phase 3 program. *Osteoporosis Int* 2002;**13**(Suppl 1):S30.

Rizzoli R. Vertebral and non-vertebral antifracture efficacy of strontium ranelate. *Osteoporosis Int* 2003;**14**(Suppl 7):S106.

Rizzoli R, Reginster JY, Diaz-Curiel M, Ortolani S, Benhamou MC, Compston J, *et al*. Patients at high risk of hip fracture benefit from treatment with strontium ranelate. *Osteoporosis Int* 2004;**15**(Suppl 1):S18.

SOTI and TROPOS: pooled data

Reginster JY, Balogh A, Badurski J, Spector TD, Pors-Nielsen S, Felsenberg D, *et al*. Strontium ranelate reduces the risk of vertebral fractures in osteoporotic postmenopausal women without prevalent vertebral fracture. *Osteoporosis Int* 2003;**14**(Suppl 7):S7–8.

Sawicki A, Reginster JY, Roux C, Rubinacci A, Diaz-Curiel M, Kaufman J, *et al*. Strontium ranelate reduces the risk of vertebral fractures in postmenopausal women with osteopenia. *Osteoporosis Int* 2004;**15**(Suppl 1):S119–20.

Seeman E, Devogelaer JP, Lorenc RS, Spector R, Brixen K, Vellas B, *et al*. Strontium ranelate: the first anti-osteoporotic agent to reduce the risk of vertebral fracture in patients with lumbar osteopenia. *Osteoporosis Int* 2004;**15**:507–8.

Seeman E, Vellas B, Roux C, Adami S, Aquino J, Semler J, *et al*. First demonstration of the efficacy of an anti-osteoporotic treatment in very elderly osteoporotic women. ASBMR 26th Annual Meeting 2004; Presentation No. 1219.

Appendix 6

Studies excluded from the review of clinical effectiveness

TABLE 66 *Excluded studies*

Study	Reason for exclusion
Meunier, 1996[99]	No fracture data
Reginster, 2002[100]	Exact duplicate of Reginster, 2002[67]
Reginster, 2004[101]	Duplicate of Reginster, 2003[70]

Appendix 7

Evidence tables

TABLE 67 *Summary of study characteristics: general information*

Study	Study site	Length of study	Primary outcome measure	Population	Mean age (years)	Intervention/dose	Comparison(s)
STRATOS[63]	31 centres in 9 European countries	2 years	Change in lumbar spine BMD	Postmenopausal Caucasian women with established vertebral osteoporosis	66	Rx1: Strontium ranelate 0.5 g per day Rx2: Strontium ranelate 1 g per day Rx3: Strontium ranelate 2 g per day In each case taken as two identical tablets twice daily All participants received 500 mg per day calcium and 800 IU per day Vitamin D_3	Identical placebo taken twice daily, plus 500 mg per day calcium and 800 IU per day vitamin D_3
SOTI[64]	72 centres in 11 European countries and Australia	3 years	Incidence of new vertebral fractures	Postmenopausal Caucasian women with osteoporosis and a history of vertebral fracture	69.3 + 7.2 (range 50.0–96.0)[68]	Strontium ranelate 2 g per day taken as a powder mixed with water either once daily at bedtime or twice daily, 30 minutes before breakfast and at bedtime. Supplements of up to 1000 mg elemental calcium, taken at lunchtime, to maintain a daily calcium intake above 1500 mg, and vitamin D 400–800 IU depending on baseline serum concentration of 25-hydroxyvitamin D	Identical placebo. Supplements of up to 1000 mg elemental calcium to maintain a daily calcium intake above 1500 mg, and vitamin D 400–800 IU depending on baseline serum concentration of 25-hydroxyvitamin D
TROPOS[65]	75 centres in 11 European countries and Australia	3 years	Incidence of non-vertebral osteoporotic fracture	Aged osteoporotic Caucasian women with femoral neck BMD <0.600 g cm^{-2}	76.8±5.0- (range 55.0–100.0)[68]	Strontium ranelate 2 g per day taken either once daily at bedtime or twice daily, 30 minutes before breakfast and at bedtime. Supplements of up to 1000 mg elemental calcium to maintain a daily calcium intake above 1500 mg, and vitamin D 400–800 IU depending on baseline serum concentration of 25-hydroxyvitamin D	Identical placebo. Supplements of up to 1000 mg elemental calcium to maintain a daily calcium intake above 1500 mg, and vitamin D 400–800 IU depending on baseline serum concentration of 25-hydroxyvitamin D

TABLE 68 *Summary of study characteristics: inclusion and exclusion criteria, baseline comparability and fracture definition*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
STRATOS[63]	Non-obese Causasian women aged 45–78 years, and ≥ 12 months postmenopausal, who had at least one vertebral fracture occurring under no or minimal trauma and a lumbar *T*-score < –2.4	More than two documented vertebral crush fractures between L1 and L4, documented secondary osteoporosis, osteomalacia, severe scoliosis, Paget's disease, evolving cancer, multiple myeloma or bone metastasis, life expectancy <2 years, renal insufficiency (creatinine >120 μmol l^{-1}), liver insufficiency (prothrombin time <70%), alcohol intake ≥ 160 g pure alcohol per day treatment with calcitonin, oestrogen, corticosteroids, anabolic steroids or vitamin D >800 IU per day within the previous 3 months, treatment with phosphorus, thiazide diuretics or calcium >500 mg per day within the previous month, treatment with etidronate or pamidronate for >30 days, or any treatment with another bisphosphonate Treatment with etidronate or pamidronate for 15–30 days required a 3-month washout period; treatment with fluoride for >2 months required a 5-year washout, and treatment with fluoride for <2 months required a 3-month washout	Groups were largely comparable at baseline. Although there was a significant difference between Rx2 and Rx3 in terms of BMI, the investigators thought this was neither clinically relevant nor likely to have an impact on efficacy assessment. In addition, a noticeably higher proportion of participants receiving Rx2 had received previous antiosteoporotic therapy	A decrease of ≥ 20% in one of the ratios of vertebral height in previously intact vertebrae	
SOTI[64]	Ambulatory Caucasian women ≥ 50 years old, ≥ 5 years postmenopausal, with at least one vertebral fracture occurring under no or minimal trauma and lumbar spine BMD ≤ 0.840 g cm^{-2} measured with Hologic instruments (corresponding to a *T*-score ≤ –2.4[66])	Severe diseases or conditions that could interfere with bone metabolism; use of antiosteoporotic treatments (fluoride salts or bisphosphonates taken for >14 days within the previous 12 months, or oestrogen, calcitonin or calcitriol taken for >1 month in the previous 6 months);[64] life expectancy <4 years or unlikely to be fully compliant with the study protocol[66]	Data were only presented for the ITT population (i.e. all participants who had taken at least one packet of study medication and for whom at least one spinal radiograph was obtained after baseline); these groups were comparable at baseline. The groups as randomised were also said to be comparable at baseline	A grade of ≥ 1 (using the semi-quantitative method of Genant) in a previously non-deformed vertebra. A secondary quantitative assessment was also undertaken using a 15% fracture definition	

