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

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Produced by: The University of Sheffield, School of Health and Related Research (ScHARR)

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

PUBLICATION INFORMATION

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute of Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

CONTRIBUTIONS OF AUTHORS

Matt Stevenson 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 updated the previous models and ran the new models to produce the cost-effectiveness results.

Myfanwy Lloyd Jones carried out the review of the clinical effectiveness review.

Catherine Beverley undertook the electronic literature searches.

CONFLICTS OF INTEREST

None

Source of funding

This report was commissioned by the NHS R&D HTA Programme.

Relationship of reviewer(s) with sponsor

None

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All responsibility for the contents of the report remains with the authors. This work has been built on the foundations of work undertaken for the NCCHTA, whose authors included Professor John Kanis, Dr Neill Calvert, Professor John Brazier, Dr Jeremy Oakley, Enrico De Nigris and Dr Eugene McCloskey.

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

The cost effectiveness analyses have relied heavily on soon-to-be published work for the World Health Organisation (WHO) undertaken by Professor Kanis and colleagues. This has been supplied in the strictest confidence.

Andrea Shippam, Project Administrator at ScHARR, helped in the retrieval of papers and in preparing and formatting the report.

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EXECUTIVE SUMMARY

Description of proposed service

The focus of this report is to establish whether strontium ranelate can be used cost-effectively in the treatment of women at risk of osteoporotic fracture. The evaluation of cost-effectiveness has been divided into women who have sustained a prior fracture and those who had not. In this latter group additional costs need to be considered as patients at risk would need to be identified.

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 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.

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 which reported fracture outcomes. Participants also received calcium and vitamin D supplements, with the exception of participants in the SOTI and TROPOS studies whose daily dietary calcium intake exceeded 1000 mg; these women only received vitamin D supplements.

Pooled data from the SOTI and TROPOS studies indicate that strontium ranelate therapy is associated with a significant reduction in the risk of vertebral fracture (relative risk compared with placebo 0.60, 95% confidence intervals 0.53 to 0.69, $p<0.001$) and non-vertebral fracture (relative risk 0.84, 95% confidence intervals 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 (relative risk 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 these issues are being addressed within the ongoing extension of the SOTI and TROPOS studies and by post-marketing surveillance.

Summary of benefits

Benefits have been measured in terms of "quality adjusted life-years" (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 is strongly related to the absolute risk of fracture.

Cost effectiveness of identification and treatment strategies.

The report uses a modified version of a soon-to-be published algorithm that estimates absolute fracture risk from patient characteristics. Risk factors used within our algorithm are age, sex, bone mineral density (BMD), prior fracture history, parental history of hip fracture, smoking status, alcohol consumption, rheumatoid arthritis and corticosteroid use. 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 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 (GDG), 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 our probabilistic sensitivity analyses, strontium ranelate is not expected to be the first-line therapy the introduction of this intervention is unlikely to significantly change the overall costs associated with current osteoporosis treatments such as bisphosphonates. It is noted that 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.

2 Need for further 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 dependant either on age, or on 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 in order 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.

LIST OF ABBREVIATIONS

AOPS	Alendronate Osteoporosis Prevention Study
BMD	bone mineral density
BMI	body mass index
CEAC	Cost-effectiveness acceptability curve
CEE	conjugated equine oestrogen
CHD	coronary heart disease
CI	confidence interval
CRF	clinical risk factors
DXA	dual energy x-ray absorptiometry
DSU	Decision Support Unit
GDG	(NICE osteoporosis) Guidelines development group
GI	gastrointestinal
HRT	hormone replacement therapy
ICER	incremental cost-effectiveness ratio
MAICER	maximum acceptable incremental cost-effectiveness ratio
MI	myocardial infarction
MPA	medroxyprogesterone acetate
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NSAIDs	Non Steroidal Anti-Inflammatory drugs
NOF	National Osteoporosis Foundation
PTH	parathyroid hormone
QALY	Quality-adjusted life-year
RCP	Royal College of Physicians
RNI	Reference Nutrient Intake
RR(s)	relative risk(s)
SERMs	selective oestrogen receptor modulators
SHEMO	Sheffield Health Economic Model of Osteoporosis
SD	Standard deviations
TTO	Time trade off
WHO	World Health Organisation

GLOSSARY

Body Mass Index	BMI equals a person's weight in kilograms divided by height in metres squared. Units are expressed in kg/m^2.
Osteopenia	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	The level of intake of a nutrient which is sufficient to cover the needs of nearly all the population group for which it is recommended; as it is set 2 standard deviations 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 that 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 that 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.

Comment on generic text.

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" written by Kanis JA, Brazier J, Stevenson M, McCloskey EV, Davis S and Lloyd Jones M. This was undertaken for the National Co-ordinating Centre for Health Technology Assessment and is currently under peer review.

Another report is " A systematic review and economic evaluation of interventions for the prevention and treatment of post-menopausal osteoporosis" written by Stevenson M, Lloyd Jones M, de Nigris E, Brewer N, Oakley J and Davis S. This was undertaken for the National Co-ordinating Centre for Health Technology Assessment and is currently in press.

1 THE AIM OF THE REVIEW

The review aims to estimate the clinical and cost effectiveness of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal 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 this 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 has been calculated. This analysis therefore has two components:

1. Establishing the cost-effectiveness of strontium ranelate at different levels of absolute fracture risk in post-menopausal women with osteoporosis, who have and have not had a fracture.

2. Estimating how alternative approaches for the identification of osteoporotic women who have not had a fracture impact on the cost-effectiveness of the strontium ranelate.

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 woman 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 incidences of fracture are strongly related to age, with a fairly linear increase as a woman 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 a 1/3 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 analyses 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 due to underlying comorbidities

It has been estimated that the cost of treating osteoporotic fractures in post-menopausal females 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 focussed on post-menopausal women due to the deterioration of bone quality following the menopause, which is strongly correlated with a rise in fracture incidence.

2.1 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 determine 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 (SD) from the

average BMD of healthy young women. A Z-score is defined as the number of SD that a woman is from the average BMD of women of the same age.

Two thresholds of bone mineral density (BMD) have been proposed for Caucasian women based on the T-score.[7,8] The first, osteoporosis, denotes a value for bone mineral density that is two and a half standard deviations (SD) 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 <-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 focussed on their application to epidemiology, clinical trials and patient care. Several problems have emerged, however, largely due 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 that we have chosen to use 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 women minus average T-Score for that age and sex) have been undertaken at this site.[10,11]

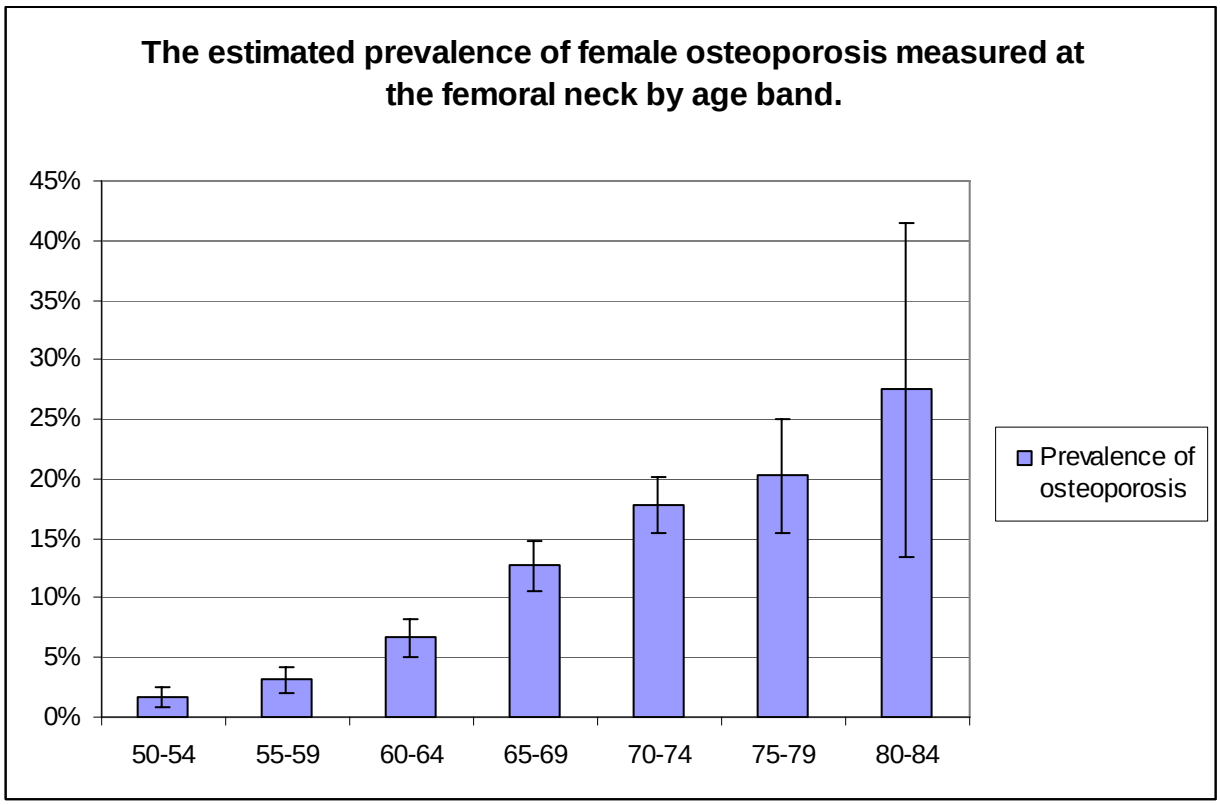
Epidemiological data

The prevalence of female osteoporosis by age

Raw data were taken from a UK population based study by Holt et al[12] and used to calculate the relationship between T-Score and age. The prevalence of osteoporosis within the UK has also been estimated from this data. This data set contained observations on 5,713 women aged between 50 and 85 years and used the NHANES III reference data for women aged 20 –29 years.

The percentage of women with a T-Score of -2.5SD or below, as measured at the femoral neck, was recorded. These data are shown in Figure 17 and exhibit a marked increase with age. The database taken from the Holt et al 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 17. Assuming however that the midpoint value 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.

Figure 17: The estimated prevalence of female osteoporosis by age band



The average T-Score at the femoral neck at 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. It is seen that above 85 years of age, the T-score for the average women almost reaches the threshold for osteoporosis.

Table 1: The average T-Scores for women by age band

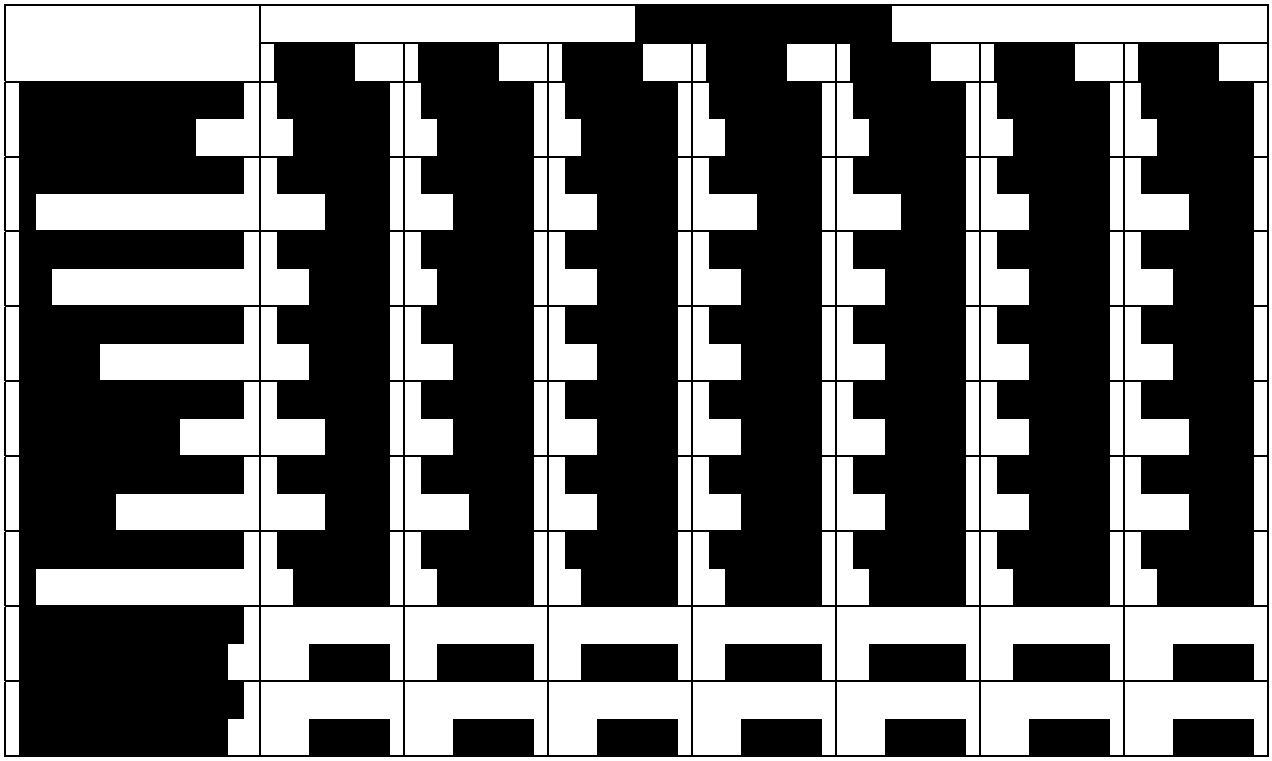
Age (Years)	Average UK T-Score, Holt[12] *	Z-Score at threshold of osteoporosis (T-Score of –2.5 SD) *
50-54	-0.66	-1.84
55-59	-0.92	-1.58
60-64	-1.17	-1.33
65-69	-1.43	-1.07
70-74	-1.69	-0.81
75-79	-1.94	-0.56
80-84	-2.20	-0.3
85-89	-2.45	-0.05

*Compared with the NHANES III reference data for women aged 20 – 29 years

The 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, sex, BMD, BMI, prior fracture, parental fracture, smoking, corticosteroid use, rheumatoid arthritis and alcohol consumption (>2 units per day). The data provided by the WHO study was broken into age bands of 5 years and T-Score bands of 0.5SD. We aggregated the data across the T-Score bands. The WHO study was a multi-centre study and not all risk factors were not recorded at every centre, meaning that the number of patients with data available varies for each risk factor combination. We assumed that there as 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 clinical risk factor combinations. Table 2 gives the prevalence of CRFs provided by the WHO data for women by age-band. The cohort size indicated in brackets for single risk factors. The prevalence given is for all women regardless of their BMD or BMI.

Table 2: Prevalence of clinical risk factors for osteoporotic fracture in women (academic in confidence)



The incidence of osteoporotic fractures by age

In previous NICE assessments of interventions for the prevention of osteoporotic fractures in post-menopausal 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 NICE

submissions by manufacturers of the drugs.[14,15,16,17,18,19] In order to present as accurate results as possible the NICE Osteoporosis Guidelines Development Group (GDG) 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 is 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 step wise 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.

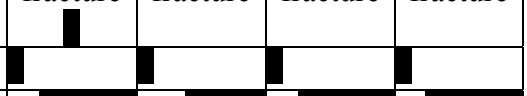
The annual risks of fracture was calculated from the algorithm used by the assessment team as follows: More detail is given in Appendix 12.

For each patient the following variables are input:
Sex (2 for women in our analyses), current age (in years), BMI (assumed to be 26 for all women in our analyses), and whether any of the following variables are present : has the patient sustained a previous fracture, did either parent suffer a previous hip fracture, do the patient smoke, does the patient consume an average of more than 2 units of alcohol per day, has the parent ever used corticosteroids and does the patient suffer from rheumatoid arthritis. (0 = no, 1 if yes)
These values were multiplied by the appropriate coefficients contained in Table A, 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 were calculated these were summed, and the resulting value exponentiated.
We have also been provided with age normalising factors and UK normalising factors, these are presented in Table B. In our analysis we have assumed a normalising factor that is an average of the 5-year band, (i.e. for a woman aged 68 we would use the mean from 65 -70). These factors have been chosen in order that the data is calibrated against the data presented in Singer et al. [21]
Thus, for a women 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,

[redacted]

If her Z-Score was -1, the risk would become

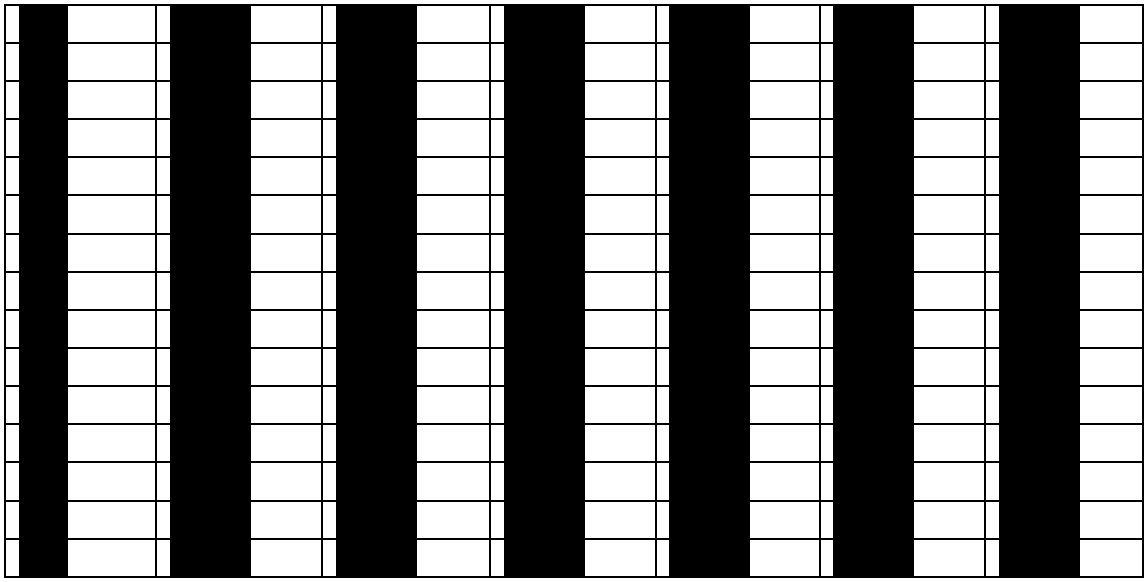
Table A. Risk Coefficients derived from the WHO cohort analysis.

	Without BMD		With BMD	
	Owh* fracture	Hip fracture	Owh* fracture	Hip fracture
				
Sex (1/2)				
Min (BMI, 25)				
Max (BMI-25,0)				
Previous fracture (0/1)				
Mother/Father (0/1)				
Current smoke (0/1)				
Corticosteroids (0/1)				
RA (0/1)				
Alcohol (0/1)				
Sex x current age				
Previous fracture x min(current age,80)				
Mother/Father x max(0,min(age-65,10))				
Min (Z-Score, 0)				
Max (Z-Score,0)				
Z-Score x current age				

*Owh denotes vertebral, wrist and proximal humerus.

Table B: Normalising factors for the UK population and for the normalising the risk.

	Factor reflecting the risk in UK		Factor for normalising the risk			
Age	for OWH* fracture	for Hip fracture	for OWH* without BMD	for OWH* with BMD	for Hip without BMD	for Hip with BMD



*Owh denotes vertebral, wrist and proximal humerus.

From communication with John 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. On communication with 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 has been provided however the full write-up of the methodology, (including normalizing factors) and of the final algorithm has not been completed as of June 2005.

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 needs 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 reported by Singer et al data,[21] and assuming that the ratio of hip to vertebral fractures seen in Malmo, Sweden,[22] was applicable to the UK are shown in Table 3. 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 are greater than those we previously used in economic evaluations.[23] This will be favourable to the intervention.

Table 3: The proportion of total vertebral, wrist and proximal humerus fractures by fracture site.

Age	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%

The inclusion of fractures other than hip, vertebral, wrist and proximal humerus.

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

In order to still use the meta-model developed for the original assessment report[23,25,26] which only considered hip, vertebral, wrist and proximal humerus fractures, we have approximated the additional fracture types to those of the existing model. As described in section 4.1.1 the disutilities associated with pelvis and other femoral fractures resulted in these being grouped with hip fracture. Tibia, fibula and humeral shaft were grouped with proximal humerus, whilst rib, scapula, clavicle and sternum were grouped with wrist fractures.

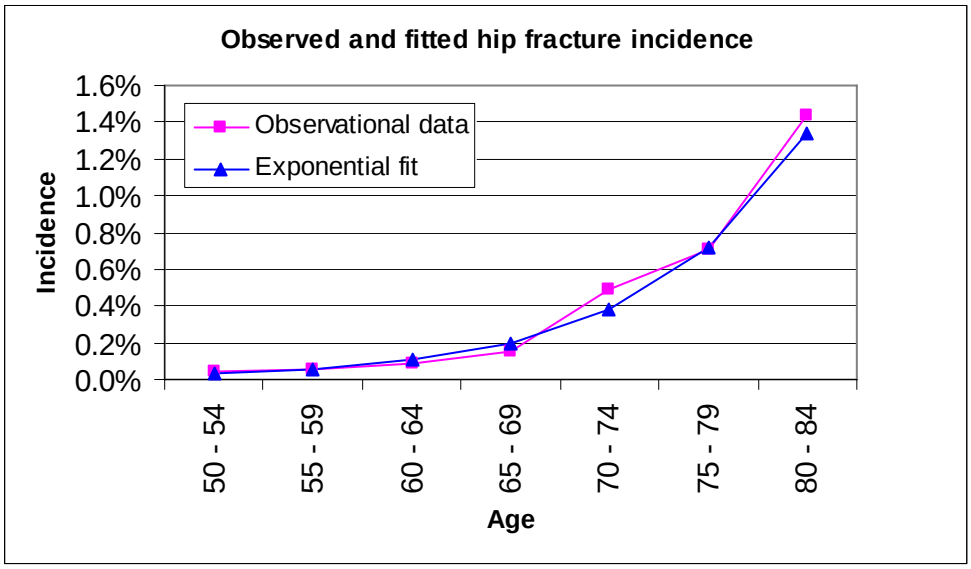
The incidence of fractures other than hip, vertebral, wrist and proximal humerus.

Data on the incidence of hip, wrist, proximal humerus, humeral shaft and other femoral fractures in females have been taken from a large scale Scottish study by Singer et al.[21]

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

In a similar manner we assumed an exponential relationship between the incidence of other femoral fractures seen in Singer et al[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.

Figure 2: The annual incidence of osteoporotic hip fracture in UK females



Data on the incidence of pelvis fractures have been derived from a Welsh study.[29] However this study includes fractures in children aged 0-14, 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 et al[29] could be used to impute pelvis fracture incidence from the Singer et al data.[21] The ratio of pelvis fracture to hip fracture was assumed to apply at all age bands.

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 Malmo, Sweden,[22] was applicable to the UK.

Given our grouping of additional fractures the estimated increase in the incidence of the original fracture types are shown in Table 4.

Table 4: Increase in incidence of hip, wrist and proximal humerus fractures to incorporate fractures at other sites

Age	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%

The increased risk of fracture following a previous fracture

There is a breadth of published literature, meta-analysed in Klotzbeucher et al.,[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 was not available when the individual patient model, which forms the foundation for all the cost-effectiveness analyses, was originally developed the increase in fracture risk experienced by individuals who sustaina fracture during the timeframe of the model was taken from Klotzbeucher et al.[30] and is summarised in Table 5. The RR point estimates, for peri/post-menopausal women, were used within the model to increase the risk of subsequent fractures following an initial fracture.

It has been assumed that the risk of secondary fractures at the proximal humerus are equivalent to the pooled non-spinal fractures category reported by Klotzbeucher et al.[30] It was also assumed that proximal humerus had the predictive power equal to that of the 'other' category reported by Klotzbeucher et al.[30] There have been no prior studies upon the future effect that hip fractures have upon 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 greatest 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).

Table 5: The 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]

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 has necessitated that a biasd be entered into the modelling. Our previous work has specified the fracture status of women entering the model. For example, women entering the model with a prior vertebral fracture would start with elevated fracture risk and these would not be increased further were another vertebral fracture 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 sustained, the risks have been further elevated. This will be favourable towards the interventions, particularly those with 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 upon age.[31] However, case control studies that adjust for pre-fracture 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 one year after hip fracture were totally unrelated to the hip fracture, 42% were possibly related and 25% directly related. These figures were not however available stratified by age, sex or residential status; but have been assumed to be constant for all population subsets.

It is likely that there was further mortality between 91 days 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 days 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 hip fracture are given in Table 6. 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 60-69 years.

Table 6: Percentage of hip fractures that result directly in mortality

Residential Status	Age Band	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%

Mortality following vertebral fracture.

Several studies have shown an increase in mortality following vertebral fracture.[3,36,37,38] In one study, women with one or more vertebral fracture had a 1.23 fold greater age-adjusted mortality rate (95% CI = 1.10-1.37).[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 = 1.70-2.14),[36] and in another study, the risk was more than 8-fold higher.[38] A study on clinical fractures from the UK compared mortality in women with osteoporosis (and no fracture) to mortality in women with osteoporosis and a previous vertebral fracture.[37] The hazard ratio was 4.4 (95% CI 1.85-10.6) 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

We have assumed no increase in mortality from forearm fractures consistent with published surveys.[3,38,40] For humeral fractures, we 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 we have assumed a mortality rate the same as that for hip. For, tibia, fibula and humeral shaft fractures we have assumed a mortality rate equal to that of proximal humerus fractures. For rib, sternum, scapula and clavicle fracture, no excess mortality was assumed.

Entry into nursing home following an osteoporotic fracture

Entry into a nursing home following a hip fracture

Data was 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 have been used in some models[41] have not been 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 7. It is assumed that women who enter a nursing home will remain there for the remainder of their lives.

Table 7: The percentage of women who move from the community to a nursing home following a hip fracture

Age Band	Percentage of women that 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%

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 remainder 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 ranges 50 – 69 years.

It is likely that the values we have assumed for entering a nursing home are underestimates as women who were initially discharged to the community, but subsequently have to reside in a nursing home are unlikely to be included within 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 would not cause a woman to move from community living into nursing home accommodation.

Death due to other causes

These data have been taken from interim life tables.[42]

Several studies have shown an increased mortality associated with low bone mineral density 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 bone mineral density adjusted for age,[43] and this factor has been used within the model, although it is unsure how much excess mortality may be related to comorbidities. 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 8. The general population mortality rates have not been adjusted to take into account the osteoporotic population, meaning that these death rates are likely to be slight over-estimates. As these apply to all interventions it is unlikely that this will bias results between interventions, but will be slightly unfavourable to all interventions.

A study[45] has 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 effects towards intervention.[23] As such we have still retained an increase in mortality associated with osteoporosis, in addition to those attributed to fracture, as this was fundamentally within the individual patient model.

Table 8: The 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%

2.2 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 these prescriptions are for women with osteoporosis, this would equate to 42% of the female osteoporotic population being prescribed medication.

2.3 Description of Interventions

2.3.1 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.

2.3.2 Interventions

This report focuses on strontium ranelate which is licensed for use in postmenopausal women who have, or are at risk of, osteoporosis (see section 2.3.2.1 below).

2.3.2.1 Summary of Product Characteristics

(a) 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/day for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.[47] The UK license for strontium ranelate is held by Servier Laboratories Limited.

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 three 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 two 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/min). No dosage reduction is required in patients with mild to moderate renal impairment (creatinine clearance 30-70 ml/min), 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]

2.3.3 Personnel involved

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

2.3.4 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 necessary to determine bone mineral density and thus ascertain the appropriateness of therapy with these or other anti-osteoporotic agents.

2.3.5 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 RCTs have been conducted with a duration of longer than 5 years, and in order to keep the results comparable with previous assessment reports we have assumed a 5-year treatment period and a 10-year time horizon.

2.3.6 Degree of diffusion

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

3 CLINICAL EFFECTIVENESS

3.1 Methods for Reviewing Effectiveness

3.1.1 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.

3.1.1.1 Sources searched

Fourteen electronic bibliographic databases were included in the clinical effectiveness searches; these are listed in Appendix 1. In addition, the reference lists of relevant articles and sponsor submissions were hand searched.

3.1.1.2 Search terms

The clinical effectiveness search strategy utilised terms specific to strontium ranelate. A copy of the Medline search strategy is included in Appendix 2. Search strategies for the other databases are available on request.

3.1.1.3 Search restrictions

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

3.1.2 Inclusion and exclusion criteria

3.1.2.1 Inclusion criteria

- **Participants:** postmenopausal women with osteoporosis, with or without previous fracture

- **Intervention:** strontium ranelate

- **Comparators**:
  - the bisphosphonate alendronate

- **Outcome measures:**
  - survival
  - incident vertebral fracture
  - incident nonvertebral fracture
  - adverse effects
  - continuance
  - compliance
  - cost
  - health-related quality of life

- **Study design:**
  - randomised controlled trials
  - 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 which 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 FIT study, 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 which require a 20% reduction in vertebral height are generally recognised as producing fewer false negatives and false positives than those which only require 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 comorbidities), and because they are not powered to identify rare, though 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 (eg self-reported questionnaire)
- pill counts
- self-recorded diaries
- electronic devices which 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 are 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 (ie within $\pm$ 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 which 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.

3.1.2.2 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 which did not report results in the necessary detail.

3.1.2.3 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 which seemed from their abstracts to be relevant were then read in full. Studies for which abstracts were not available were also read in full.

3.1.3 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 nonvertebral fractures
- incident hip fractures
- incident wrist fractures
- incident humeral fractures
- adverse effects
- continuance and compliance.

3.1.4 Quality assessment strategy

The methodological quality of all trials which met the inclusion criteria was assessed using the tool developed by Gillespie et al.[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 et al 1988[59] were incorporated in the tool (see Appendix 3).

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]

3.1.5 Meta-analysis strategy

Studies which met the review's entry criteria were eligible for inclusion in the meta-analyses, if this was appropriate (ie 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 which 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.[62] 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 have also been calculated in Review Manager using the random-effects model. Where this has not been possible, but relative risks have been calculated by the study investigators, these have been reported, and the fact that they are the investigators' calculations has been noted.

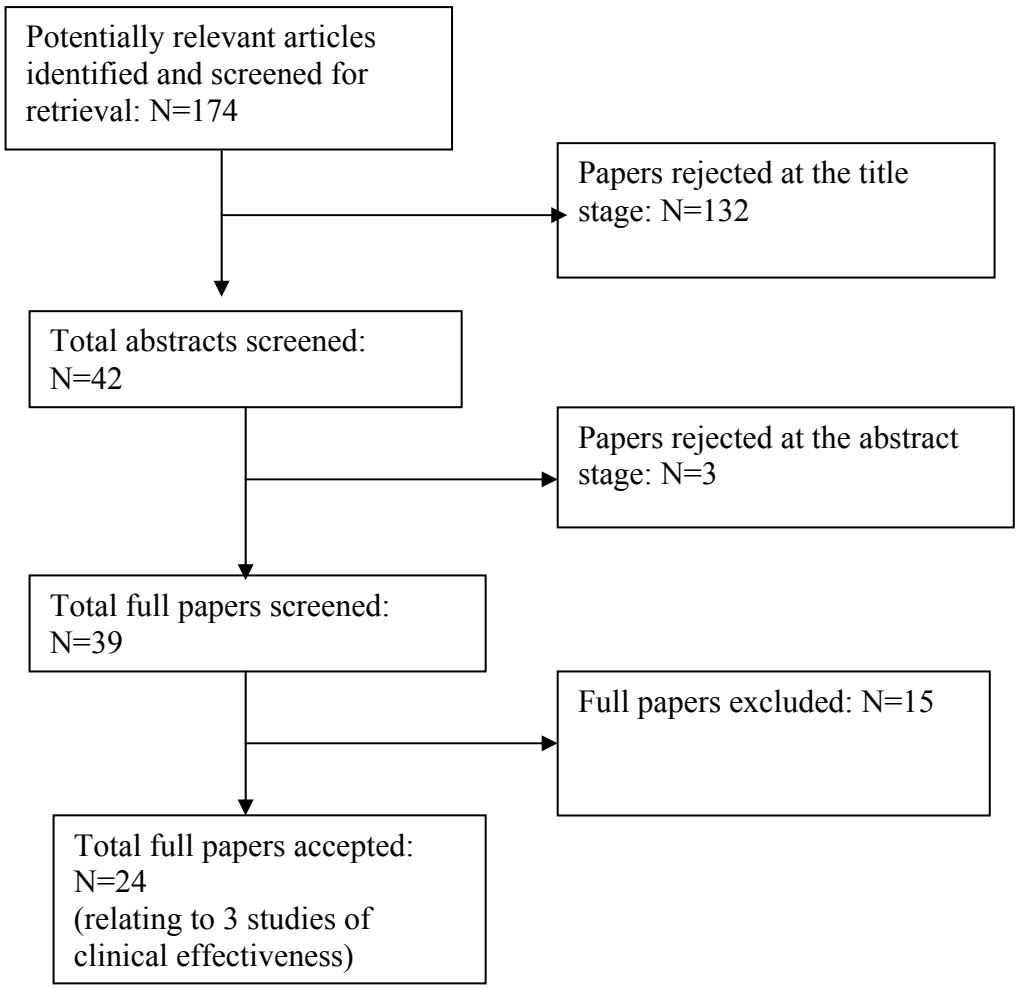
3.2 Results

3.2.1 Quantity and quality of research available

3.2.1.1 Number of studies of clinical efficacy identified

The electronic literature searches identified 174 potentially relevant articles. Of these, 24 articles related to three trials which compared strontium ranelate with a relevant comparator in postmenopausal women with osteoporosis (see Figure 3).