continued

TABLE 68 *Summary of study characteristics: inclusion and exclusion criteria, baseline comparability and fracture definition (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
TROPOS[65]	Ambulatory Caucasian women, aged ≥ 74 years or, if aged 70–74, with at least one additional risk factor (personal history of postmenopausal osteoporotic fracture, residence in a retirement home, maternal history of osteoporotic fracture (or more than four falls per year[68]), femoral neck BMD <0.600 g/cm^2 (corresponding to a *T*-score of < –2.5), postmenopausal for ≥ 5 years, with a life expectancy of >4 years	Presence of major medical conditions, bone disease other than osteoporosis, or secondary osteoporosis; previous concomitant therapies known to interfere with bone metabolism (bisphosphonates taken for >14 days in the previous year; oestrogen, calcitonin, fluoride salts, calcitriol or 1α-vitamin D taken for >1 month in the previous 6 months), factors that could modify full compliance with the protocol	Yes	Fracture identified using the semi-quantitative method of Genant in a previously non-deformed vertebra. A secondary quantitative assessment was also undertaken using a fracture definition of a decrease of 15% or 3 mm in any vertebral height	Vertebral X-rays were not mandatory, and only 3640 participants (71%) had a baseline and at least one follow-up vertebral X-ray

ITT, intention-to-treat; Rx, treatment.

TABLE 69 *Summary of study characteristics: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% completing study protocol	Source of funding
STRATOS[63]	3	1	3	2	NA	3	12/15 (80%)	Rx1: 85 Rx2: 90 Rx3: 87 C: 91	Rx1: 65 (77%) Rx2: 66 (73%) Rx3: 67 (77%) C: 74 (81%)	Servier
SOTI[64]	1	3	3	3	3	3	16/18 (89%)	Rx: 828 C: 821	Rx: 628 (77%) C: 632 (77%)	Servier
TROPOS[65]	1	1	3	3	3	3	14/18 (78%)	Rx: 2554 C: 2537	Rx: 1687 (66%) C: 1633 (64%)	Servier

C, control; Rx, treatment.

TABLE 70 *Strontium ranelate: toxicity*

Study	No. of participants reporting AEs	No. of participants reporting GI disorders	Withdrawals/discontinuation of study medication due to AEs
STRATOS[63]	Number of emergent AEs related to treatment: Rx1: 70/85 (82%) Rx2: 71/90 (79%) Rx3: 78/87 (90%) C: 83/91 (91%)	Abdominal pain: Rx1: 8.2% Rx2: 7.8% Rx3: 10.3% C: 13.2% Nausea: Rx1: 3.5% Rx2: 4.4% Rx3: 9.2% C: 6.6% Dyspepsia: Rx1: 5.9% Rx2: 4.4% Rx3: 3.4% C: 7.7% Gastritis: Rx1: 4.7% Rx2: 2.2% Rx3: 5.7% C: 2.2% Diarrhoea: Rx1: 3.5% Rx2: 6.7% Rx3: 3.4% C: 6.6%	Rx1: 15/85 (17%) Rx2: 15/90 (17%) Rx3: 11/87 (13%) C: 14/91 (15%)
SOTI[64]	AEs thought to be related to treatment:[68] Rx: 169/826 (20.5%) C: 135/814 (16.6%) Serum creatine kinase at least twice upper limit of normal:[64] Rx: 3.4% C: 1.8%	Diarrhoea:[64] Rx: 6.1% C: 3.6% $p = 0.02$ Gastritis:[64] Rx: 3.6% C: 5.5% $p = 0.07$	Emergent AE leading to treatment discontinuation:[68] Rx: 179/826 (21.7%) C: 131/814 (16.1%) Deaths (none attributed to study treatment):[68] Rx: 29/826 (3.5%) C: 21/814 (2.6%)

continued

TABLE 70 *Strontium ranelate: toxicity (cont'd)*

Study	No. of participants reporting AEs	No. of participants reporting GI disorders	Withdrawals/discontinuation of study medication due to AEs
		Upper GI AEs thought to be related to treatment:[68] Rx: 119/826 (14.4%) C: 100/814 (12.3%)	Non-fatal SAE leading to treatment withdrawal:[68] Rx: 39/826 (4.7%) C: 28/814 (3.4%) Treatment-related SAE leading to treatment withdrawal:[68] Rx: 2/826 (one gastric erosions, one unspecified hypersensitivity) C: 3/814 (one constipation, one GI disorder, one oesophagitis)
TROPOS[65]	SAEs: Rx: 24.7% C: 24.4%	Nausea and diarrhoea were reported more commonly in the SR group in the first 3 months of treatment (nausea Rx: 7.2%, C: 4.4%; diarrhoea Rx: 6.7%; C: 5.0%); after 3 months there was no difference between the groups	Withdrawals due to AEs: Rx: 24.2% C: 21.6%

AE, adverse event; GI, gastrointestinal; SAE, serious adverse event.

Appendix 8

Assessing the quality of modelling within the submissions

The *BMJ* checklist for economic evaluations[80] was used to assess the quality of the submitted models. The checklist questions are duplicated below. The reviewer's comments are produced separately for each model, along with a discussion of the potential impact of different methodologies or assumptions. Where the questions have been answered appropriately and sufficiently the term 'OK' has been used. The submission by Servier presents results from two economic models.[19] The 'core' model presented in Section 3 of the submission[19] is based on a previous version of the SHEMO model previously developed by the assessment group.[82] This submission model will be referred to as the Servier core model. An alternative model developed by Stockholm Heath Economics is presented in Appendix 4 of the submission.[19] This will be referred to as the SHE model.

Quality assessment questions

1. The research question is stated.
2. The economic importance of the research question is stated.
3. The viewpoint(s) of the analysis are clearly stated.
4. The rationale for choosing the alternative programmes or interventions compared is stated.
5. The alternatives being compared are clearly described.
6. The form of economic evaluation used is stated.
7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. The source(s) of effectiveness estimates used are stated.
9. Details of the design and results of effectiveness study are given (if based on a single study).
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).
11. The primary outcome measure(s) for the economic evaluation are clearly stated.
12. Methods to value health states and other benefits are stated.
13. Details of the subjects from whom valuations were obtained are given.
14. Productivity changes (if included) are reported separately.
15. The relevance of productivity changes to the study question is discussed.
16. Quantities of resources are reported separately from their unit costs.
17. Methods for the estimation of quantities and unit costs are described.
18. Currency and price data are recorded.
19. Details of currency of price adjustments for inflation or currency conversion are given.
20. Details of any model used are given.
21. The choice of model used and the key parameters on which it is based are justified.
22. Time-horizon of costs and benefits is stated.
23. The discount rate(s) is stated.
24. The choice of rate(s) is justified.
25. An explanation is given if costs or benefits are not discounted.
26. Details of statistical tests and confidence intervals are given for stochastic data.
27. The approach to sensitivity analysis is given.
28. The choice of variables for sensitivity analysis is justified.
29. The ranges over which the variables are varied are stated.
30. Relevant alternatives are compared.
31. Incremental analysis is reported.
32. Major outcomes are presented in a disaggregated as well as an aggregated form.
33. The answer to the study question is given.
34. Conclusions follow from the data reported.
35. Conclusions are accompanied by the appropriate caveats.