Figure 3: Summary of Study Selection and Exclusion: Electronic Literature Searches



An additional reference[63] relating to one of the included studies was identified only from a citation.

3.2.1.2 Number and type of studies included

A total of three individual RCTs, the SOTI, STRATOS and TROPOS studies, met the review inclusion criteria. The various publications relating to these studies are listed in Appendix 4.

3.2.1.3 Number and type of studies excluded, with reasons

As may be seen from section 3.2.1.1 above, a substantial number of the references identified by the electronic searches did not relate to studies which met the inclusion criteria; these were excluded as part of the sifting process. Details are therefore given only of those references which 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 5.

No studies which would otherwise have been included were excluded for either of the reasons listed in section 3.1.2.2.

3.2.1.4 Tabulation of quality of studies

3.2.1.5 Tabulation and discussion of results: assessment of effectiveness

As noted in section 3.1.2.1 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.

3.2.1.5.1.1 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, multi-centre, double-blind, 2-year phase II dose-ranging study (the STRATOS study[64]) and two randomised, multi-centre, double-blind, 3-year phase III studies, the SOTI[65] and TROPOS[66] studies (for further details of study design and reporting quality, see Appendix 6).

The aim of the STRATOS study was to identify the smallest dose of strontium ranelate which was effective in treating postmenopausal vertebral osteoporosis, using BMD of the lumbar spine adjusted for bone strontium content as the primary endpoint. Participants were randomised to strontium ranelate at doses of 0.5, 1 and 2 g/day, or to placebo. In addition, all participants received 500 mg calcium and 800 IU vitamin D_3 daily.[64] Recruitment for the STRATOS study began in 1992, and the 2-year follow-up of the last patient ended in 1995.[67]

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

- to start normalising calcium and vitamin D status;
- to select participants for inclusion in either the SOTI or the TROPOS study according to the inclusion criteria of each study;[68] and
- to exclude patients most likely to prematurely discontinue the trial.[69]

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/d: 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/d, subsequently increased to 800 IU/d 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.[68]

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.[68]

9,196 women who were considered to be suitable candidates for SOTI or TROPOS were recruited to the FIRST study. However, only 6,740 (73.3%) were in fact eligible for inclusion in those studies. Of the remainder, 1,173 failed to meet the inclusion/exclusion criteria, and 338 had a concomitant medical condition which precluded their inclusion. Despite the short duration of the FIRST study (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.[69]

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.[65] However, in the event only 86.9% of the study population actually had prevalent vertebral fractures.[70] The aim of the TROPOS study was to assess the efficacy of strontium ranelate in reducing the incidence of nonvertebral fractures in postmenopausal with osteoporosis with or without fracture.[66]

3.2.1.5.1.2 Assessment of effectiveness of strontium ranelate

Vertebral fracture

All three studies only reported fractures which occurred in previously intact vertebrae. In the TROPOS study, 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.[66]

Table 9: Strontium ranelate: vertebral fracture data

Study	Dose	Fracture definition	Number in each group suffering vertebral fracture	Number needed to treat for a given period to avoid an event (95% CI)
STRATOS[64]	0.5, 1 and 2 g/d	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 (0.71-1.67) 1 g: 39.7%, RR 1.18 (0.78-1.78) 2 g: 29.7%, RR 0.88 (0.56-1.40) Placebo: 33.7% Months 12-24: 0.5 g: 24.2%, RR 0.51 (0.31-0.84) 1 g: 40.9%, RR 0.87 (0.59-1.26) 2 g: 26.5%, RR 0.56 (0.35-0.89) Placebo: 33.7% Months 1-24: 0.5 g: 38.8%, RR 0.71 (0.49-1.02) 1 g: 56.7%, RR 1.04 (0.77-1.39) 2 g: 42.0%, RR 0.77 (0.54-1.09) Placebo: 54.7%	Not calculable
SOTI[65]	2 g/d	Semiquantitative (method of Genant)	Months 1-12: SR: 44/686 Placebo: 85/699[71] RR 0.53 (0.37-0.75), p=0.003 Months 1-36: SR: 139/719 Placebo: 222/723[71] RR 0.63 (0.52-0.67), p<0.0001 Months 25-36:[72] RR 0.49 (0.33-0.74), p<0.001 (investigators' calculations) Clinical fracture, months 1-12: SR: 22/686 Placebo: 46/699[71] RR 0.49 (0.30-0.80), p=0.005 Clinical fracture, months 1-36: SR: 75/719 Placebo: 117/723[71] RR 0.64 (0.49-0.85), 0.001	Radiographic fracture 1 year: 18 (11-37) 3 years: 9 (6-14) Clinical fracture 1 year: 30 (18-90) 3 years: 18 (11-44)
TROPOS[66]	2 g/d	Semiquantitative (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	Not calculable

			investigators. Months 1-12: SR: ?/1817 Placebo: ?/1823 RR 0.55 (0.39-0.77), p<0.001 Months 1-36: SR: ?/1817 Placebo: ?/1823 RR 0.61 (0.51-0.73), 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 1 baseline fracture: SR (n=587): 22.7% Placebo (n=637): 31.5% RR 0.68 (0.53-0.85), <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 (0.53-0.69), p<0.001	NNT calculated by Topol: 11[47]

The STRATOS study 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 two 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/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 the SOTI and TROPOS studies 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 three-year period (see Table 9).

It was not possible to combine the results of the SOTI, STRATOS and TROPOS studies by meta-analysis as the SOTI and TROPOS studies did not publish the actual numbers of participants who sustained incident vertebral fracture, and vertebral fracture data relating to the TROPOS study 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 three years of 0.60 (95% CI 0.53-0.69).[47]

The investigators carried out a number of pre-planned 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 10.

Table 10: SOTI and TROPOS subgroup analyses: incident vertebral fractures over 3 years

Subgroup	No of patients with fracture	Relative risk (95% CI)	Number needed to treat for 3 years to avoid an event (95% CI)
Women aged ≥80 years (n=895)[63]	SR: 19.1% Placebo: 26.5%[48]	0.68 (0.50-0.92)[46] p=0.013[63]	13[47]
Postmenopausal women with osteoporosis but without prevalent vertebral fracture (n=2605)[73]	SR: 87/1285 Placebo: 161/1320	0.56 (0.43-0.71) p<0.00001	19 (13-31)
Postmenopausal women with lumbar and/or femoral neck osteopenia with or without prevalent fractures (n=409)[74]	SR: 8.1% Placebo: 18.6%[47]	Investigators' calculations 0.38 (0.21-0.70) p=0.001[74]	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 (0.07-0.99) p=0.045[74]	12[47]
Postmenopausal women with lumbar osteopenia with or without prevalent vertebral fracture (n=1170)[75]	SR: 11.1% Placebo: 17.8%[47]	Investigators' calculations 0.60 (0.43-0.83) p=0.002[75]	15[47]
Postmenopausal women with lumbar osteopenia with prevalent vertebral fracture (n=722)[75]	SR: 15.5% Placebo: 23.6%[47]	Investigators' calculations 0.63 (0.44-0.89) P=0.008[75]	12[47]
Postmenopausal women with lumbar osteopenia without prevalent vertebral fracture (n=448)[75]	SR: 3.5% Placebo: 8.6%[47]	Investigators' calculations 0.41 (0.17-0.99) P=0.038[75]	20[47]

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 (see Table 11).

Table 11: Strontium ranelate: all non-vertebral fractures

Study	Dose	Number in each group suffering nonvertebral fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS[64]	0.5, 1 and 2 g/d	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 relative risk, nor was this reported by the study investigators.	Not calculable
SOTI[65]	2 g/d	All nonvertebral fractures: Strontium ranelate: 112/826 Placebo: 122/814 RR 0.90 (0.71-1.15), p=0.41	71*
TROPOS[66]	2 g/d	Patients with at least 1 incident osteoporosis-related peripheral fracture at 3 years:[66] SR: 233/2479 Placebo: 276/2453 RR 0.86 (0.73-1.02)	54 (28-647)
SOTI + TROPOS[46]	2 g/d	Peripheral osteoporosis-related fractures: SR: 331/3295 Placebo: 389/3256 RR 0.84 (0.73-0.97), p=0.01 NB because of the form in which the data were available, it was only possible calculate the relative risk 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 (29-259)

*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)

In the TROPOS study, the incidence over time of patients with at least one incident osteoporosis-related peripheral fracture was lower in the strontium ranelate group than in the placebo group from the first months of treatment onwards.[70] [redacted]

Again, the investigators carried out a pre-planned subgroup analysis pooling nonvertebral fracture data from SOTI and TROPOS relating to women aged 80 and over (see Table 12). However, the same caveats apply as to the subgroup analyses of vertebral fracture data discussed above. Again, the results were presented in a form which did not permit the calculation of the relative risk and confidence intervals, and those reported here were calculated by another investigator.[47]

Table 12: Subgroup analyses: incident non-vertebral fracture

Subgroup	No of patients with fracture	Relative risk (95% CI)	Number needed to treat for 3 years to avoid an event (95% CI)
Women aged ≥80 (n=1488)[63]	SR: 14.2% Placebo: 19.7%[47]	0.69 (0.52-0.92) p=0.011[47]	18[47]

Hip, wrist and other non-vertebral fractures

None of the studies were 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 or wrist fracture in relation to its full intention-to-treat population (see Table 13 and Table 14). Although, in the TROPOS study, a significant reduction in hip fracture was seen in the subgroup of women who were aged over 74 and were osteoporotic at study entry (see Table 13), it should again be born in mind that this is not a true randomised comparison.

Table 13: Strontium ranelate in postmenopausal osteoporosis or osteopenia: hip fracture data

Study	Dose	Number of women in each group suffering hip fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS	0.5, 1 and 2 g/d	Not reported	-
SOTI	2 g/d	Not reported	-
TROPOS	2 g/d	All participants:[70] Strontium ranelate: [redacted]/2479 Placebo: [redacted]/2453 RR [redacted] Participants aged over 74 and osteoporotic at baseline:[70] Strontium ranelate: 32/982 Placebo: 51/995 RR 0.64 (0.41-0.98), p=0.04	[redacted] Aged over 74 and osteoporotic at baseline: 54 (28-968)

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

Study	Dose	Number of women in each group suffering wrist fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS	0.5, 1 and 2 g/d	Not reported	-
SOTI	2 g/d	Not reported	-
TROPOS	2 g/d	Strontium ranelate: [redacted]/2479[redacted] Placebo: [redacted]/2453[70] RR [redacted]	[redacted]

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

Study	Dose	Number of women in each group suffering humerus fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS	0.5, 1 and 2 g/d	Not reported	-
SOTI	2 g/d	Not reported	-
TROPOS	2 g/d	Strontium ranelate: [redacted]/2479[redacted] Placebo: [redacted]2453[70] RR [redacted]	[redacted]

3.2.1.5.1.3 Adverse effects

Pooled data from the SOTI and TROPOS studies 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 (ie those which occurred in more than 1% of the treatment or placebo group) are set out in Table 16. 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.[64]

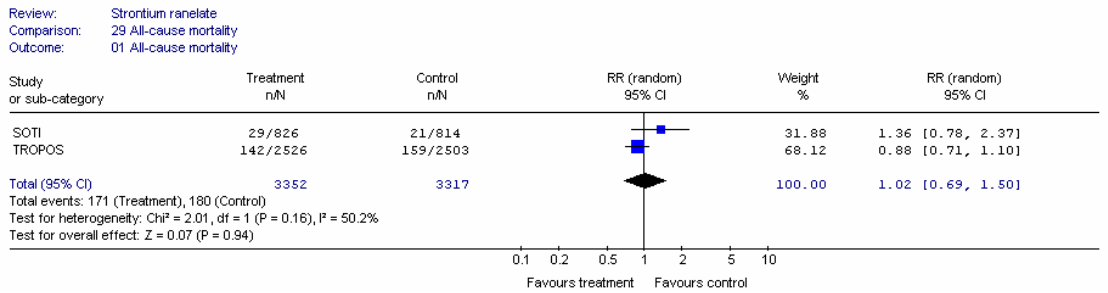
Table 16: Number of patients with common emergent adverse events – pooled data from the SOTI and TROPOS studies

Adverse event	Strontium ranelate (n=3352)	Placebo (n=3317)	RR (95% CI)	p value
Nervous system disorders				
Headache[46]	101 (3.0%)	79 (2.4%)	1.27 (0.95-1.69)	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 (1.26-1.90)	>0.0001
Diarrhoea[46]	219 (6.5%)	154 (4.6%)	1.41 (1.15-1.72)	0.0008
Loose stools[46]	36 (1.1%)	6 (0.2%)	5.94 (2.51-14.07)	<0.0001
Skin and subcutaneous tissue disorders				
Dermatitis[46]	69 (2.1%)	54 (1.6%)	1.26 (0.89-1.80)	0.19
Eczema[46]	50 (1.5%)	40 (1.2%)	1.24 (0.82-1.87)	0.31
Allergic dermatitis[46]	33 (1.0%)	18 (0.5%)	1.81 (1.02-3.22)	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 (1.02-1.98)	0.036[48]
Pulmonary embolism as serious AE[46]	25	14	1.77 (0.92-3.39)	0.09
Fatal pulmonary embolism[46]	6	3	1.98 (0.50-7.91)	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 (1.52-1.85)	<0.00001
Creatine kinase >3 times upper limit of normal[48]	1.0%	0.4%	Not calculable	

The most serious adverse event associated with strontium ranelate therapy, an increased incidence of venous thromboembolism (VTE), including pulmonary embolism, was less common, and was only identified when data from the SOTI and TROPOS studies were pooled. The relative risk of VTE in patients receiving strontium ranelate compared with placebo, was 1.42 (95% CI 1.02-1.98, 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 SR group reported pulmonary embolism as a serious AE 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 within the ongoing extension of the SOTI and TROPOS studies and by post-marketing 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 the SOTI and TROPOS studies did not indicate an increase in all-cause mortality in patients receiving strontium ranelate (RR 1.02, 95% CI 0.69-1.50) (see Figure 4). However, there was an increased death rate due to cardiac disorders in patients receiving active treatment during the first year of therapy, but not thereafter. Deaths which 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]

Figure 4: All-cause mortality



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 (see Table 17).

Table 17: Number of patients discontinuing because of emergent adverse events considered possibly related to study therapy – pooled data from the SOTI and TROPOS studies[46]

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

3.2.1.5.1.4 Quality of life

Both the SOTI and the TROPOS studies recorded health-related quality of life every 6 months using the SF36; the SOTI study also used the QUALIOST questionnaire.[68]

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 SF36 general scale compared with placebo.[70]

No quality of life results were presented for the TROPOS study.

3.2.1.5.1.5 Continuance and compliance

Both the STRATOS and SOTI studies presented data relating to compliance, but neither gave their definition of compliance and only the STRATOS study indicated how it had been measured (see Table 18).

Table 18: Compliance with study treatment

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

All three studies provided information on the proportion of participants who completed follow-up for the planned length of the study (see Table 19). However, while it is clear that, in the STRATOS study, this figure represents the proportion who continued to take the study medication for the length of the study period, it is not clear whether all the participants who completed follow-up in the SOTI and TROPOS studies were still taking the study medication at the end of the three-year period.

Table 19: Proportion of participants completing study

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

It is generally accepted that continuance and compliance with medication is higher in RCTs than in general clinical practice. This is particularly likely to be true of the SOTI and TROPOS studies, 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 adverse reactions or low compliance.[69] Unfortunately, no UK studies have been identified which 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 1st January 1998 to 30th 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, compared with 31% of those using two HRTs. Older patients were generally likely to continue therapy for slightly longer than those under 55 years of age.[76] 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.[77] A survey of 813 women treated with alendronate found that, at six months, 29% stated that they had discontinued treatment, while prescription refill records suggested that, in fact, 30% had discontinued treatment.[78]

Table 20: Real-life continuance with non-hormonal anti-osteoporotic therapies

Medication	%age of patients still taking medication		
	At 6 months	At 1 year	At 2 years
Alendronate[78]	70%	No data	No data
Bisphosphonates[76]	No data	24%	No data
Raloxifene[76]	No data	18%	No data
Raloxifene[77]	No data	No data	44%

3.3 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 nonvertebral fracture. The numbers needed to treat for three years to avoid an event are 9 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 which stimulate bone formation.[79] A recent small prospective non-randomised study has 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.[80] There is as yet no evidence to indicate whether prior alendronate therapy also reduces the effectiveness of strontium ranelate.