Reviewer's comments for the Servier core model

1. OK. Analysis is confined to those with a prior fracture.
2. The clinical importance of strontium ranelate as an alternative to bisphosphonates is discussed (Chapter 1 of the submission), but

the economic importance of the cost-effectiveness of strontium ranelate is not discussed.

3. The viewpoint of the analysis is not explicitly discussed but the use of a model previously employed by NICE suggests a societal perspective.
4. Strontium ranelate is compared with no treatment. The rationale for this choice is not given and no attempt has been made to compare the cost-effectiveness of strontium ranelate and alternative treatments.
5. The assumed number of GP visits and BMD scans associated with treatment with strontium ranelate is not given, which leaves a gap in the description of the alternative interventions.
6. OK.
7. OK. Rationale for using an individual patient model in combination with Gaussian processing techniques rather than a cohort based model is discussed.
8. OK.
9. Details of SOTI and TROPOS studies are provided within the submission. The submission model uses vertebral fracture efficacy from the SOTI study full analysis set, while the appraisal model uses a pooled analysis from both the SOTI and TROPOS studies. These efficacy estimates are similar, but the appraisal model assumes slightly higher efficacy. The submission model assumes the hip fracture efficacy seen in the TROPOS subgroup analysis of osteoporotic women over the age of 74, while the appraisal model uses the pooled efficacy from the SOTI and TROPOS trials. This difference means that the submission model will be more substantially more favourable to treatment than the appraisal model. The submission model assumes that the efficacy from the TROPOS study full analysis set for major osteoporosis-related fractures is applicable to wrist and proximal humerus fracture. The submission model uses a pooled analysis from the SOTI and TROPOS trials for all non-vertebral osteoporosis-related fractures for both wrist and proximal humerus fractures. The submission model assumed efficacy for wrist and proximal humerus is slightly favourable to treatment compared with the appraisal model assumed efficacy.
10. NA.
11. Cost per QALY is the primary outcome measure.
12. References for utility multipliers are provided, but no discussion or these sources is given. The appraisal model uses recent health state utility values for fracture from Kanis *et al*.[9] These are lower than those used in the submission model, so this factor will make the appraisal model more favourable to treatment.
13. See 12.
14. NA.
15. NA.
16. Not given in either the submission or the appraisal model.
17. Methodology and sources for calculating costs are presented elsewhere and references to these are provided. Appraisal uses same methodology and sources for costs, but inflates them to 2003/04 values, whereas submission has referenced costs inflated to 2001/02 values. This factor will make the appraisal model more favourable to the interventions as the cost consequences of preventing fracture are higher.
18. OK. See 17.
19. Price year for costs is that of the source reference. See 17.
20. OK. The model used is one developed by the authors of this report.
21. Epidemiological inputs are not fully described. It is unclear what population risk of fracture has been used and whether this has been adjusted to give the risk in those with average BMD and no prior fracture. The Marshall factor used is the risk relative to those at average BMD and should therefore only be applied to a population adjusted to average BMD. Adjusting to average BMD would have reduced the risk of fracture and therefore increased the cost per QALY. Similarly, the population risk of fracture should have been adjusted to account for the proportion of the population with a prior fracture in order for the risk multiplier for prior fracture to be applied in the way described. It is unclear whether the population risk has been adjusted, but not adjusting it would cause an error in favour of the interventions.
    It is unclear whether the submission employed an age-dependent factor for the relative risk of hip fracture due to changes in *T*-score, as the appraisal model did, or used a fixed value. The latter option will underestimate the risk of hip fracture at the threshold of osteoporosis for younger ages and overestimate the risk at higher ages.
    The submission model considers the impact of prior fracture on cost-effectiveness, while the appraisal model also considers the impact of other risk factors.

Data on mortality and entry into a nursing home are not discussed so we have assumed that they have not changed from the values used in the analysis for NCCHTA for which this model was developed. It is therefore the same as that used in the appraisal model.
The differences in health state utility values and costs used in the submission model and the appraisal model are discussed in points 12 and 17 above.
The appraisal model has included other types of osteoporotic fractures in addition to vertebral, hip, wrist and proximal humerus. The exclusion of these from the submission model will bias the results in favour of no treatment, especially at younger ages where other fracture types form a larger proportion of the total fracture risk.

22. OK.
23. OK.
24. OK. The submission model calculated costs and benefits discounted at 6% and 1.5%. These have then been scaled to reflect discounting of 3.5% for both costs and benefits. The appraisal model discounts at 6% and 1.5%. The effect of the difference will change dependent on the scenarios analysed.
25. NA.
26. CEACs and 95% confidence intervals are provided for the probabilistic sensitivity analysis. The method for calculating 95% confidence intervals is discussed.
27. OK.
28. OK. A sensitivity analysis including additional fracture types could have been included. The effect of changing *T*-score has not been considered, although the effect of doubling fracture risk has been. Reporting the results for a discount rate of 6% for costs and 1.5% for benefits would have assisted the comparison with previous technology assessments for other osteoporosis interventions.
29. OK.
30. No other osteoporosis treatments have been included for comparison.
31. Incremental analysis relates to no treatment only.
32. In the base case and double fracture risk case the results are disaggregated into total cost and QALYs and marginal costs and QALYs, although the costs and QALYs associated with no treatment are not specifically reported. All other results are given in cost per QALY form only.
    Results are provided for two age groups (ages 65–75 and ages 75+), but the method of aggregation is not given. It is stated earlier that the desired age group for analysis is 75. It is therefore unclear whether the results reported as ages 75+ are in fact a threshold value using age 75 alone.
33. OK.
34. OK.
35. OK.

Reviewer's comments for the SHE model

1. OK.
2. OK.
3. OK.
4. Strontium ranelate is compared with no treatment. The rationale for this choice is not given and no attempt has been made to compare the cost-effectiveness of strontium ranelate and alternative treatments.
5. OK.
6. OK.
7. Choice of form of economic evaluation is not discussed.
8. Sources of effectiveness estimates used are stated, but the RR of vertebral fracture appears to differ between the text in Section 2.3 and *Table 8*.
9. Details of SOTI and TROPOS studies not provided in the report of this model but are provided within the Servier Laboratories Ltd submission. The submission model uses vertebral fracture efficacy from the SOTI study full analysis set, while the appraisal model uses a pooled analysis from both the SOTI and TROPOS studies. These efficacy estimates are similar, but the appraisal model assumes slightly higher efficacy. The submission model assumes the hip fracture efficacy seen in the TROPOS subgroup analysis of osteoporotic women over the age of 74, while the appraisal model uses the pooled efficacy from the SOTI and TROPOS trials. This difference means that the submission model will be substantially more favourable to treatment than the appraisal model. The submission model assumes that the efficacy from the TOPOS study full analysis set for major osteoporosis-related fractures is applicable to wrist and proximal humerus fracture. The submission model uses a pooled analysis from the SOTI and TROPOS trials for all non-vertebral osteoporosis related fractures for both wrist and proximal humerus fractures. The submission model assumed efficacy for wrist

and proximal humerus is slightly favourable to treatment compared with the appraisal model assumed efficacy

10. NA.
11. Costs, life-years gained, QALYs gained, cost per life-year gained and cost per QALY gained are all reported, but none is identified as the primary outcome measure.
12. OK. Proximal humerus multiplier varies between the text in Section 2.9 and Table 5. The referenced HTA monograph does not give a multiplier value of 0.794 for proximal humerus. The main source used for the utility multipliers in the submission by Kanis *et al.*[9] is the same as in the appraisal model; however, the discussion and referencing of these utility values within the submission are unclear.
13. See 12.
14. NA.
15. NA.
16. Not given in either this submission or the appraisal model
17. Sources for fracture costs are unclear. For example, Table 4 quotes reference 28, while Section 2.7 quotes reference 20. The methodology of calculating the costs presented from the references provided is not given and is not obvious. For example, reference 28 divides hip fracture costs into costs for uncomplicated hip fracture, cost for confinement to nursing home and cost of death due to hip fracture; however the submission gives only one cost for hip fracture and does not state how the above costs are used to comprise the one value.
18. OK. The submission model assumes that 10% of hip fracture patients will remain at a nursing home for the rest of their lives. The appraisal model assumes an age-dependent proportion which is zero at age 50 and 12% for ages 80–89. Even at ages 70–79 the appraisal model uses a lower nursing home rate of 4%. This is favourable to the intervention. Wrist, vertebral and proximal humerus costs are close to the values used in the appraisal model.
19. OK.
20. OK.
21. The model is a Markov model and therefore does not retain the individual's prior history. In order to get around this, a postvertebral fracture state and posthip fracture state have been included. However, transitions from the postvertebral state are restricted to hip fracture and death and transitions from the posthip state are limited to death. It is not clear whether the initial utility for patients with prior vertebral fractures is adjusted to reflect their prior fracture. The utility appears to depend on the most severe fracture, rather than an interaction between multiple fractures.

It is not clear how patients with a prior vertebral fracture have been handled. If they start in the well state to allow the full range of transitions, then the utility of the well state and all those they move into should be adjusted to reflect the utility detriment of their prior fracture. Not adjusting will overestimate QALY gains by a factor of $1/0.929 = 1.07$. If they begin in the vertebral or postvertebral state, then their transitions are limited to another vertebral fracture, hip fracture and death. This would underestimate the future risk of wrist fractures and therefore overestimate the cost per QALY.

A 3-year treatment and offset time is used in the submission model in the base case, whereas a 5-year treatment and offset time is used in the appraisal model. Increasing the treatment and offset times to those used in the appraisal was explored in a sensitivity analysis and increased the cost per QALY. With regard to the baseline analysis in the submission model, this assumption is favourable to the intervention.

The incidence data from proximal humerus fractures have been taken from a Swedish study and the data in Table 2 appear to be for men rather than women. This will underestimate the risk of proximal humerus fracture as the incidence is higher in women than in men. The submission model will therefore underestimate the potential benefit of preventing proximal humerus fractures, but this will not impact on the base-case cost-effectiveness as this assumes no intervention effect on proximal humerus fractures.

The appraisal model employed an age-dependent factor for the relative risk of hip fracture due to *T*-score rather than the fixed valued employed by the submission model. This will underestimate the risk of hip fracture at the threshold of osteoporosis for younger ages and overestimate this risk at greater ages.

The population risk of fracture has been adjusted to account for prevalent fractures, but this has been restricted to only vertebral fractures. Therefore, prevalent hip, wrist and other fractures have not been accounted for and the risk to those without a prior fracture has been overestimated. This makes the

submission model favourable to the interventions.
The submission model considers the impact of prior fracture on cost-effectiveness, while the appraisal model also considers the impact of other risk factors.
The differences in health state utility values and costs used in the submission model and the appraisal model are discussed in points 12 and 17 above.
Different mortality data have been used in the appraisal and submission models. Only 30% of the excess mortality following hip fracture has been attributed to hip fracture in the submission model and 42% in the appraisal model. The submission model has an increased mortality for both the first and second years following hip fractures whereas the appraisal model assumes no increased mortality in the second year. The overall effect of these differences is less favourable to the intervention in the submission model. The appraisal model assumes a mortality hazard ratio of 4.4 following vertebral fracture and that 28% of all deaths following vertebral fractures are causally related to the fracture. The submission model, however, has an age-dependent hazard ratio, which is 14.8 at age 50 decreasing to 2.9 at age 80. This will therefore favour the intervention in the younger age group and favour no treatment in the elderly. The same hazard ratio for proximal humerus fracture has been used in both models; however, the appraisal model assumes that 28% of deaths following fracture are causally related, while the submission model does not state a value for this and therefore suggests that all deaths were deemed to be causally related. If true, this will favour the intervention, but only in the sensitivity analysis where the intervention is assumed to have an effect on proximal humerus fractures.
The appraisal model has included other types of osteoporotic fractures in addition to vertebral, hip, wrist and proximal humerus. The submission model has a state for other osteoporotic fractures, but use of this state is said to be limited by the data available and the only data described relate to proximal humerus fractures, so it is assumed that this is the only additional fracture type included. Exclusion of other fracture types (e.g. pelvis, other femoral, tibia and fibula) from the submission model will significantly favour no treatment, especially at younger ages where other fracture types form a larger proportion of the total fracture risk.

22. The submission model assumes the time-horizon to be the patient's lifetime or age 100 years. The appraisal model assumes a time-horizon of 10 years. The assumption made by the submission model favours the intervention.
23. Base-case discount rate is 3.5% for both costs and benefits. Sensitivity analyses using 6% and 0% rates for both and 6% for costs and 0% for benefits have been carried out. However, analyses using 6% for costs and 1.5% for benefits have not, which limits comparability with previous assessments for other osteoporosis interventions.
24. See 23.
25. NA.
26. Stochastic results are presented using a CEAC rather than statistical test/confidence intervals. Only the efficacy estimates were allowed to vary stochastically. Table 8 suggests that the RRs are log-normally distributed, since the Gaussian distribution described has a mean, which is the natural logarithm of the midpoint RR. This is the same distribution as assumed in the appraisal model. The method of calculation for dispersion is not given, and we are unsure whether the same range of uncertainty has been used in the appraisal and the submission model.
27. OK.
28. OK. An effect on proximal humerus is included as a sensitivity analysis, but this appears to be the only use of the 'other osteoporotic fracture' state. A sensitivity including additional fracture types could have been included.
    See 23 for sensitivity analysis surrounding the choice of discount rate.
29. The sensitivity on starting age varies the age from 65 to 80, although cost and utility data have been provided from 50 to 80. This suggests that the range was restricted when presenting the results.
30. No other osteoporosis treatments have been included for comparison.
31. Incremental analysis relates to no treatment only.
32. OK.
33. OK.
34. OK.
35. OK.

Appendix 9

Modelling methodology

The first example concerns the accuracy with which the probability of fractures can be calculated, based on the patient history. There is a breadth of published literature that indicates that an initial fracture greatly increases the risk of subsequent fractures.[30] Implementing these relationships in an individual patient model is far simpler than in a cohort model. Consider an example of two identical osteoporotic women at the cohort model initiation, who are simulated for 5 years of life. Patient A may suffer no fractures for the first 4 years and suffer a wrist fracture in the fifth year. Patient B suffers no fractures in the first 2 years and then suffers a hip, vertebral and wrist fracture in the next 3 years. In a simple cohort model both women now reside in the wrist fracture state. However, if the values from the available data are used, patient B would have a much greater risk of vertebral fracture and a greater risk of hip fracture than patient A. Without adjusting for this increased probability of fracture the model would underestimate the number of fractures that occur.