3.4 Efficacy data used in the model

With their wide knowledge of the vast published literature clinicians within the GDG believe that there is no plausible reason for fracture efficacy to be altered following a fracture as in many RCTs the confidence intervals of efficacy in women with fracture and those without have similar midpoints and overlapping confidence intervals. As such, RCT results on women have been pooled regardless of fracture history.

Based on similar evidence the GDG also believe that the efficacy of interventions for osteoporosis should be assumed to be the same for women with osteopenia and women with osteoporosis. We have therefore 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 will be used for these fractures also. It was assumed that the efficacy in reducing hip, pelvis and other femoral fractures would be equivalent to that for hip fractures alone.

The meta-analysed fracture efficacy data is summarised in Table 21. The assessment group was unable to carry out an independent meta-analysis of the SOTI and TROPOS trials for vertebral fracture and non-vertebral fracture due to inadequate reporting of the data. Instead the RRs are taken from published meta-analyses.

Table 21: RR of fracture for women with severe osteoporosis, osteoporosis or osteopenia. Assumes efficacy seen in women with osteoporosis, severe osteoporosis and osteopenia.

Drug	Vertebral	Hip*	All non-vertebral fractures**
Strontium ranelate	0.60 (0.53 – 0.69)[47]	[redacted]	0.84 (0.73 – 0.97)[46]

*Assumed applicable to other femoral and pelvis fractures
** Assumed applicable to wrist, humerus, rib, sternum, scapula, clavicle, tibia and fibula fractures.

We have 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.

3.5 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.

3.5.1 ALENDRONATE

Alendronate is an oral bisphosphonate that is licensed in the UK at 5 mg/day for the prevention of postmenopausal osteoporosis and the treatment of corticosteroid-induced osteoporosis, and at 10 mg/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/week for the treatment of postmenopausal osteoporosis.[81]

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 to 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 mls or 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

Due to lack of experience, Fosamax® is not recommended for patients with renal impairment where GFR is less than 35 ml/min. It should not be given to pregnant or lactating women.[14]

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

3.5.2 Efficacy

The clinical effectiveness of alendronate in the treatment of post-menopausal osteoporosis has been recently reviewed and reported.[82] The results of the previous review, which are summarised in Table 22 will be used in the current analysis.

Table 22: RR 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*	All non-vertebral fractures**
Alendronate	0.56 (0.46 – 0.68)	0.62 (0.40 – 0.98)	0.81 (0.68 – 0.97)

*Assumed applicable to other femoral and pelvis fractures
** Assumed applicable to wrist, humerus, rib, sternum, scapula, clavicle, tibia and fibula fractures.

4 ECONOMIC ANALYSIS

The assessment group have reviewed the existing economic analysis evidence, taken to be the submission documents[19] using the quality assessment checklist presented by Drummond.[83] These are presented in Appendix 7. The remainder of this section relates to the economic model constructed by the assessment group.

This section is divided into the following two components:

1. 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.
2. 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.

4.1. Cost effectiveness of interventions at different levels of absolute risk

Methods for economic analyses.

The assessment group has constructed a peer-reviewed model to estimate the cost-effectiveness of osteoporosis interventions.[84,85] 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 section 2, other fracture types are subsumed into these groups, but for reasons of brevity we will refer to just the 4 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 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 has been calculated against a no treatment option in order to evaluate if it can be given cost-effectively. An incremental analysis against alendronate has also been conducted to estimate the cost-effectiveness of strontium ranelate relative to a current standard treatment.

This section is divided into the following sub-sections.

- 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 within the model
- The costs associated with each event contained within the model.
- The cost-effectiveness ratios calculated for each intervention

The 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) that has been previously reported.[84,85] 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.[86,87]

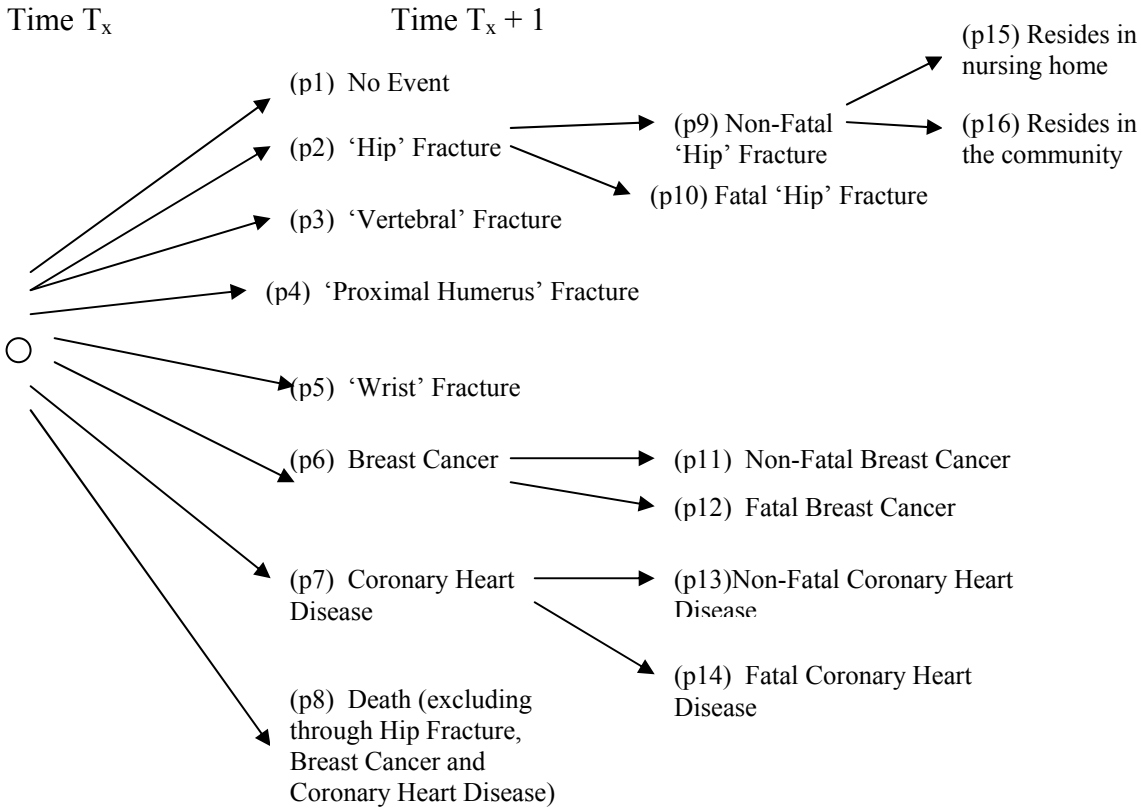
The basic design of SHEMO is similar, in many ways, to the conventional state transition models used in the area of osteoporosis, where women pass through states using a set of time dependent transition probabilities, and each state has its associated costs, mortality rates and health state utility values. However, it differs in a crucial respect to 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 occurred in the forthcoming year and then a mean estimate is taken of costs and QALYs for each cohort.

The full patient history is recorded and factors such as prior fractures and current residential status can be used therefore to determine the likelihood of events in the next time period. Following the simulated event, the quality of life of the patient and costs incurred in that time 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 have 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 8.

The time horizon of the model was constrained to a 10-year period, due to the likely treatment effects being confined within this period. In addition 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 due to mortality within the time horizon. This methodology is explained in Appendix 9.

A diagram of the model structure is provided in Figure 5. The original fracture has been written, although the additional fractures are included. For example, ‘hip’ also includes pelvis and other femoral fracture.

Figure 5: The structure of the model



Logical Constraints:

$p1 = 1- p2-p3-p4-p5-p6-p7-p8$ $p9 + p10 = p2$ $p15 + p16 = p9$

$p11 + p12 = p6$ $p13 + p14 = p7$

The exact values of p2: p14 will be determined by the patient age, patient history regarding the presence of previous fracture at each site, and the residential status of the patient. 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 which 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 slightly 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 et al.[30] The increased risk of fracture as the woman ages, has been taken from the underlying rise in fracture rates reported in Singer et al[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 has been set to 6% per annum, in accordance with published guidelines.[88] The default discount rate for QALYs has been set to 1.5% per annum.[89]

As a patient moves into a transition state, there is an initial one-off cost incurred and an on-going cost incurred that is assumed to last until the end of the simulation. By using such a methodology, states with high on-going 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 has been assumed that only the one-off costs will be incurred with the on-going 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/year, a further vertebral fracture in the same individual would cost a further £600 however the recurrent costs would not increase from £300/year. This may underestimate the costs involved but few data were found on the additional on-going 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 their quality of life. It has been 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. By using this methodology, states from which the patient will recover but not to the level prior to the event can be modelled. It is assumed that when a patient suffers a transition state for a second or more time that only the initial year 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 than the first, or a second vertebral fracture. However due 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 have been calculated. The efficacy of each treatment is modelled by the use of relative risks (RRs) in entering a transition state. It is expected that a cohort using a treatment with a RR of 0.5 for hip fracture would, in the next time 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 RRs were sampled from the meta-analysis of efficacy undertaken.

The effect of treatment on fracture probability was assumed 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 have been 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 time period of 5 years. Sensitivity analyses have been conducted using the assumption of lifetime treatment.

The cost savings and QALY gains associated with a set of RRs is dependent on the underlying fracture probability, with the beneficial effects of a 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 our model the absolute risks of fracture are calculated from age, T-Score, and the presence of CRF. As the simulation progresses, the presence of prior fragility fractures impacts on the risk of fracture as described in section 2.

Each treatment option has also been assigned GP costs in addition to drug acquisition, Following GDG 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 1/3 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 months of drug costs but receives no health benefits.

It has been assumed that for a year in which death occurred, the QALYs gained are half that 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 was converted into a meta-model by the use of 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 RRs can be instantly calculated with the benefits associated with an individual patient methodology retained.

Formulating cost-effectiveness results.

In order 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 to a no-treatment option, divided by the additional life years gained compared to 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 quality adjusted life year" (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 of time, 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.[90]

The QALY approach thus 'quality adjusts' survival. A person expected to survive 10 years at a quality of 0.8 has eight 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 eight and one, respectively).

Recent NICE guidance (http://www.nice.org.uk/pdf/TAP_Methods.pdf) suggests that cost per QALY values of less than £20,000 will be deemed cost-effective, whilst those between £20,000 - £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 are 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 (£9,999/ 0.99) and if this is below our 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, whilst conversely a minimal health loss would provide a large negative cost per QALY value.

Net Benefit:

Due to potential difficulties in interpreting cost per QALY values, the use of "Net Benefit" is becoming more widespread. Whilst 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 directly compared across interventions and Net Benefit is a continuous variable.

Net Benefit is calculated from the formula:

$$NB = \lambda Q - C$$

Where: NB denotes Net Benefit,
λ denotes the maximum cost per QALY that society is prepared to pay; (in the following example we will assume this is £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 our example, the Net Benefit of the first intervention would be equal to:

£30,000 * 0.01 - £1 = £299,

Our second intervention would have a Net Benefit of:

£30,000 * 1 - £10,000 = £20,000.

As both Net Benefits are positive, both treatments are cost-effective. However the more cost-effective is the second intervention as it has a higher Net Benefit.

4.1.1 A 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 previously reported.[23] Recent searches have identified only one additional study. This study by Kanis et al.[91] estimates utility multipliers for hip, vertebral, wrist and humerus fractures in both the first and second years following fracture. This was a comprehensive study which provides a recent and coherent source of health state utility values for all the fracture types which are used within the model. The values provided are not too dissimilar to those reported by other studies and the data from this new source was therefore used in the model.

The utilities reported by Kanis et al[91] 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 23. The only case where the utility data did not match closely was for tibia and fibula fractures (multiplier of 0.926) compared to proximal humerus fractures (multiplier of 0.973) in the 2nd year. To

prevent the disutility of tibia and fibula fractures being underestimated we have calculated a weighted mean 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 ages 50-54 to 0.966 at ages 80 years and over.

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

Table 23: Health state utility values according to site of fracture for women.[91]

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 2nd and subsequent years following fracture is 0.813 for hip fracture but greater than 0.9 for all other fractures. A sensitivity was carried out to assess the extent to which this error favours intervention in women with a previous fracture, it was seen that if the cost per QALYs are underestimated by approximately 5%, by assuming no long term disutility for women with a prior fracture. (see appendix 11) Thus we have favoured interventions in women with prior fractures, particularly in the hip or vertebrae, where the residual effect is greatest.

4.1.2 Cost Data used in the treatment model

This report uses the costs reported in a systematic review by Kanis et al.[92] having inflated, where applicable to 2003/2004 prices.[93] The costs of fatality were inadvertently omitted from the parameters that were varied in the construction of the Gaussian Process model, thus these have had to remain constant at the 1999/2000 value. This error is not expected to have significant impact on the cost-effectiveness ratios, but will slightly favour no treatment over interventions with beneficial effects on the incidences of hip fracture.

The costs presented have been 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 have also been 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 et al.[92] with the updated costs given in Table 24. 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 http://www.nice.org.uk/pdf/Alz_assessment_report_0205.pdf. 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 has been estimated at £18.00,[93] the cost of a BMD scan has been estimated at £35 as previously used in a NICE assessment.[23]

Table 24: The costs of each event, by age and by initial and subsequent years.

	Ages 50 – 54 costs (£)		Ages 60 - 64 costs (£)		Ages 70 – 74 costs (£)		Ages 80 - 84 costs (£)	
State	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 *	5,157	-	5,157	-	6,487	-	8,538	-
Hip Fracture Leading to Nursing Home entry *	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 ***	359	-	359	-	359	-	585	-
Proximal Humerus Fracture **	1,024	-	1,024	-	1,024	-	1,674	-

* Assumed applicable for pelvis and other femoral fracture
** Assumed applicable for rib, sternum, clavicle and scapula
*** Assumed applicable for tibia, fibula and humeral shaft fractures
Cost at ages 55 - 59, 65 – 69 and 75 - 79 years have been interpolated from the above data.

The report from Kanis et al[92] did not age-weight proximal humerus fracture, nor make a distinction between the costs of wrist fracture between 50 years and 70 years. If such a weighting does exist the model is expected to slightly favour treatment in the young at the expense of the old.

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 25 and came from the British National Formulary.[94]

Table 25: The cost for each intervention per annum.

Intervention	Assumed Dosage	Cost per Annum (£)
Strontium ranelate	2g per day	334
Alendronate	10 mg per day	301

4.1.3 Calculation of the cost-effectiveness of each intervention.

In our previous analyses of treatments for the prevention of osteoporosis[95] 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 RRs. 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 we now assess 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 have been conducted for some selected analyses and cost-effectiveness acceptability curves produced.

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

$$\mu = 10^{\left(\left[2m+S^2\right]/2\right)}.$$

Using this formula the point estimates in Table 26 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 cost-effectiveness acceptability curves (CEACs) as only a mid-point estimate is generated. However, as the efficacy data typically does not have highly skewed upper limits, the loss in accuracy is not expected to be large.

Table 26: The assumed RR of fracture for each intervention in women with osteoporosis.

	hip	spine	wrist	All non-vertebral fractures
Strontium ranelate	[redacted]	0.60	0.84	0.84
Alendronate	0.63	0.56	0.81	0.81

In order 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.

The cost-effectiveness analysis stopped after a time horizon of 10 years. In order 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 9 for the full methodology).

4.1.4 Cost-effectiveness analyses results

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
    - Intervention thresholds by age and clinical risk factors
    - Probabilistic sensitivity analysis
- Results for patients without a prior fracture
    - Intervention thresholds by age and clinical risk factors

Cost effectiveness for different levels of absolute risk

This section establishes the cost-effectiveness of strontium ranelate compared to 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 the relative risks associated with T-Score. If the contribution of 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 CRF. 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 5 where the cost-effectiveness is shown by absolute fracture risk thresholds for women aged 70-74 with different CRF. 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 6: Cost-effectiveness of strontium ranelate compared to no treatment at ages 70-74 for women with different clinical risk factors (CRFs)

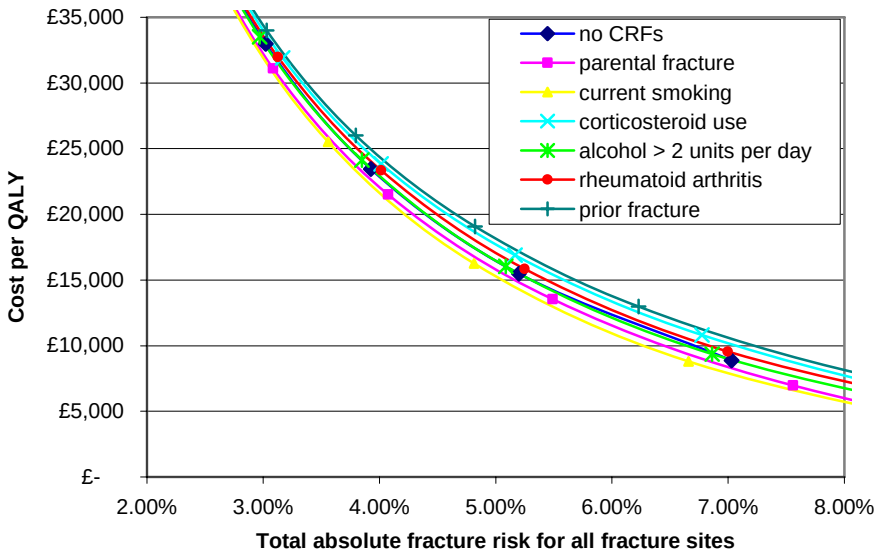


Figure 7 gives the cost-effectiveness of strontium ranelate for women, at different ages, with no CRF. The results are broadly comparable across age. Differences in the values are accounted for by the ratio of the increases in hip to non-hip fracture risk as a women ages and also other factors such as 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 10.