A further example is that a large component of costs comprise those associated with nursing homes following a hip fracture. If a model does not track the residential status of a patient there is a probability that additional nursing home costs are added for women already in nursing homes, whose marginal care costs could be zero.

Finally, a patient-based model can accommodate new information. For future modelling uses, where data on the duration of the elevated risk of fracture become available, the ability to have data on the periods in which the fractures have occurred may affect the results. This can be incorporated into an individual-based patient model, but would be difficult to undertake in a cohort model without a large number of transition states. It is also uncertain whether the costs of fractures are dependent on the number of previous fractures at that site, for example whether the cost of treating a second hip fracture is significantly different from treating the first hip fracture. Similarly, the ongoing costs of treating vertebral fractures may differ following a second vertebral fracture. Indeed, interaction of all prior fractures in determining the initial and follow-up treatment costs are not quantified. For such costs to be accurately totalled, the full patient history would need to be recorded through an individual patient-based method.

Similar considerations pertain to the accuracy with which the quality of life changes due to fractures can be calculated when gaps in the current knowledge are bridged. Data are required to determine whether the quality of life decrements associated with a given fracture are dependent on the number of previous fractures at that site or elsewhere. For example, it may be shown that the quality of life decrease is different for a first hip fracture and for a second hip fracture. Similarly, the quality of life loss associated with a first vertebral fracture may be different depending on whether a patient had previously suffered a hip fracture. If these relationships are shown to wane with time, then the period during which the fractures occurred needs to be noted. These factors can only be incorporated in an individual-based patient model.

The only alternative manner in which all data can be taken into consideration is by the use of a decision tree. If a simple model with only four transition states is assumed (no fracture event, hip fracture, vertebral fracture and wrist fracture), the tree would have 4^{10} branches in a 10-year period in order that all conceivable combinations of events are recorded. This totals over 1 million branches at year 10. Clearly, this number would be greatly increased with the addition of extra states (breast cancer, other fracture states) and would need to be duplicated with the tracking of residential status (community or nursing home). To replicate the patient-based model presented in this report using a decision-tree format would require over 1 billion branches to maintain accuracy. This would essentially be what was required to maintain the structure in a cohort approach.

Appendix 10

Calculation of the additional QALYs lost through a death from a hip fracture, vertebral fracture or proximal humerus fracture

The model builds on the work undertaken for an HTA report,[90] which used a time-horizon of 10 years. This, however, would mean that any mortality prevented within this period would not be given full weight, which would bias against beneficial treatments, and adjustments were needed to correct for this error. To adjust for this factor, an estimation of the QALYs that could be gained by prevention of mortality, at each age, was made. Calculations were only needed from the end of the 10-year modelling horizon, since any QALY impacts within this period would be explicitly calculated in the model. The methodology for this was as follows.

The life expectancy for a patient at the threshold of osteoporosis was calculated from standard life tables, as shown in *Table 10* of the main report. It was assumed that any increase in mortality rate due to low bone mass would continue until death or an age of 110 years.

Since the final QALY score of each patient in the individual patient model was not estimated by the Gaussian model, it was assumed, slightly favouring the interventions, that individuals would have a quality of life score equal to that of the general population, as reported by Kind and colleagues.[102] Life-years were discounted at 1.5% per annum, starting from the time of intervention.

Using these assumptions it was estimated that an average patient alive at the end of the model would accrue expected QALYs as given in *Table 71*.

TABLE 71 *Expected lifetime QALYs for women alive at the end of the model*

Age (years) at start of intervention	Expected QALYs
50	12.443
60	6.636
70	3.225
80	0.663

Having established the gains associated with preventing mortality, the expected number of potentially preventable deaths through hip fracture or breast cancer needed to be calculated. The methodology for this was based on the standard rate of hip fracture at each age, and the expected mortality associated at that age.

For example, the expected hip fracture rate at the age of 60, for healthy women at the threshold of osteoporosis, is estimated to be 0.1%. When analysing women with severe osteoporosis it was assumed that this risk can be doubled in accordance with data reported by Klotzbeucher and colleagues.[30] This would equate to an estimate of the hip fracture rate of 0.2% per annum, or 1.0% over a 5-year treatment period, assuming no additional mortality, which is one hip fracture for a cohort of 100 women.

The mortality rate following hip fracture is estimated to be 6% at the age of 60 (*Table 8* of the main report), which can result in a maximum of 0.06 hip fractures that were preventable over the intervention period. The number that were preventable are assumed to be equal to the sampled relative risk for each treatment; thus, if a relative risk of hip fracture of 0.5 was estimated, then it was assumed that 0.03 deaths associated with hip fractures would be saved. Where the relative risk was above 1, the model assumed that an additional number of deaths would occur and subtracted the expected QALYs from that estimated for the intervention.

The expected numbers of additional QALYs for women with severe osteoporosis suffering death from hip fracture are given in *Table 72*.

The methodology had to be altered slightly for death assumed to be associated with vertebral fractures, since unlike mortalities associated with hip fracture or breast cancer, these were not explicitly calculated within the 10-year horizon.

TABLE 72 *Maximum number of QALYs lost assumed to be preventable due to hip fracture mortality*

Age (years)	Maximum QALYs gained from preventing hip fracture mortality
50	0.174
60	0.398
70	0.832
80	0.807

It was assumed that all deaths from vertebral fracture would happen in year 3, the midpoint of the treatment period, and assuming a 66% increase in the mortality rate in the year of a vertebral fracture as reported by Center and colleagues[36] and that all of these deaths were attributable to the vertebral fracture. By calculating the expected number of vertebral fractures per year and the expected associated mortality assuming 5 years of no treatment, the maximum number of QALYs that could be prevented was estimated. These are shown in *Table 73*.

It was assumed that the number of mortalities that could be prevented is proportionate to the relative risk of the treatment. Hence, a treatment with a relative risk of 0.5 for vertebral fractures would be assumed to prevent 50% of mortalities from vertebral fractures.

TABLE 73 *Maximum number of QALYs lost assumed to be preventable due to mortality associated with vertebral fracture*

Age (years)	Maximum QALYs gained from preventing vertebral mortality
50	0.062
60	0.098
70	0.686
80	0.544

TABLE 74 *Maximum number of QALYs lost assumed to be preventable due to mortality associated with proximal humerus fracture*

Age (years)	Maximum QALYs gained from preventing vertebral mortality
50	0.007
60	0.023
70	0.048
80	0.047

A similar methodology was used for mortality associated with fractures of the proximal humerus. The maximum number of QALYs lost assumed to be preventable due to proximal humerus fracture is shown in *Table 74*.