Figure 7: Cost-effectiveness of strontium ranelate compared to no treatment for women with no clinical risk factors according to age

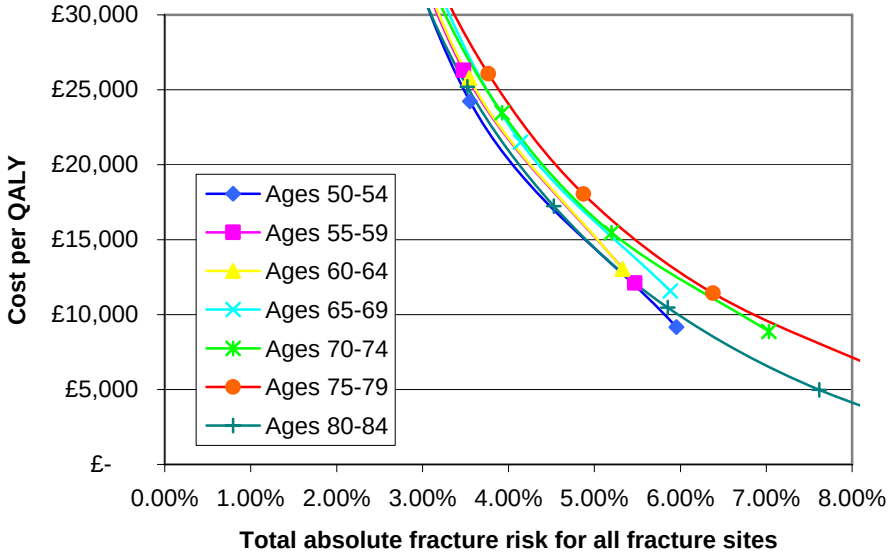
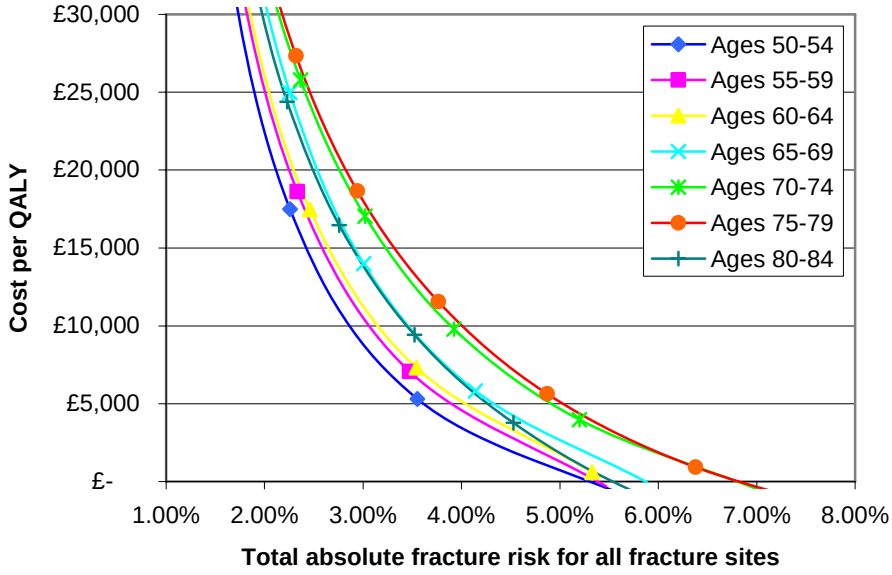


Figure 8: Cost-effectiveness of alendronate compared to no treatment for women with no clinical risk factors according to age



Results for patients with prior fracture.

The results provided in Table 27 through to Table 40 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 then the absolute risk threshold was not calculated. Whilst the calculations of the cost-effectiveness ratios presented in this report is based on absolute fracture risk of hip and non-hip fractures, it is acknowledged that clinicians would need practical advice which is related to the T-Score of the woman, and thus this information has been provided. It is seen that based on our results alendronate appears more cost-effective than strontium ranelate. One caveat is that strontium ranelate has efficacy data in the elderly (those aged 80 years and above) whereas bisphosphonates have relatively fewer 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 –3.5SD, to be cost-effective assuming a MAICER of £20,000. This is given in Table 27.

Table 27: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 50 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 28: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 55 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 29: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 60 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 30: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 65 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 31: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 70 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 32: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 75 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 33: T-Scores and risk thresholds by CRF for strontium ranelate in the secondary prevention of osteoporotic fractures at 80 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 34: T-Scores and risk thresholds by CRF for alendronate at 50 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 35: T-Scores and risk thresholds by CRF for alendronate at 55 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 36: T-Scores and risk thresholds by CRF for alendronate at 60 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 37: T-Scores and risk thresholds by CRF for alendronate at 65 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 38: T-Scores and risk thresholds by CRF for alendronate at 70 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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 39: T-Scores and risk thresholds by CRF for alendronate at 75 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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	N/A

Table 40: T-Scores and risk thresholds by CRF for alendronate at 80 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	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	N/A
3 risk factors including prior fracture and parental fracture	>1	N/A	>1	N/A

Probabilistic sensitivity analysis

The results provided in Table 27 through to Table 40 have assumed that the midpoint efficacy is correct. In order 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 –2.8SD, -2.8SD, -3.0 SD and –3.1 SD respectively, and have been taken from the Holt et al data.[12]

Figure 9 shows the cost-effectiveness acceptability curve for strontium ranelate. Figure 10 shows this for alendronate. The wider spread of the curves in Figure 9, particularly at ages 70 and 80 years is due to the wider uncertainty in hip fracture efficacy with strontium ranelate.

Formal probabilistic sensitivity analyses regarding the optimal intervention has been 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 cost-effectiveness acceptability curves are given in Figure 11 to Figure 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.

Figure 9: **The cost-effectiveness acceptability curve for strontium ranelate for women with a prior fracture but no other clinical risk factors and at average BMD for women who are osteoporotic.**

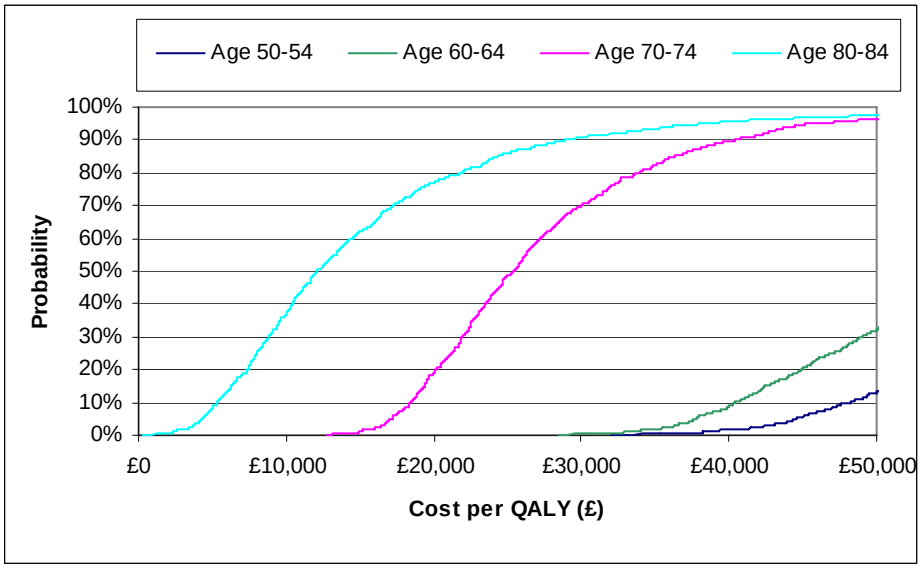


Figure 10: **The cost-effectiveness acceptability curve for alendronate for women with a prior fracture but no other clinical risk factors and at average BMD for women who are osteoporotic.**

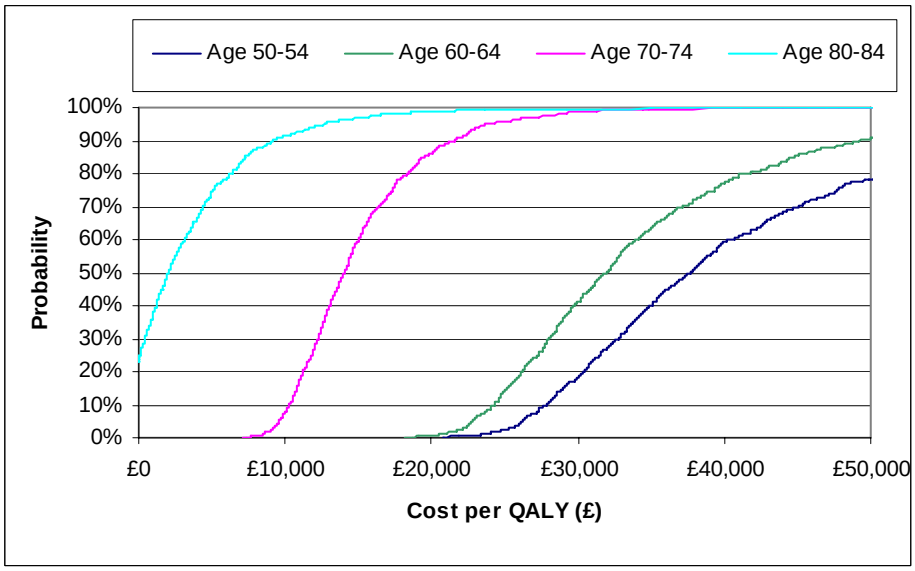


Figure 11: **The multi-interventional cost-effectiveness acceptability curve for women with a T-Score equal to that of all osteoporotic women at 50 years of age, with a prior fracture but no other clinical risk factors.**

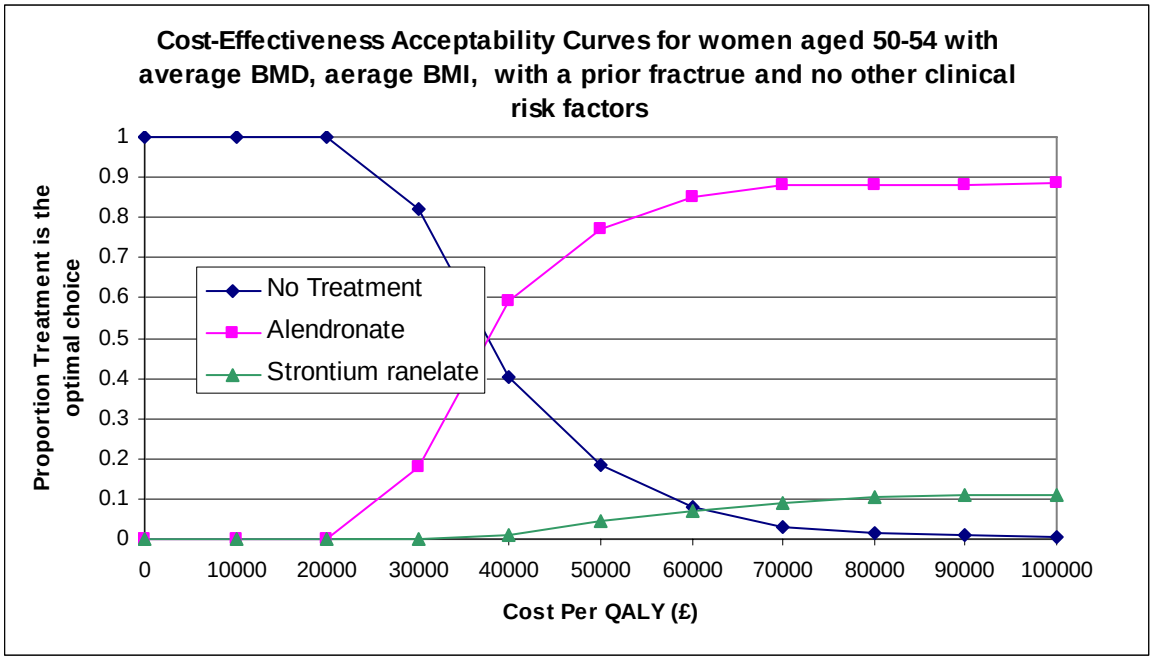


Figure 12: **The multi-interventional cost-effectiveness acceptability curve for women with a T-Score equal to that of all osteoporotic women at 60 years of age, with a prior fracture but no other clinical risk factors.**

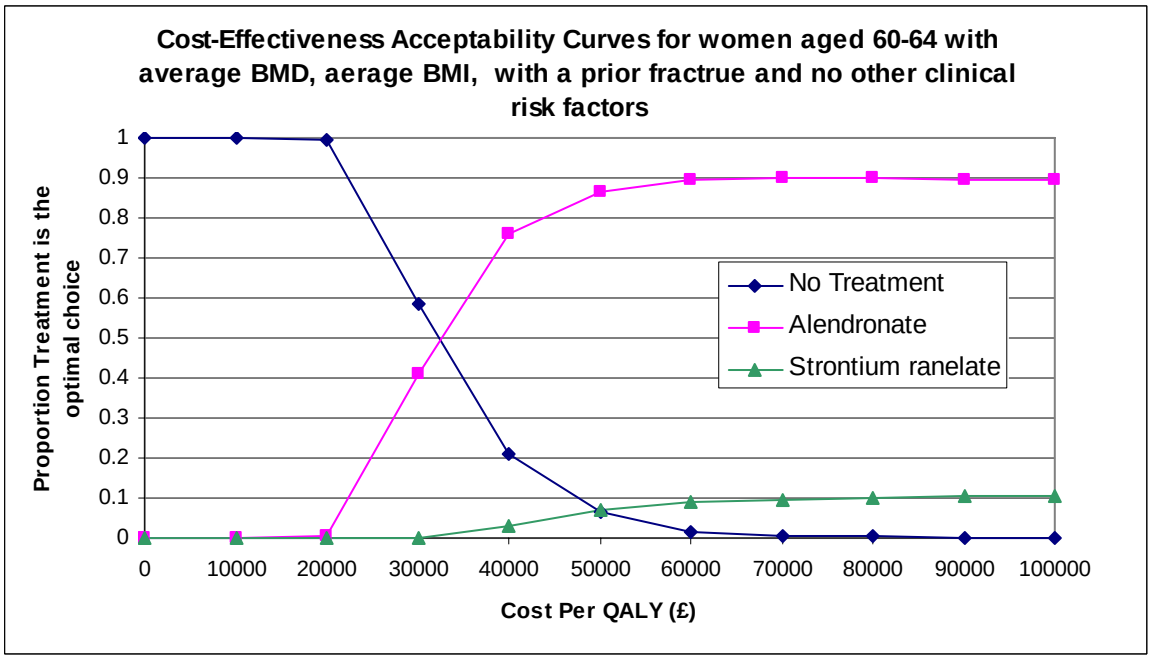


Figure 13: **The multi-interventional cost-effectiveness acceptability curve for women with a T-Score equal to that of all osteoporotic women at 70 years of age, with a prior fracture but no other clinical risk factors.**