Appendix 11

Sensitivity analyses

Inclusion of all morphometric vertebral fractures

The base-case analysis presented includes only clinical vertebral fractures. A sensitivity analysis was carried out assuming that 23% of all vertebral fractures are clinical and that the utility decrement of subclinical vertebral fractures is one-third that of clinical vertebral fractures.[89] The impact of including all morphometric vertebral fractures is shown in *Figure 20*.

Lower nursing home cost

The base-case analysis assumes an ongoing cost for patients with a hip fracture leading to nursing home entry of £25,357 at 80 years of age. An alternative cost for nursing home care of £18,471 per annum is provided by the technology assessment report for the current review of treatments for Alzheimer's disease.[92] The impact on cost-effectiveness of changing the ongoing cost for patients entering a nursing home to this lower estimate is shown for women aged 80–84 years in *Figure 21*. The impact is smaller at lower ages, where the probability of patients entering a nursing home following hip fracture is lower.

Baseline utility for patients with a previous fracture

In the base-case analysis patients with a previous fracture were assumed to enter the model with the same utility as patients without a previous fracture. This does not take into account the utility decrement due to the previous fracture. *Table 25* in the main report gives the utility decrement for various fracture types in the second year following fracture. It was assumed that these utility multipliers can be applied to women entering the model with a previous fracture. The distribution of fracture types in women with severe osteoporosis was estimated by calculating the cumulative incidence from the age of 50 years of each of the four main fracture types using the incidence data described in Chapter 2 of this report. These were then proportioned to provide the percentages

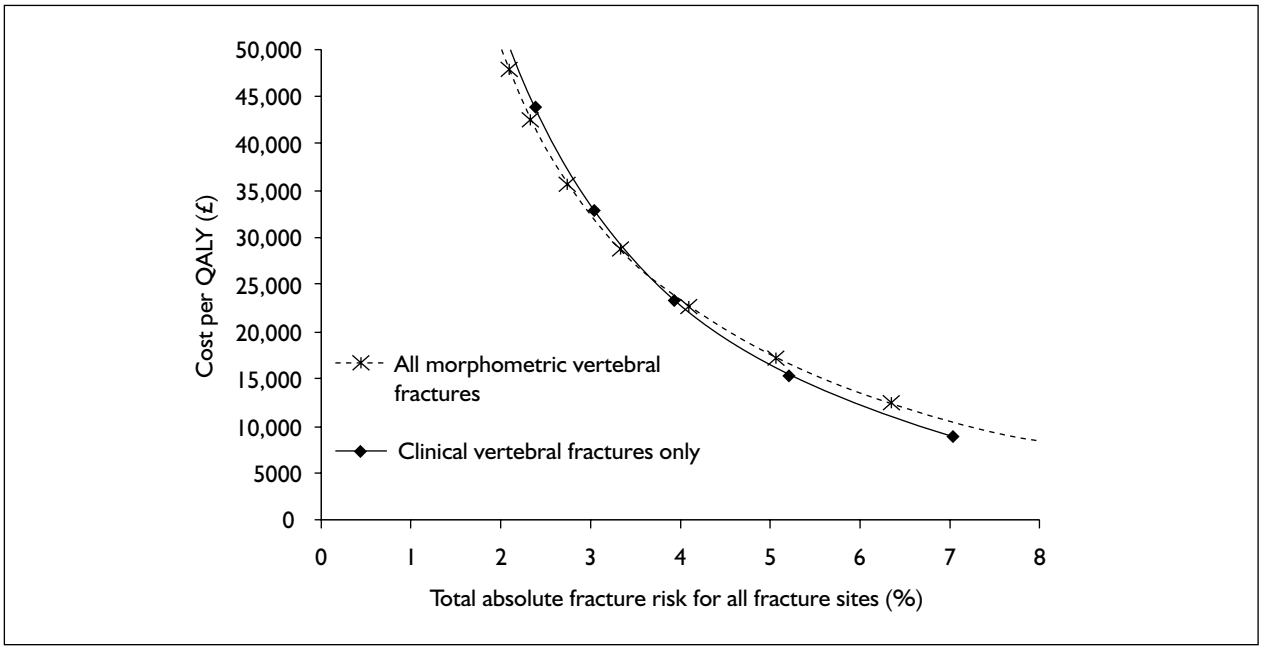

FIGURE 20 *Cost-effectiveness of treatment with strontium ranelate at 70 years of age for women with no CRFs when including only clinical vertebral fractures in the analysis or including all morphometric vertebral fractures in the analysis*

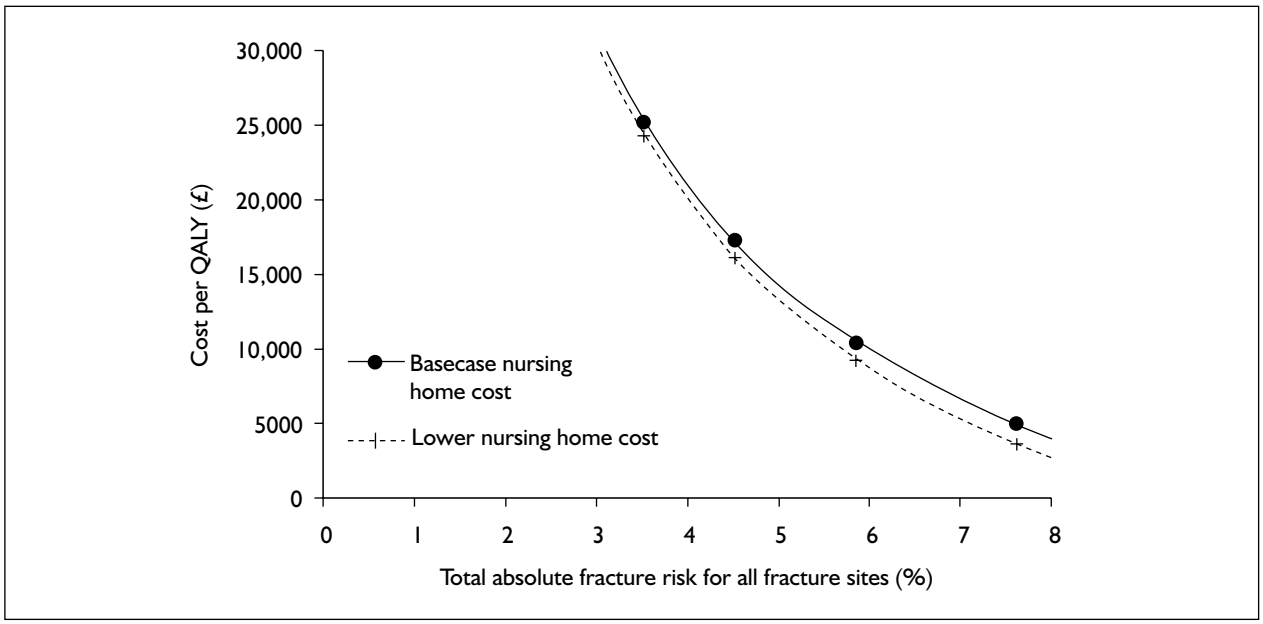

FIGURE 21 *Cost-effectiveness for women aged 80–84 years with no CRFs using two different estimations of nursing home cost*

TABLE 75 *Assumed distribution of prior fractures by age*

	Age (years)			
Fracture site	**50–54**	**60–64**	**70–74**	**80–84**
Hip	8	8	11	21
Vertebral	31	22	19	22
Wrist	50	57	56	43
Proximal humerus	11	13	14	14

shown in *Table 75*. For example, 8% of osteoporotic fractures up to the age of 50 years were hip fractures. This figure rose with age and hip fractures accounted for 21% of all osteoporotic fractures at the age of 80 years. Thus, in each cohort of 100 individual patients at the age of 70 years, 11% are assumed to have had hip fractures, 19% vertebral fractures, 56% wrist fractures and 14% proximal humerus fractures.

From this the estimated average utility multiplier due to previous fracture for women at the ages of 50–54, 60–64, 70–74 and 80–84 years is 0.953, 0.961, 0.958 and 0.937, respectively. To estimate the impact of this decreased starting utility, it was assumed that the QALY gain would be scaled down according to these starting utility multipliers. The impact of this on the cost-effectiveness is to scale up the cost per QALY by 4.9%, 4.1%, 4.4% and 6.8%, respectively.

Doubling the GP time required to perform the initial risk factor assessment and discuss a DXA scan where this is indicated

When the GP time is doubled the overall net benefit of implementing the identification strategy is decreased, but it is still cost-effective to identify women aged 70 years and above (*Table 76*).

Halving the GP time required to perform the initial risk factor assessment and discuss a DXA scan where this is indicated

Halving the GP time reduces the cost of identifying women for treatment. This means that it is possible to find an identification that is cost-effective at the ages of 65–69 years (*Table 77*).

Adding £5 to the cost of a DXA scan to cover administration costs

The overall net benefit of implementing the identification strategy is decreased, but it is still cost-effective to identify women aged 70 years and above (*Table 78*).

TABLE 76 *Optimum strategy results when assuming treatment with alendronate and a MAICER of £20,000: sensitivity analysis where the time to assess risk factors is doubled*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
50–69	0	0	0	0	0	0	0
70–74	774	234	22.4	51	34.5	45.8	23.4
75–79	581	566	39.3	145	73.9	155.9	116.6
≥ 80	900	809	52.6	502	177.3	536.3	483.7
Total	2255	1609	114.3	698	285.7	738.0	623.7

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 77 *Optimum strategy results when assuming treatment with alendronate and a MAICER of £20,000: sensitivity analysis where the time to assess risk factors is halved*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
50–64	0	0	0	0	0	0	0
65–69	879	67	6.1	8	5.3	6.6	0.5
70–74	774	234	14.4	51	34.5	45.8	31.4
75–79	581	566	31.0	145	73.9	155.9	124.9
≥ 80	900	809	40.1	502	177.3	536.3	496.2
Total	3134	1676	91.6	706	291.0	744.6	653.0

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 78 *Optimum strategy results when assuming treatment with alendronate and a MAICER of £20,000: sensitivity analysis where the cost of DXA scanning is increased by £5*

Age (years)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
50–69	0	0	0	0	0	0	0
70–74	774	234	18.2	51	34.5	45.8	27.6
75–79	581	566	36.6	145	73.9	155.9	119.3
≥ 80	900	809	48.3	502	177.3	536.3	488.0
Total	2255	1609	103.1	698	285.7	738.0	634.9

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

Compliance and switching therapies

The effects of non-compliance and patients switching therapies were evaluated assuming that the identification strategies previously defined are in use. The lowest ages at which identification strategies were cost-effective assuming a £20,000 cost per QALY threshold were used to look at the values in compliance and non-compliance necessary to cause this age group to be no longer cost-effective.

TABLE 79 *Optimum strategy results at age 70–74 years of age when assuming treatment with alendronate and a MAICER of £20,000: effect of compliance on net benefit of implementing the optimum strategy when assuming that non-compliant patients accrue 1 month's drug costs*

Compliance (%)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
100	774	234	17.0	51	34.5	45.8	28.8
75	774	234	17.0	51	26.2	34.0	17.0
50	774	234	17.0	51	17.9	22.2	5.2
25	774	234	17.0	51	9.6	10.5	–6.5

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 80 *Optimum strategy results at 70–74 years of age when assuming treatment with alendronate and a MAICER of £20,000: effect of compliance on net benefit of implementing the optimum strategy when assuming that non-compliant patients accrue 6 months' drug costs*

Compliance (%)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£ million)	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[a]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
100	774	234	17.0	51	34.5	45.8	28.8
75	774	234	17.0	53	27.8	32.4	15.4
50	774	234	17.0	53	21.1	19.0	2.0
25	774	234	17.0	53	14.4	5.7	–11.3

[a] Acquisition cost minus the costs recouped through reduced incidence of fracture.

TABLE 81 *Optimum strategy results at 70–74 years of age when assuming treatment with alendronate and a MAICER of £20,000: effect of patients receiving a GP appointment to switch therapies when it is assumed that the net benefit of treatment is not affected by the change in therapy*

Patients switching therapies (%)	No. of assessment tests undertaken (thousand)	No. of BMD scans undertaken (thousand)	Cost of identification strategy (£ million)[a]	No. who can be cost-effectively treated (thousand)	Net cost of treatment (£ million)[b]	Net benefit of treating cost-effective women (£ million)	Total net benefit of identification strategy (£ million)
0	774	234	17.0	51	34.5	45.8	28.8
25	774	234	17.3	51	34.5	45.8	28.5
50	774	234	17.5	51	34.5	45.8	28.3
75	774	234	17.8	51	34.5	45.8	28.0

[a] Includes the cost of assessment tests, BMD scans and GP appointments for patients who switch treatment.
[b] Acquisition cost minus the costs recouped through reduced incidence of fracture.

Tables 79 and *80* show that it is still cost-effective to implement the optimum strategy to identify women for treatment at 70–74 years of age when compliance falls to 50%, but not when compliance falls to 25% if non-compliant patients accrue either 1 month's drug costs or 6 months' drug costs. *Table 81* shows it is still cost-effective to identify women at 70–74 years of age if up to 75% of those women switch therapies when it is assumed that this requires an additional GP appointment but does not affect the net benefit of treating. However, the impact of patients switching therapies could be higher if the therapy to which they switch has a lower net benefit.