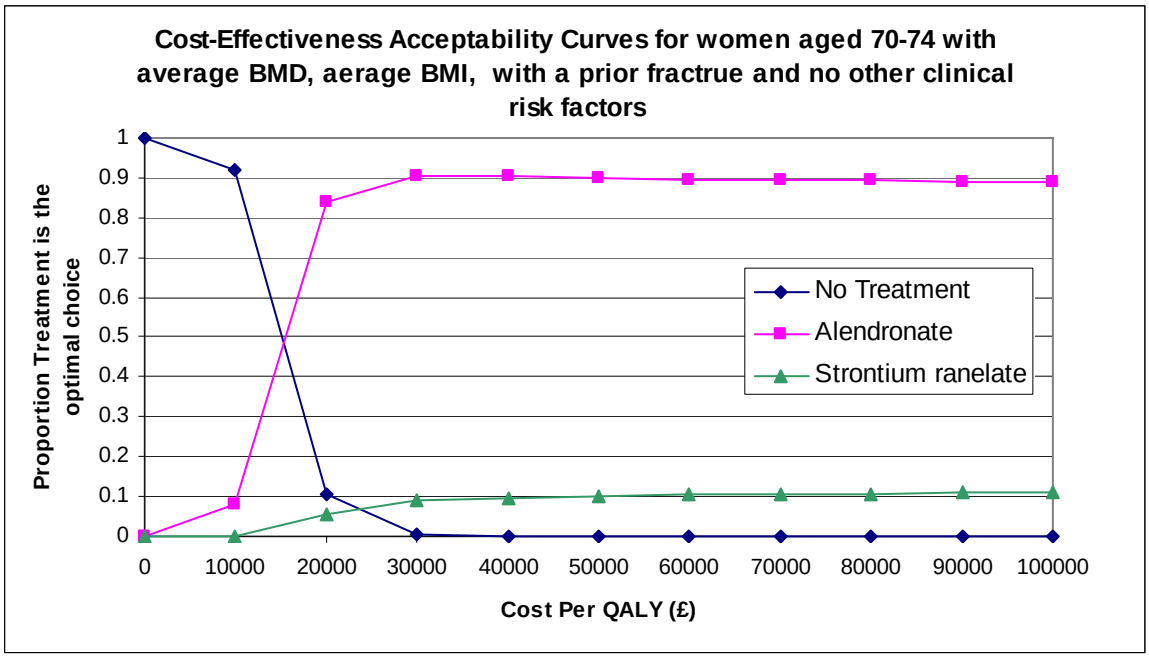
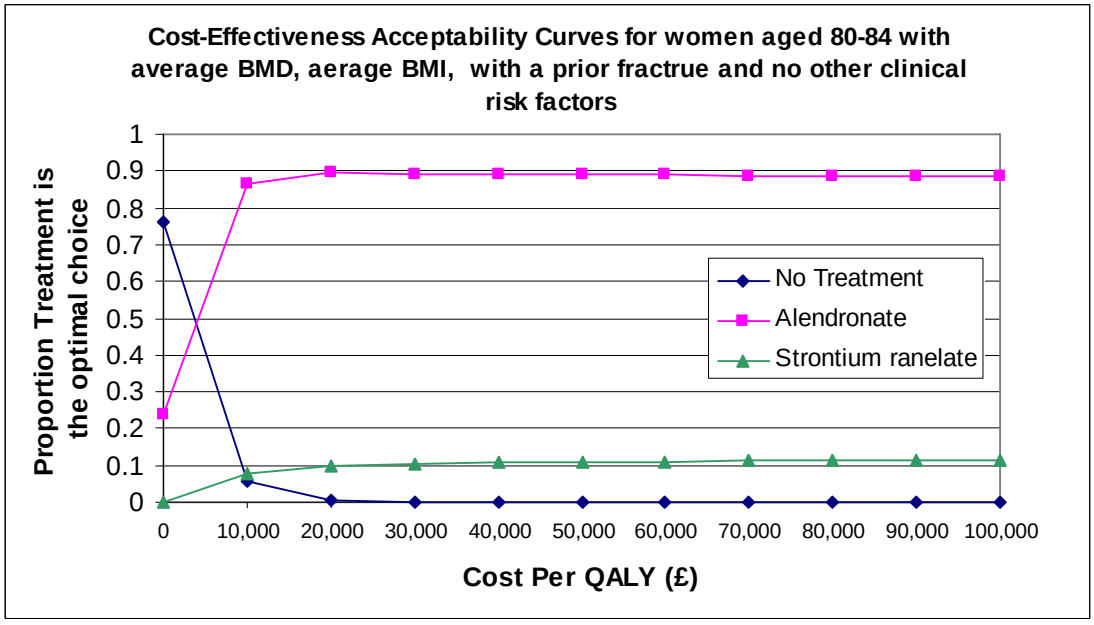


Figure 14: **The multi-interventional cost-effectiveness acceptability curve for women with a T-Score equal to that of all osteoporotic women at 80 years of age, with a prior fracture but no other clinical risk factors.**



Results for women without prior fracture.

The results provided in Table 41 through to Table 54 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 then the absolute risk threshold was not calculated. Whilst the calculations of the cost-effectiveness ratios presented in this report is based on absolute fracture risk of hip and non-hip fractures, it is acknowledged that clinicians would need practical advice which is related to the T-Score of the woman, and thus this information has been provided.

Table 41: T-Scores and risk thresholds by CRF for strontium ranelate at 50 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 42: T-Scores and risk thresholds by CRF for strontium ranelate at 55 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 43: T-Scores and risk thresholds by CRF for strontium ranelate at 60 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 44: T-Scores and risk thresholds by CRF for strontium ranelate at 65 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 45: T-Scores and risk thresholds by CRF for strontium ranelate at 70 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 46: T-Scores and risk thresholds by CRF for strontium ranelate at 75 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 47: T-Scores and risk thresholds by CRF for strontium ranelate at 80 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 48: T-Scores and risk thresholds by CRF for alendronate at 50 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 49: T-Scores and risk thresholds by CRF for alendronate at 55 years of age.

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 50: T-Scores and risk thresholds by CRF for alendronate at 60 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 51: T-Scores and risk thresholds by CRF for alendronate at 65 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 52: T-Scores and risk thresholds by CRF for alendronate at 70 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 53: T-Scores and risk thresholds by CRF for alendronate at 75 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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 54: T-Scores and risk thresholds by CRF for alendronate at 80 years of age

Clinical risk factors present	MAICER of £20K		MAICER of £30K	
	T-Score threshold (SD)	Annual absolute risk threshold	T-Score threshold (SD)	Annual absolute risk threshold
No clinical risk factors	-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	N/A
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	N/A	>1	N/A

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 is section 4.2.

4.2. 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 if 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 Royal College of Physicians (RCP) selective case finding approach. The aim of selective case finding approaches is to identify those women who will benefit the most from treatment without incurring large costs whilst 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 they 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 that 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 –2.5SD. The GDG have 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. We will therefore consider identification strategies that allow fracture risk assessment both with and without DXA scanning.

Methodology for finding the optimum identification strategy

In order to assess the percentage of the population which would be identified by a selective case finding approach data was needed on the prevalence of CRFs in UK women. The CRFs were those identified in the WHO study. These were age, sex, 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, we have omitted it from our analyses for a number of reasons. Firstly the correlation of BMI with BMD seen in the Holt study [12] is low (an r^2 of 0.1). Were both BMI and BMD 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 that 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 CRF, and a very low BMI may incorrectly not receive a DXA scan.

The following set of groups was defined.

No risk factors
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
3 risk factors including parental history of hip fracture
3 risk factors excluding parental history of hip fracture

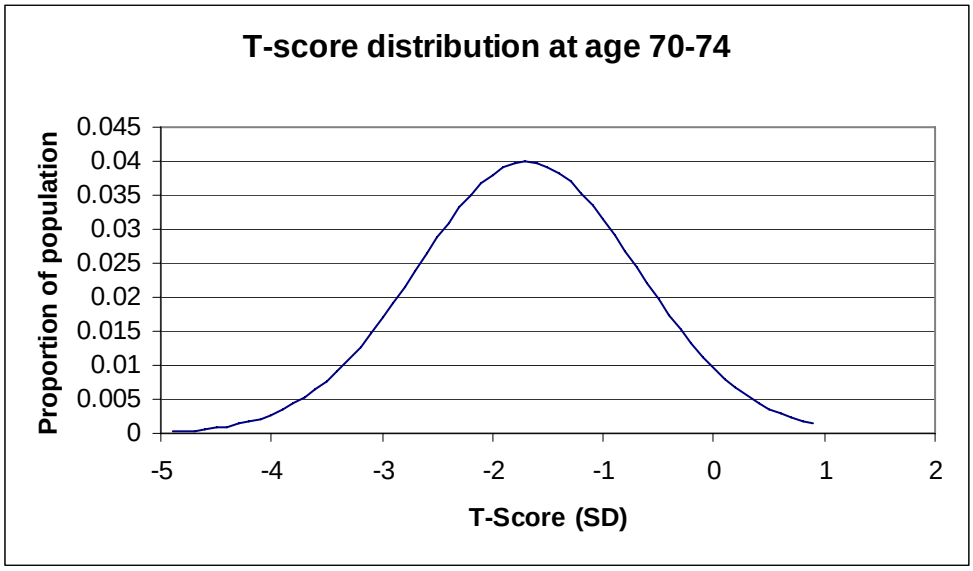
The distinction between 3 risk factors was made due to the relatively large risk conferred by parental history of hip fracture at advanced ages.

We wished to correlate BMD with the combinations of the CRF. However the data from the WHO study was not sufficient to find robust correlations between BMD with single, and particularly, multiple CRF. The correlation between age and BMD was however taken from the Holt data. [12] As such we had to assume 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 over-estimating the risk in patients with relatively few risk factors and under-estimating 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 that receive BMD scans. In older women this may result in some women incorrectly receive treatment without BMD scanning, and that some incorrectly receive a BMD scan. Establishing how the CRF 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 over estimate the risk of women without a prior fracture with the effect being largest in the higher ages where a higher proportion of women have 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 ages 70 – 74 with a mean T-Score of –1.69SD is shown in Figure 15. Any values below a T-Score of –5 SD, or above a T-Score of 1SD were truncated to –5SD and 1SD respectively.

Figure 15: T-Score distribution at age 70-74 with a mean of -1.69SD



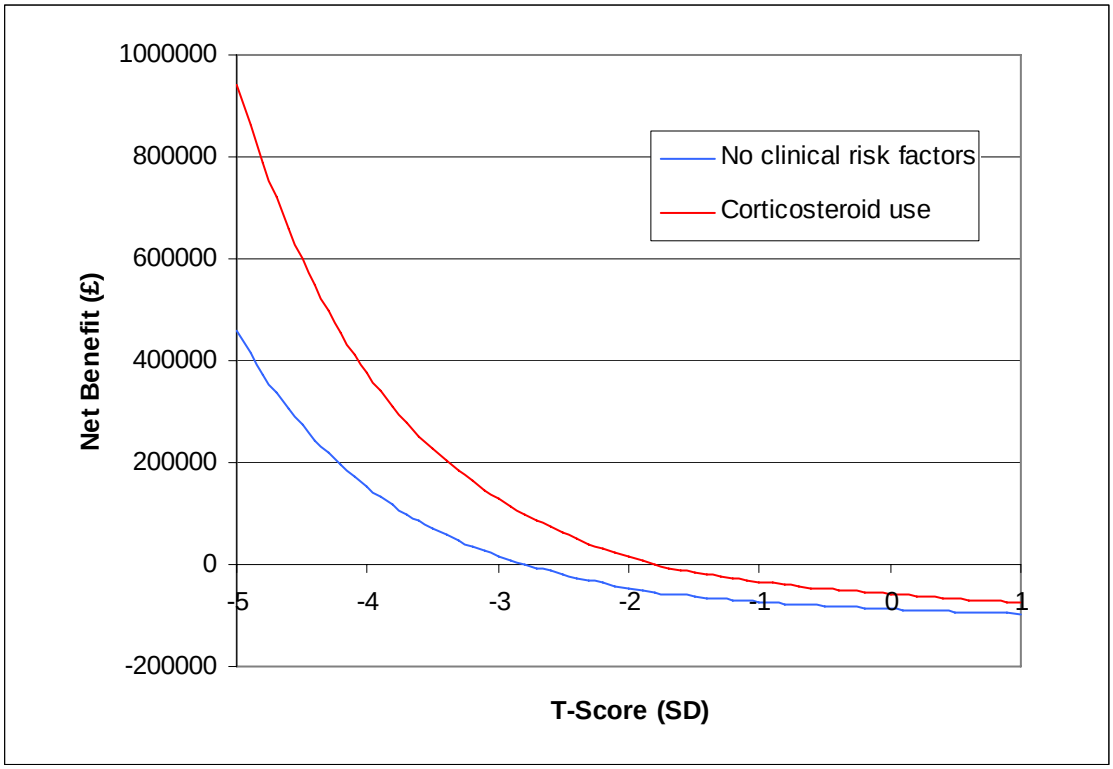
For each of the defined groups the total risk of fracture was assessed using the methods described in section 2 of this report.

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 to 74 years with no CRF 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 – 74 with no clinical risk factors 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. This is the data contained in Table 52.

Alendronate has been 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 GDG is undertaking work on identification strategies, where the use of other bisphosphonates and other classes of drugs will be analysed.

Figure 16: Example net benefit distribution for an individual woman aged 70-74 assuming treatment with Alendronate and a cost-effectiveness threshold of £20,000



The T-Score value for singular and combinations of risk factors for the cost-effective treatment of an individual has been calculated, however the costs of identifying these women have not been incorporated into the model, and if this costs more 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 CRF 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 level shows they can be treated cost-effectively.

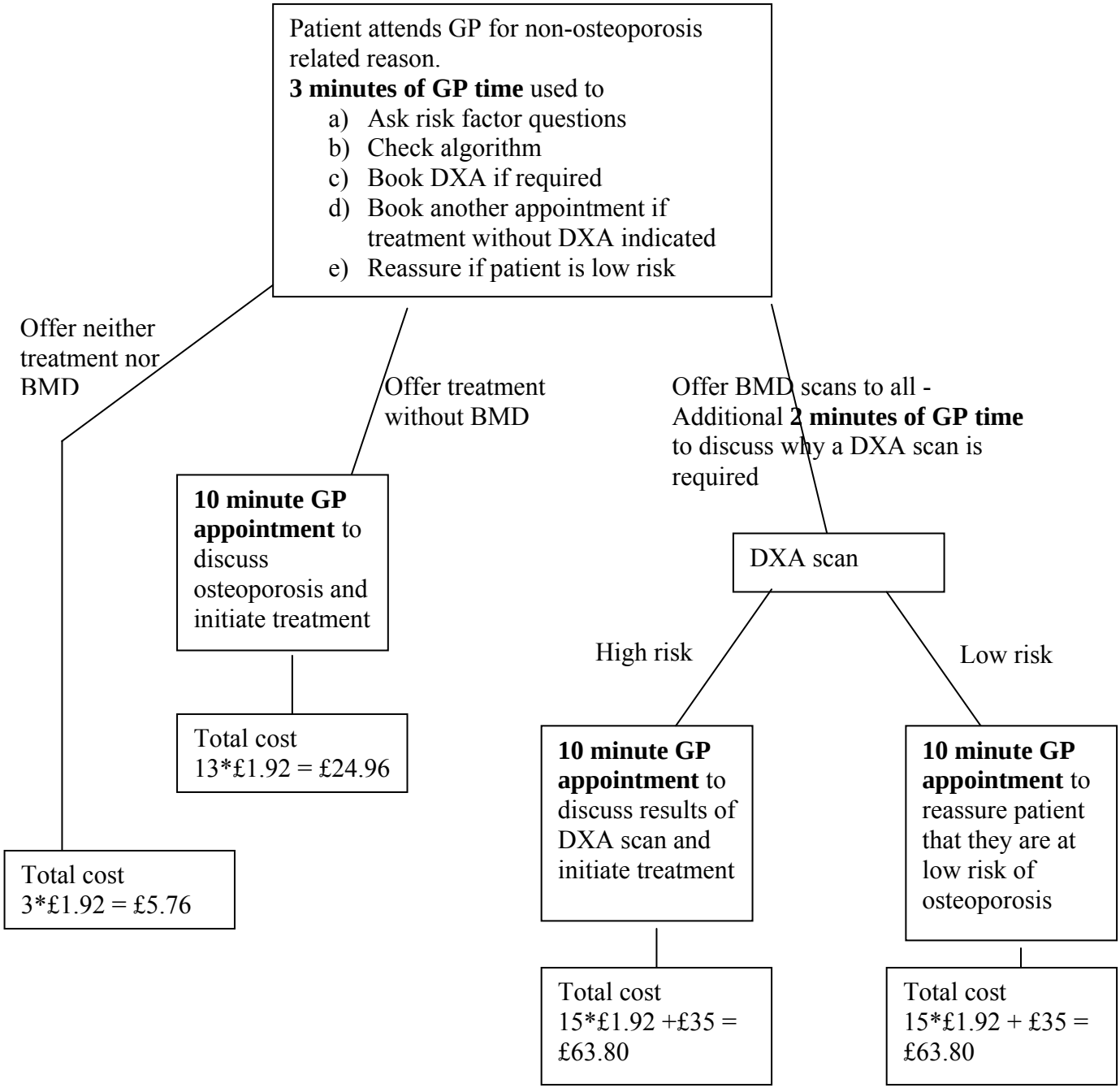
The net benefit for option a) is assumed to be zero minus the costs of identification, which would include the costs of asking the initial questions. The net benefit for option b) is the number of women in each T-Score band who can be treated cost-effectively multiplied by the appropriate net benefit 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 of 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 this latter example, it is acknowledged that some patients could have been treated cost-effectively, however 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 –2.5SD 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 the woman's CRF. This would be opportunistic and occur whilst the woman is 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[93] 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 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 in order to discuss why they are being refereed for a scan.