Appendix 12

Absolute annual fracture risk by age, BMD and clinical risk factors

TABLE 82 *Absolute annual fracture risk (%) at 50–54 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	6.0	3.6	2.3	1.5	1.1	0.9	0.7	0.6	0.5	0.5	0.4	0.4	0.4
Parental fracture	7.7	5.0	3.5	2.6	2.1	1.7	1.5	1.3	1.1	1.0	0.9	0.9	0.9
Current smoking	9.4	5.3	3.1	2.0	1.3	1.0	0.8	0.6	0.5	0.5	0.4	0.4	0.4
Corticosteroid use	10.9	6.4	4.0	2.7	1.9	1.5	1.2	1.0	0.9	0.8	0.7	0.7	0.7
Alcohol >2 units per day	8.6	5.0	3.1	2.0	1.5	1.1	0.9	0.7	0.6	0.6	0.5	0.5	0.5
Rheumatoid arthritis	8.3	4.9	3.1	2.1	1.5	1.2	0.9	0.8	0.7	0.6	0.6	0.5	0.5
Prior fracture	12.0	7.1	4.4	3.0	2.2	1.7	1.4	1.1	1.0	0.9	0.8	0.8	0.7

TABLE 83 *Absolute annual fracture risk (%) at 55–59 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	5.5	3.5	2.3	1.7	1.2	1.0	0.8	0.7	0.6	0.5	0.5	0.5	0.4
Parental fracture	7.4	5.1	3.7	2.9	2.3	1.9	1.6	1.4	1.2	1.1	1.0	1.0	0.9
Current smoking	8.4	5.0	3.1	2.1	1.5	1.1	0.8	0.7	0.6	0.5	0.5	0.4	0.4
Corticosteroid use	10.0	6.2	4.1	2.9	2.1	1.6	1.3	1.1	0.9	0.8	0.8	0.7	0.7
Alcohol >2 units per day	7.8	4.8	3.1	2.2	1.6	1.2	1.0	0.8	0.7	0.6	0.6	0.5	0.5
Rheumatoid arthritis	7.6	4.8	3.2	2.2	1.7	1.3	1.0	0.9	0.7	0.7	0.6	0.6	0.5
Prior fracture	10.2	6.5	4.3	3.0	2.3	1.8	1.4	1.2	1.0	0.9	0.9	0.8	0.8

TABLE 84 *Absolute annual fracture risk (%) at 60–64 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	5.3	3.5	2.5	1.8	1.3	1.1	0.8	0.7	0.6	0.5	0.5	0.5	0.4
Parental fracture	7.5	5.4	4.0	3.1	2.5	2.0	1.7	1.4	1.2	1.1	1.1	1.0	0.9
Current smoking	7.9	5.0	3.3	2.2	1.6	1.2	0.9	0.7	0.6	0.5	0.5	0.4	0.4
Corticosteroid use	9.6	6.3	4.3	3.1	2.3	1.8	1.4	1.2	1.0	0.9	0.8	0.8	0.7
Alcohol >2 units per day	7.5	4.9	3.3	2.3	1.7	1.3	1.0	0.8	0.7	0.6	0.6	0.5	0.5
Rheumatoid arthritis	7.4	4.8	3.3	2.4	1.8	1.4	1.1	0.9	0.8	0.7	0.6	0.6	0.6
Prior fracture	9.3	6.2	4.3	3.1	2.3	1.8	1.5	1.2	1.0	0.9	0.9	0.8	0.7

TABLE 85 *Absolute annual fracture risk (%) at 65–69 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	5.9	4.1	3.0	2.3	1.7	1.4	1.1	0.9	0.8	0.7	0.6	0.6	0.5
Parental fracture	9.6	6.9	5.1	3.9	3.0	2.4	2.0	1.6	1.4	1.3	1.2	1.1	1.0
Current smoking	8.4	5.6	3.9	2.7	2.0	1.5	1.2	0.9	0.8	0.7	0.6	0.6	0.5
Corticosteroid use	10.5	7.3	5.2	3.9	3.0	2.3	1.8	1.5	1.3	1.2	1.1	1.0	0.9
Alcohol >2 units per day	8.1	5.6	4.0	2.9	2.2	1.7	1.4	1.1	1.0	0.9	0.8	0.7	0.6
Rheumatoid arthritis	8.1	5.6	4.1	3.0	2.3	1.8	1.4	1.2	1.0	0.9	0.8	0.8	0.7
Prior fracture	9.7	6.8	5.0	3.7	2.9	2.3	1.8	1.5	1.3	1.2	1.1	1.0	0.9

TABLE 86 *Absolute annual fracture risk (%) at 65–69 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	7.0	5.2	3.9	3.0	2.4	1.9	1.5	1.3	1.1	1.0	0.9	0.8	0.7
Parental fracture	15.3	10.6	7.6	5.5	4.1	3.1	2.4	1.9	1.6	1.4	1.3	1.1	1.0
Current smoking	9.4	6.7	4.8	3.6	2.7	2.1	1.6	1.3	1.1	1.0	0.9	0.8	0.7
Corticosteroid use	12.4	9.1	6.8	5.2	4.0	3.2	2.5	2.1	1.9	1.6	1.5	1.3	1.2
Alcohol >2 units per day	9.5	6.9	5.1	3.8	3.0	2.3	1.9	1.5	1.3	1.2	1.1	1.0	0.9
Rheumatoid arthritis	9.5	7.0	5.2	4.0	3.1	2.5	2.0	1.7	1.5	1.3	1.2	1.0	0.9
Prior fracture	11.0	8.2	6.2	4.8	3.8	3.0	2.4	2.1	1.8	1.6	1.5	1.3	1.2

TABLE 87 *Absolute annual fracture risk (%) at 75–79 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	8.5	6.4	4.9	3.8	2.9	2.3	1.8	1.6	1.4	1.2	1.1	0.9	0.8
Parental fracture	22.1	15.5	11.0	7.9	5.7	4.2	3.1	2.5	2.1	1.7	1.4	1.2	1.1
Current smoking	11.1	8.1	6.0	4.5	3.4	2.6	2.0	1.7	1.4	1.2	1.1	0.9	0.8
Corticosteroid use	14.8	11.1	8.4	6.5	5.0	3.9	3.1	2.6	2.3	2.0	1.8	1.5	1.4
Alcohol >2 units per day	11.3	8.4	6.3	4.8	3.7	2.9	2.3	1.9	1.7	1.4	1.3	1.1	1.0
Rheumatoid arthritis	11.4	8.6	6.5	5.0	3.9	3.1	2.4	2.1	1.8	1.6	1.4	1.2	1.1
Prior fracture	12.6	9.6	7.4	5.7	4.5	3.6	2.9	2.5	2.1	1.9	1.7	1.5	1.3

TABLE 88 *Absolute annual fracture risk (%) at 80–84 years of age by BMD and CRFs*

	T-score (SD)												
CRFs	**–5**	**–4.5**	**–4**	**–3.5**	**–3**	**–2.5**	**–2**	**–1.5**	**–1**	**–0.5**	**0**	**0.5**	**1**
No CRFs	10.0	7.6	5.9	4.5	3.5	2.8	2.2	1.9	1.6	1.4	1.2	1.0	0.9
Parental fracture	26.2	19.0	13.8	10.1	7.5	5.5	4.2	3.4	2.7	2.2	1.8	1.5	1.3
Current smoking	13.2	9.8	7.3	5.5	4.2	3.2	2.5	2.1	1.8	1.5	1.3	1.1	0.9
Corticosteroid use	17.5	13.3	10.2	7.8	6.0	4.7	3.8	3.2	2.7	2.3	2.0	1.7	1.5
Alcohol >2 units per day	13.3	10.1	7.7	5.9	4.5	3.5	2.8	2.4	2.0	1.7	1.5	1.3	1.1
Rheumatoid arthritis	13.5	10.3	7.9	6.1	4.7	3.7	2.9	2.5	2.1	1.8	1.6	1.4	1.2
Prior fracture	14.5	11.1	8.6	6.7	5.3	4.1	3.4	2.9	2.5	2.1	1.8	1.6	1.4

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We look forward to hearing from you.

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