Following initiation of treatment the GDG 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 as other medication were reviewed, and a marginal cost of zero was applied. For women under 75 years of age, the GPs on the GDG estimated that 2/3 of the population would already be on long-term medication, and that an additional 1/3 of the population would be reviewed annually, each incurring a cost of £18.[93]

It is 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.

In order that the full costs of identification strategies are estimated the number of women in England and Wales are needed. These are given in Table 55.[96]

Table 55: The number of women in England and Wales.

Age (years)	Number of women in England and Wales (‘000)
50 –54	1242
55 –59	1310
60 –64	982
65 – 69	879
70 –74	774
75 –79	581
80 and over	900

4.3 Results

4.3.1 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 those without CRF, those who smoke only, those who consume alcohol only and those with rheumatoid arthritis only.

Between 70 and 74 years

Treat women with 3 or more CRF 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 3 or more CRF 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 clinical risk factor and offer BMD scans to those with no clinical risk factors.

4.3.2 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 those without CRF.

Between 75 and 79 years

Treat women with 3 or more risk factors 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, excluding those with no CRF, or who smoke only. These women should be offered BMD scans.

The expected net benefit of implementing an identification strategy assuming a MAICER of £30,000 for each age band is presented in Table 56. Whilst 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 65 and above that enough benefit is achieved from treating to make it worthwhile employing 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 57.

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 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 at their 65^{th}, 70^{th}, 75^{th} and 80^{th} birthdays as appropriate. It is seen that the majority of these costs are associated with the acquisition of the intervention.

Table 56: 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)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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 and over	900	716	37.0	692	346.8	924.0	887.0
Total	3,134	2,177	126.9	1147	712.0	1,375.2	1,248.3

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

Table 57: 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)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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 and over	900	809	44.3	502	177.3	536.3	492.0
Total	2255	1609	95.1	698	285.7	738.0	642.9

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

In order that the costs from the identification strategy can be compared with the current guidelines the RCP approach (assuming that it is fully utilised) have also been estimated. These are detailed in Table 58 and Table 59.

It is seen that at both MAICERs the RCP guideline is, on average, treating patients that 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 not made on cost-effectiveness grounds, but on whether the woman has a T-Score below –2.5SD.

Whilst 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.

Table 58: 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)	Number who are treated (thousand)	Net cost of treatment (£ million) *	Net Benefit of treatment (£ million)	Total Net benefit of identification strategy (£ million)
50 - 54	1,242	287	23.6	11	11.8	-3.7	-27.3
55 - 59	1,310	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 and over	900	184	14.5	74	-33.7	300.0	285.5
Total	6668	2007	149.4	297	135.3	544.3	394.9

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

Table 59: 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)	Number who are treated (thousand)	Net cost of treatment (£ million) *	Net Benefit of treating cost-effective women (£ million)	Total Net benefit of identification strategy (£ million)
50 - 54	1,242	287	23.6	11	11.8	-6.4	-30
55 - 59	1,310	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
80 and over	900	184	14.5	74	-33.7	211.2	196.8
Total	6,668	2,007	149.4	298	135.3	317.7	168.4

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

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

If such an identification strategy as that proposed from the WHO algorithm is ratified by the GDG, and is implemented by health care decision makers, the use of strontium ranelate for the prevention of osteoporotic fractures in women without a prior fracture will be limited to the ages of the identification strategy. From the cost-effectiveness results previously presented, strontium ranelate appears to be less cost-effective than the bisphosphonate alendronate. Thus to maximise the net benefit it appears that strontium ranelate should be reserved for women unable or unwilling to take more cost-effective interventions. The characteristics of women in which strontium ranelate can be used cost-effectively have been given in Table 41 through to Table 47. Given that the number of women who will be treated with strontium ranelate is expected to be low, the cost-implications have not be evaluated, however it is noted that the expected net benefit of the identification strategy is likely to be decreased and the total costs of acquiring drugs for osteoporosis likely to increase.

Sensitivity analyses

A number of sensitivity analyses have been run to explore the impact that changing variables has on the cost-effectiveness for identification strategies. These are contained in detail in Appendix 11.

It is seen that the inclusion of morphometric vertebral fractures within the model has little impact on the overall cost-effectiveness.

It is seen that doubling the time required for 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 years 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 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 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.

5. Implications for other parties

The main work-load increase that could arise for the intervention strategies evaluated in this report is for GPs, and on the work-force that undertake DXA scanning. The time implications for GPs may be quite considerable, however a costing of this has been undertaken. Similarly the costs of DXA scanning have been incorporated, but no evaluation of whether there is capacity within the UK system to perform these scans has been undertaken. If there are substantial costs in establishing scanning centres in order 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 £600m, 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.

6. Factors relevant to the NHS (optional)

7 DISCUSSION

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

On the advice of the GDG, 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.

The cost-effectiveness results in the current report differ somewhat from those recently published by Kanis et al in 2005.[97] 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.

Firstly, the costs of the hip fracture differ, not because of the unit costs themselves, since they are taken from the same source,[92] but due to differences in the proportion of patients assumed to enter nursing homes. Kanis et al assume that 25% of patients enter a nursing home after hip fracture as given by Dolan and Torgerson [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 80-89 years. Thus, the difference in overall hip fracture costs are most marked at younger age, being £5,157 at the age of 50 years in the present report and £ 12,488 in the report of Kanis et al. The differences are less marked at higher ages. The 25% is likely to be an over-estimation 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 original 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 et al 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 et al [98] and found to be reasonably appropriate, at least in a US healthcare setting. Since then, utility losses, particularly for vertebral fracture have been upwards revised [91] and used in the both the present report and that of Kanis et al. 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 80-85 years (**6**). 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 upward revised. 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 et al.

A third way in which the two approaches differ relates to the efficacy assumed for treatment. Kanis et al have assumed an overall relative risk reduction (RRR) of 35%, whereas the present report used individual estimates for the RRR 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. As noted by Kanis et al, [97] the impact of this assumption is very small and would not account for any real differences in cost-effectiveness.

A further difference relates to the time horizon used in the respective models. Our model limits the period of analysis to 10 years, but the mathematical model of Kanis et al [97] continues until the death of the patient. Our results will underestimate, therefore, 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, (for example 10 years after fracture) is fairly poorly researched, and this may be an area for future research. Notwithstanding, Kanis et al discount disutilities at 10% per annum [97], so that 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 our individual patient model and the modelling structure from Kanis et al, 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 in order that the full costs of hip fracture are considered.

In general, the assumptions made by Kanis et al [97] have been more favourable to the intervention in younger patients, than those used in this report, primarily due to the increased costs assumed for fracture. Whilst we have detailed the methodology used in our estimate of fracture risk, and consider these to be appropriate for the UK, the data presented by Kanis et al, may prove to be correct once further research is undertaken

Vertebral and proximal humerus fractures are proportionally more common in the young, and this is reflected in the results of Kanis et al [97] with an increasing risk of hip fracture required for cost-effectiveness as a woman ages. This increase is not seen in our results, mainly due to our 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. In order to reach the cost-effectiveness threshold, these women require a lower T-score at all combinations than in the Kanis et al paper.[97] Since worsening Z-Scores have a much greater effect on the hip, than at other

sites,[10] particularly in the young,[99] 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 are different, though it has not been possible to compare results directly. This is because the starting base for the analysis of Kanis is the general population with average risk on which additional risks (e.g. prior fracture, low BMD etc) 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 et al, [97] suggest that the women at average risk could be treated at the age of 75 years, assuming no identification costs and a MAICER of £30,000. Whilst the results are not directly comparable, as we have not evaluated 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 we estimate that the majority of women aged 75 years with at least one CRF could all be treated cost-effectively, with T-score thresholds of –2.0SD or lower needed for cost-effectiveness (Table 39 and Table 53) compared with an expected T-Score of –1.94 at this age. For women without CRF (and thus with risk of fracture below that of the general population) a T-Score threshold of –2.4SD is needed to be able to be treated cost-effectively.

Given that our modelling assumptions are less favourable to the interventions than that of other model, it is expected that where we show scenarios to be cost-effective that these results are robust.

8 CONCLUSIONS

Strontium ranelate has 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 we have 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 GDG 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.

9 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 also strengthened at older ages. The database that we have used to produce these results contained only 40 women aged between 80 and 84 years, and we have 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 our 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 > 2 units daily, rheumatoid arthritis and prior fracture after 50 years, are also recorded. This data would allow the correlations between each CRF and T-score, as well as the prevalence in the community to be estimated. Presently we have assumed no relationship between CRF, bar age, and BMD. Gaining further evidence on these correlations would allow the identification strategies to become more sensitive and specific.

The head to head comparisons of strontium ranelate and bisphosphonates have not been undertaken. This may be of most benefit in the over 80-age group as at these ages bisphosphonates have relatively fewer efficacy data. However it is acknowledged that the number of patients needed to be recruited to prove statistical significane 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.

For resource reasons our results have been estimated run 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 has been a Gaussian Process model based on an individual patient model. The Gaussian model has had to be adapted in order that it could be used in conjunction with the WHO algorithm, and this has 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. Whilst 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.

There is some debate on the actual costs of hip and other fractures, with the main UK costing paper being relatively old [5,6] with 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 more accurately estimate these figures.

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

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

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

APPENDIX 1: 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 SEARCHED]]

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

APPENDIX 2: MEDLINE CLINICAL EFFECTIVENESS SEARCH STRATEGY

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

APPENDIX 3: QUALITY ASSESSMENT TOOL (developed from Gillespie[58] and Prendiville[59]

	Score
Was randomisation to the study groups blinded?	
not randomised	0
states random but no description or quasi-randomised *(ie allocation by date of birth, hospital record no, admission dates, alternately etc)*	1
small but real chance of disclosure of assignment *(eg sealed envelopes)*	2
method does not allow disclosure of assignment *(eg 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 %age of possible score)	

APPENDIX 4: Publications Relating to the Trials which met the Inclusion Criteria for Review

* indicates the major publication for the study

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 International* 2004; 15(Suppl 1):S93-S94.

Marquis P, De la Loge C, Roux C, Meunier PJ, Reginster JY. Strontium ranelate treatment prevents health-related quality of life impairement in postmenopausal women with severe osteoporosis: results from the SOTI study. *Osteoporosis International* 2002; 13(Suppl 3):S11-O5.

Meunier PJ. Postmenopausal osteoporosis and strontium ranelate. *New England Journal of Medicine* 2004; 350(19):2002-2003.

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 International* 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 International* 2003; 14(Suppl 3):S66-S76.

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 International* 2002; 13(6):521-522.

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. *Obstetrical and Gynecological Survey* 2004; 59(7):526-527.

* 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. *New England Journal of Medicine* 2004; 350(5):459-468.

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 and Rheumatism* 2002; 46(9):S584-S585.

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 International* 2002; 13(Suppl 1):S30.

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

STRATOS

Meunier PJ, Reginster JY. Dose-related bone effects of strontium ranelate in postmenopausal women. *Osteoporosis International* 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. *Journal of Bone and Mineral Research* 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. *Journal of Clinical Endocrinology and Metabolism* 2002; 87(5):2060-2066.

Reginster JY, Meunier PJ. Strontium ranelate phase 2 dose-ranging studies: PREVOS and STRATOS studies. *Osteoporosis International* 2003; 14(Suppl 3):S56-S65.

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 International* 2004; 15(Suppl 1):S93-S94.

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 International* 2003; 14(Suppl 3):S66-S76.

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 International* 2003; 14(Suppl 7):S51-S52.

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* 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. *Journal of Clinical Endocrinology and Metabolism* 2005; 90(5):2816-2822.

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SOTI and TROPOS: pooled data

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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 5: Studies Excluded from the Review of Clinical Effectiveness

Study	Reason for exclusion
Meunier et al 1996[100]	No fracture data
Reginster et al 2002[101]	Exact duplicate of Reginster 2002[69]
Reginster et al 2004[102]	Duplicate of Reginster 2003[73]

APPENDIX 6: EVIDENCE TABLES

Table 60: Summary of study characteristics: general information

Study	Study site	Length of study	Primary outcome measure/s	Population	Mean age (range)	Intervention/dose	Comparison/s
STRATOS[64]	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/d Rx2: Strontium ranelate 1 g/d Rx3: Strontium ranelate 2 g/d in each case taken as 2 identical tablets twice daily All participants received 500 mg/d calcium and 800 IU/d vitamin D_3	Identical placebo taken twice daily, plus 500 mg/d calcium and 800 IU/d vitamin D_3
SOTI[65]	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 $\pm$7.2 (range 50.0-96.0)[70]	Strontium ranelate 2 g/d 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[66]	75 centres in 11 European countries and Australia	3 years	Incidence of nonvertebral osteoporotic fracture	Aged osteoporotic Caucasian women with femoral neck BMD $\leq$0.600 g/cm^2	76.8$\pm$5.0 (range 55.0-100.0)[70]	Strontium ranelate 2 g/d 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 61: Summary of study characteristics: inclusion and exclusion criteria etc

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
STRATOS[64]	Nonobese Causasian women aged 45-78 and at least 12 months postmenopausal who had at least 1 vertebral fracture occurring under no or minimal trauma and a lumbar T-score of <-2.4.	More than 2 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 under 2 years, renal insufficiency (creatinine >120 μmol/L), liver insufficiency (prothrombin time <70%), alcohol intake 160g or more pure alcohol/d, treatment with calcitonin, oestrogen, corticosteroids, anabolic steroids or vitamin D >800 IU/d within the previous 3 months, treatment with phosphorus, thiazide diuretics or calcium >500 mg/d within the previous month, treatment with etidronate or pamidronate for more than 30 days, or any treatment with another bisphosphonate. Treatment with etidronate or pamidronate for 15-30 days required a 3-month wash-out period; treatment with fluoride for more than 2 months required a 5-year wash-out, and treatment with fluoride for less than 2 months required a 3-month wash-out.	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 at least 20% in one of the ratios of vertebral height in previously intact vertebrae.	

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
SOTI[65]	Ambulatory Caucasian women at least 50 years old and at least 5 years postmenopausal with at least 1 vertebral fracture occurring under no or minimal trauma and lumbar-spine BMD of 0.840g/cm^2 or less measured with Hologic instruments (corresponding to a T-score $\leq$-2.4[68])	Severe diseases or conditions that could interfere with bone metabolism; use of antiosteoporotic treatments (fluoride salts or bisphosphonates taken for more than 14 days within the previous 12 months, or oestrogen, calcitonin or calcitriol taken for more than 1 month in the previous 6 months);[65] life expectancy less than 4 year or unlikely to be fully compliant with the study protocol.[68]	Data were only presented for the ITT population (ie all participants who had taken at least 1 packet of study medication and for whom at least 1 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 at least 1 (using the semiquantitative method of Genant) in a previously nondeformed vertebra. A secondary quantitative assessment was also undertaken using a 15% fracture definition.	
TROPOS[66]	Ambulatory Caucasian women, aged 74 or older 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 4 falls/year[70]), femoral neck BMD $\leq$0.600 g/cm^2 (corresponding to a T-score of $\leq$-2.5), postmenopausal for at least 5 years, with a life expectancy of more than 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 more than 14 days in the previous year; oestrogen, calcitonin, fluoride salts, calcitriol or 1-alpha-vitamin D taken for more than 1 month in the previous 6 months), factors which could modify full compliance with the protocol	Yes.	Fracture identified using the semiquantitative method of Genant in a previously nondeformed vertebra. A secondary quantitative assessment was also undertaken using a fracture definition of a decrease of 15% or 3mm 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

Table 62: Summary of study characteristics: methodological quality

Study	Random-isation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of nonvertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No of subjects randomised to study	% completing study protocol	Source of funding
STRATOS[64]	3	1	3	2	N/A	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[65]	1	3	3	3	3	3	16/18 (89%)	Rx: 828 C: 821	Rx: 628 (77%) C: 632 (77%)	Servier
TROPOS[66]	1	1	3	3	3	3	14/18 (78%)	Rx: 2554 C: 2537	Rx: 1687 (66%) C: 1633 (64%)	Servier

Table 63: Strontium ranelate - toxicity

Study	***Number of participants reporting adverse events***	**Number of participants reporting GI disorders**	**Withdrawals/discontinuation of study medication due to adverse events**
STRATOS[64]	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[65]	AEs thought to be treatment-related:[70] Rx: 169/826 (20.5%) C: 135/814 (16.6%) Serum creatine kinase at least 2 x upper limit of	Diarrhoea:[65] Rx: 6.1% C: 3.6% P=0.02	Emergent AE leading to treatment discontinuation:[70] Rx: 179/826 (21.7%) C: 131/814 (16.1%)

	normal:[65] Rx: 3.4% C: 1.8%	Gastritis:[65] Rx: 3.6% C: 5.5% P=0.07 Upper GI AEs thought to be treatment-related:[70] Rx: 119/826 (14.4%) C: 100/814 (12.3%)	Deaths (none attributed to study treatment):[70] Rx: 29/826 (3.5%) C: 21/814 (2.6%) Nonfatal serious AE leading to treatment withdrawal:[70] Rx: 39/826 (4.7%) C: 28/814 (3.4%) Treatment-related serious AE leading to treatment withdrawal:[70] Rx: 2/826 (1 gastric erosions, 1 unspecified hypersensitivity) C: 3/814 (1 constipation, 1 GI disorder, 1 oesophagitis)
TROPOS[66]	Serious AEs: 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%

APPENDIX 7 ASSESSING THE QUALITY OF MODELLING WITHIN THE SUBMISSIONS

The BMJ checklist for economic evaluations[83] 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. The "core" model presented in section 3 of the submission is based on a previous version of the SHEMO model previously developed by the assessment group. [85] 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 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 previous 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, whilst 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 whilst the appraisal model uses the pooled efficacy from the SOTI and TROPOS trials. This difference means that the submission model will be more substationally 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 to the appraisal model assumed efficacy.

10 N/A

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 HSUVs 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 N/A

15 N/A

16 Not given in either the submission or the appraisal model.

17 Methodology and sources for calculating costs are presented elsewhere and reference to these are provided. Appraisal uses same methodology and sources for costs but inflates them to 2003/2004 values whereas submission has referenced costs inflated to 2001/2002 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 if 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 valued. The latter option will underestimate the risk of hip fracture at the threshold of osteoporosis for younger ages and over-estimate the risk at higher ages..

The submission model considers the impact of prior fracture on cost-effectiveness whilst the appraisal model also considers the impact of other risk factors.

Data on mortality and entry into a nursing home is not discussed so we have assumed that it has not changed from the values used in the analysis for NCCHTA which this model was developed for. 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 dependant on the scenarios analysed.

25 N/A

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 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 if 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 Source 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, whilst 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 whilst 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 to the appraisal model assumed efficacy.

10 N/A

11 Costs, LYs gained, QALYs gained, cost per LY gained and cost per QALY gained are all reported but the none are 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 Kanis et al, [9] is the same as in the appraisal model, however, the discussion and referencing of these utility values within the submission is unclear.

13 See 12.

14 N/A

15 N/A

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 whilst 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 individuals prior history. In order to get around this a post vertebral fracture state and post hip fracture state have been included. However, transitions from the post vertebral state are restricted to hip fracture and death and transitions from the post hip 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 fracture 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 over estimate QALY gains by a factor of 1/0.929= 1.07. If they begin in the vertebral or post-vertebral 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 three year treatment and offset time is used in the submission model in the base case whereas a five 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 regards to the baseline analysis in the submission model this assumption is favourable to the intervention.

The incidence data from proximal humerus fractures has been taken from a Swedish study and the data in table 2 appears to be for men rather than women. This will underestimate the risk of proximal humerus fracture as the incidence is higher in women than 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 over-estimate 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 whilst 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 has 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 1st and 2nd years following hip fracture whereas the appraisal model assumes no increased mortality in the 2nd 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 whilst 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 relates to proximal humerus fractures so it is assumed that this is the only additional fracture type included. Exclusion of other fracture types (eg. pelvis, other femoral, tibia and fibula etc) 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 life-time 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 Basecase 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 N/A

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 lognormally 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 if 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 has 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 8: MODELLING METHODOLOGY

The first example concerns the accuracy with which the probability of fractures can be calculated, based upon 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 within 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 an increased risk of hip fracture than patient A. Without adjusting for this increased probability of fracture the model would under-estimate the number of fractures that occur.

A further example is that a large component of costs are those associated with nursing home 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 upon the duration of the elevated risk of fracture becomes 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 upon 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. In order that such costs are 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 our current knowledge are bridged. Data are required to determine whether the quality of life decrements associated with a given fracture are dependent upon 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 than for a second hip fracture. Similarly the quality of life loss associated with a first vertebral fracture may be different depending upon whether a patient had previously suffered a hip fracture. If these relationships are shown to wane with time then the time period at which the fractures occurred need 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 4 transition states is assumed (no fracture event, hip fracture, vertebral fracture and wrist fracture), the tree would have 4 ^ 10 branches on 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 9 CALCULATION OF THE ADDITIONAL QALYS LOST THROUGH A DEATH FROM A HIP FRACTURE, VETEBRAL FRACTURE OR PROXIMAL HUMERUS FRACTURE

The model builds upon the work undertaken for an HTA report[92] that used a time horizon of 10 years. This however would mean than any mortality prevented within this period would not be given full weight, which would bias against beneficial treatments, and adjustments were needed in order to correct for this error.

In order 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 within 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 8 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 within 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 et al. [103]

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 64.

Table 64: The expected lifetime QALYs for women alive at the end of the model.

Age (years) at the 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.

Calculating the number of preventable hip fracture deaths.

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 age 60, for healthy women at the threshold of osteoporosis, is estimated to be 0.1%. When analysis women with severe osteoporosis it was assumed that this risk can be doubled in accordance with data reported by Klotzbeucher et al.[30]

This would equate to an estimate of the hip fracture rate of 0.2% per annum, or 1.0% over a five year treatment period, assuming no additional mortality, which is 1 hip fracture for a cohort of 100 women.

The mortality rate following hip fracture is estimated to be 6% at age 60 (Table 6 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 one, 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 65.

Table 65: The 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

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.

It was assumed that all deaths from vertebral fracture would happen in year 3, the mid –point of the treatment period, and assuming a 66% increase in the mortality rate in the year of a vertebral fracture as reported by Center et al[36] and assuming 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 were estimated. These are shown in Table 6.

Table 66: The 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

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

A similar methodology has been 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 are shown in Table 67.

Table 67: The 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

APPENDIX 10 ABSOLUTE ANNUAL FRACTURE RISK BY AGE, BMD AND CLINICAL RISK FACTORS

Table 68: Absolute annual fracture risk at ages 50-54 by BMD and clinical risk factors

	T-Score (SD)												
Clinical risk factors	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical risk factors	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 69: Absolute annual fracture risk at ages 55-59 by BMD and clinical risk factors

	T-Score (SD)												
Clinical risk factors	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical risk factors	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 70: Absolute annual fracture risk at ages 60-64 by BMD and clinical risk factors

	T-Score (SD)												
Clinical risk factors	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical risk factors	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 71: Absolute annual fracture risk at ages 65-69 by BMD and clinical risk factors

	T-Score (SD)												
Clinical risk factors	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical risk factors	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 72: Absolute annual fracture risk at ages 70-74 by BMD and clinical risk factors

	T-Score (SD)												
Clinical risk factors	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical risk factors	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 73: Absolute annual fracture risk at ages 75-79 by BMD and clinical risk factors

	T-Score (SD)												
Clinical risk factors	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical risk factors	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 74: Absolute annual fracture risk (%) at ages 80-84 by BMD and clinical risk factors

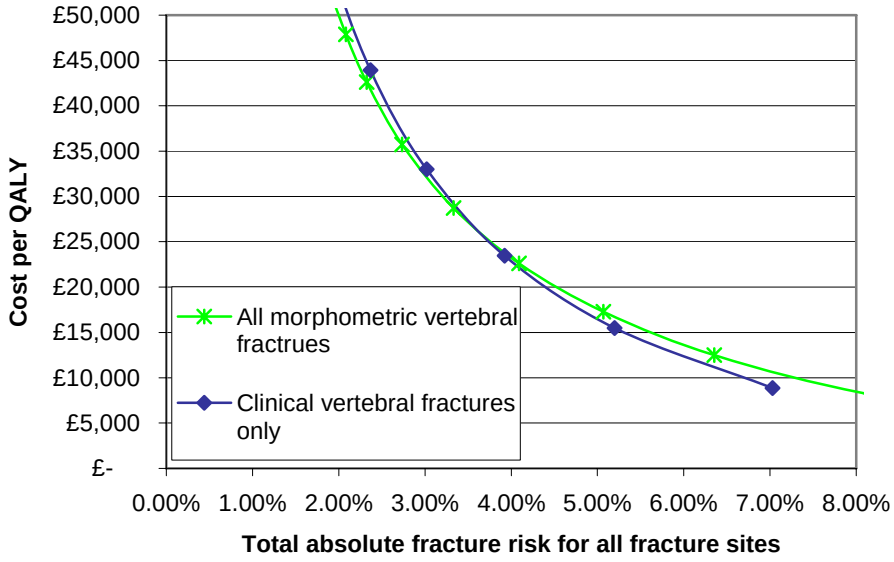
	T-Score (SD)												
Clinical risk	**-5**	**-4.5**	**-4**	**-3.5**	**-3**	**-2.5**	**-2**	**-1.5**	**-1**	**-0.5**	**0**	**0.5**	**1**
No clinical	10.0	7.6	5.9	4.5	3.5	2.8	2.2	1.9	1.6	1.4	1.2	1.0	0.9
Parental	26.2	19.0	13.8	10.1	7.5	5.5	4.2	3.4	2.7	2.2	1.8	1.5	1.3
Current	13.2	9.8	7.3	5.5	4.2	3.2	2.5	2.1	1.8	1.5	1.3	1.1	0.9
Corticosteroid	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	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	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

APPENDIX 11 SENSITIVITY ANALYSES

1) Inclusion of all morphometric vertebral fractures

The basecase analysis presented includes only clinical vertebral fractures. A sensitivity was carried out assuming that 23% of all vertebral fractures are clinical and that the utility decrement of sub-clinical vertebral fractures is one third that of clinical vertebral fractures. [91] The impact of including all morphometric vertebral fractures is shown in Figure 17.

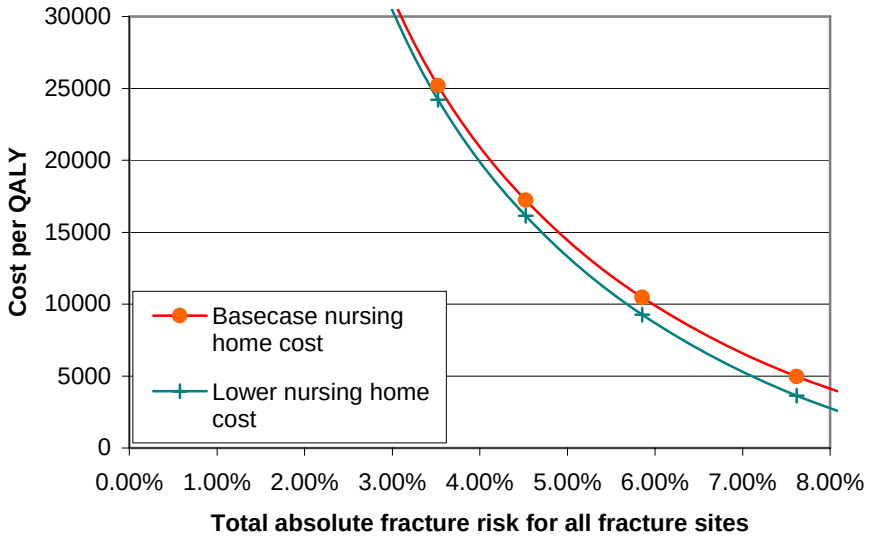
Figure 17: Cost-effectiveness of treatment with strontium ranelate at age 70 for women with no clinical risk factors when including only clinical vertebral fractures in the analysis or including all morphometric vertebral fractures in the analysis



2) Lower nursing home cost

The basecase analysis assumes an ongoing cost for patients with a hip fracture leading to nursing home entry of £25,357 at age 80. 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. http://www.nice.org.uk/pdf/Alz_assessment_report_0205.pdf . 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 in figure 18. The impact is smaller at lower ages where the probability of patients entering a nursing home following hip fracture is lower.

Figure 18: Cost-effectiveness for women aged 80-84 with no clinical risk factors using two different estimations of nursing home cost



3) Baseline utility for patients with a previous fracture

In the basecase 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 23 in the main report gives the utility decrement for various fracture types in the 2nd year following fracture. We have assumed that these utility multipliers can be applied to women entering the model with a previous fracture. We have estimated the distribution of fracture types in women with severe osteoporosis by calculating the cumulative incidence from age 50 of each of the four main fracture types using the incidence data described in section 2.1 of this report. These have then been proportioned to provide the percentages 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 age 70, 11% are assumed to have had hip fractures, 19% vertebral fractures, 56% wrist fractures and 14% proximal humerus fractures.

Table 75: The 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%

From this the estimated average utility multiplier due to previous fracture for women at ages 50-54, 60-64, 70-74, and 80-84 is 0.953, 0.961, 0.958 and 0.937 respectively.

To estimate the impact of this decreased starting utility we 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.

4) 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 at ages 70 and above.

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)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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 and over	900	753	48.2	604	266.5	668.6	620.4
Total	2255	1553	109.9	800	374.9	870.3	760.4

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

5) 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 which is cost-effective at ages 65-69.

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)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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 and over	900	784	37.3	598	260.7	669.8	632.5
Total	3134	1651	88.8	802	374.4	878.1	789.3

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

6) 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 at ages 70 and above.

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	No of Assessment tests undertaken (thousand)	No of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£million)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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 and over	900	753	43.9	604	266.5	668.6	624.7
Total	2255	1553	98.7	800	374.9	870.3	771.6

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

7) Compliance and switching therapies

The effects of non-compliance and patients switching therapies have been evaluated assuming that the identification strategies previously defined are in use. The lowest age 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 80 to Table 81 show that it is still cost-effective to implement the optimum strategy to identify women for treatment at ages 70-74 when compliance falls to 50% but not when compliance falls to 25% if non-compliant patients accrue either 1 months drug costs or 6 months drug costs. Table 81 shows it is still cost-effective to identify women at ages 70-74 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 they switch to has a lower net benefit.

Table 80: Optimum strategy results at age 70-74 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 months drug costs

Comp-liance	No of Assessment tests undertaken (thousand)	No of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£million)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

Table 81: Optimum strategy results at ages 70-74 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

Comp-liance	No of Assessment tests undertaken (thousand)	No of BMD scans undertaken (thousand)	Cost of assessment tests and BMD scans (£million)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

Table 82: Optimum strategy results at ages 70-74 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

	No of Assessment tests undertaken (thousand)	No of BMD scans undertaken (thousand)	Cost of identification strategy[§] (£million)	Number who can be cost-effectively treated (thousand)	Net cost of treatment (£ million) *	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

* Acquisition cost minus the costs recouped through reduced incidence of fracture.

[§] Includes the cost of assessment tests, BMD scans and GP appointments for patients who switch treatment

APPENDIX 12 DETAILING THE WHO METHODOLOGY

The WHO has commissioned a programme of work to identify and validate clinical risk factors for use in fracture risk assessment on an international basis, either alone, or in combination with bone mineral density 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 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 twelve prospectively studied cohorts drawn from the general population, utilising the primary data from each study.

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

Cohort	Number	% female	Person years	Mean age (years)
EVOS/EPOS	13490	52	40681	64
CaMos	9101	69	25834	62
Rochester	1001	65	6227	56
Rotterdam	6851	59	39593	69
DOES	2089	61	15994	70
Gothenburg II	1970	59	15201	78
Hiroshima	2603	70	9825	64
OFELY	430	100	2144	64
Sheffield	2170	100	6894	80
Kuopio	11691	100	56091	52
Gothenburg I	7065	100	29603	59
EPIDOS	1183	100	3947	82
TOTAL	59644	75	252034	63

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)
- Body mass index (all centres)
- Prior fragility fracture (11 centres)
- Ever use of systemic glucocorticoids (8 centres)
- Parental history of fracture (7 centres)
- Parental history of hip fracture (3 centres)
- Current smoking (10 centres)
- Alcohol intake of greater than 2 units per day (3 centres)
- Rheumatoid arthritis (3 centres)

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kg divided by height squared in m. 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 DPA at the right heel. The BMD data were also analysed excluding these two cohorts. BMD was expressed as sex- 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 expressed as units/day. A unit of alcohol is equivalent to 8g in the UK, though 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 3 of the cohorts. Prior fracture history of each individual was documented, though 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 3 cohorts did not distinguish between ever and current use. Neither the dose nor the duration of use were analysed. The presence or absence of rheumatoid arthritis was 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 the Rotterdam studies also included sequential systematic radiography to define incident vertebral deformities, but these were not used in these 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, sex 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 (RR) 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 separate from women) were then merged using weighted coefficients (examples of results are illustrated in Fig 1 and 2).

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 1: [redacted]

Figure 2: [redacted]

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

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

Four algorithms for each sex 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, sex 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 epidemiologic 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 was adjusted so that these matched that reported by Singer et al. [21]

Input parameters into the model were age, sex, weight (in kg) and height (in cm). And the dichotomised risk listed above. Femoral neck BMD can additionally be entered either as a Z-score or a T-score. When entered, 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.

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