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Vitamin K to prevent fractures in older women: systematic review and economic evaluation

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Abstract

Vitamin K to prevent fractures in older women: systematic review and economic evaluation

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Objective: To determine the clinical and cost-effectiveness of vitamin K in preventing osteoporotic fractures in postmenopausal women.

Data sources: Searches were conducted in May 2007 in MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, BIOSIS, CINAHL, DARE, NHS EED and HTA databases, AMED, NRR, Science Citation Index and Current Controlled Trials. The MEDLINE search was updated in March 2009.

Review methods: Selected studies were assessed and subjected to data extraction and quality assessment using standard methods. Where appropriate, meta-analysis was carried out. A mathematical model was constructed to estimate the cost-effectiveness of vitamin K_1.

Results: The electronic literature searches identified 1078 potentially relevant articles. Of these, 14 articles relating to five trials that compared vitamin K with a relevant comparator in postmenopausal women with osteoporosis or osteopenia met the review inclusion criteria. The double-blind ECKO trial compared 5 mg of phylloquinone (vitamin K_1) with placebo in Canadian women with osteopenia but without osteoporosis. Four open-label trials used 45 mg of menatetrenone (vitamin K_2) in Japanese women with osteoporosis; the comparators were no treatment, etidronate or calcium. The methodological quality of the ECKO trial was good; however, all four menatetrenone trials were poorly reported and three were very small ($n < 100$ in each group). Phylloquinone was associated with a statistically significant reduction in the risk of clinical fractures relative to placebo [relative risk 0.46, 95% confidence interval (CI) 0.22 to 0.99]; morphometric vertebral fractures were not reported. The smaller menatetrenone trials found that menatetrenone was associated with a reduced risk of morphometric vertebral fractures relative to no treatment or calcium; however, the larger Osteoporosis Fracture (OF) study found no evidence of a reduction in vertebral fracture risk. The three smaller trials found no significant difference between treatment groups in non-vertebral fracture incidence. In the ECKO trial, phylloquinone was not associated with an increase in adverse events. In the menatetrenone trials, adverse event reporting was generally poor; however, in the OF study, menatetrenone was associated with a significantly higher incidence of skin and skin appendage lesions. No published economic evaluations of vitamin K were found and a mathematical model was thus constructed to estimate the cost-effectiveness of vitamin K_1. Comparators were alendronate, risedronate and strontium ranelate. Vitamin K_1 and alendronate were markedly more cost-effective than either risedronate or strontium ranelate. The base-case results favoured vitamin K_1, but this relied on many assumptions, particularly on the efficacy of preventing hip and vertebral fractures. Calculation of the expected value of sampled information was conducted assuming a randomised controlled trial of 5 years' duration comparing alendronate with vitamin K_1. The costs incurred in obtaining updated efficacy data from a trial with 2000 women per arm were estimated to be a cost-effective use of resources.

Conclusions: There is currently large uncertainty over whether vitamin K_1 is more cost-effective than alendronate; further research is required. It is unlikely that the present prescribing policy (i.e. alendronate as first-line treatment) would be altered.

Contents

Glossary and list of abbreviations

Glossary

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

Osteoporosis Bone mineral density 2.5 standard deviations or more below the young adult mean (*T*-score –2.5 or less).

Severe osteoporosis Bone mineral density 2.5 standard deviations or more below the young adult mean (*T*-score –2.5 or less) plus at least one documented fracture.

***T*-score** The number of standard deviations from the average bone mineral density of healthy young women.

***Z*-score** The number of standard deviations that a woman is from the average bone mineral density of women of the same age.

Abbreviations

AiC	academic-in-confidence
BMD	bone mineral density
BNF	*British National Formulary*
CI	confidence interval
ENBS	expected net benefit of sampling
EVSI	expected value of sample information
FIT	Fracture Intervention Trial
GDG	(NICE Osteoporosis) Guideline Development Group
HRG	Healthcare Resource Group
HRT	hormone replacement therapy
MK-4	menaquinone-4
MK-7	menaquinone-7
NICE	National Institute for Health and Clinical Excellence
OF study	Osteoporosis Fracture study
QALY	quality-adjusted life-year
PSA	probabilistic sensitivity analysis
RCT	randomised controlled trial
RR	relative risk
SHEMO	Sheffield Health Economic Model for Osteoporosis
SD	standard deviation
WHO	World Health Organization
YOPS	Yamaguchi Osteoporosis Prevention Study

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

Executive summary

Description of proposed service

The focus of this report is to establish whether vitamin K can be used cost-effectively in the treatment of women who are osteoporotic and who have a previous fracture.

Epidemiology and background

Osteoporosis is a common disease in the elderly, with an estimated 0.95 million female sufferers in England and Wales. It is defined as possessing a *T*-score (the number of standard deviations from the average bone mineral density of healthy young women) of –2.5 standard deviations or lower. The main consequence of osteoporosis is an increased incidence of fractures, which increase as a woman ages. These result not only in morbidity for the patient (with a risk of mortality following fractures at some sites) but also in the consumption of scarce NHS resources. A recent estimate of the projected cost of osteoporotic fractures in women in the UK by 2010 put this figure at £2.1 billion.

Methods

The scope of this assessment was to determine the clinical effectiveness and cost-effectiveness of vitamin K in preventing osteoporotic fractures in postmenopausal women compared with either no vitamin K or specific drugs licensed in the UK for the prevention or treatment of postmenopausal osteoporosis. Relevant outcome measures included incident vertebral and non-vertebral fractures; health-related quality of life; all-cause mortality; and adverse effects of treatment.

Searches to identify relevant studies were conducted in 14 electronic databases [MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, BIOSIS, CINAHL, DARE, NHS EED and HTA databases, AMED, NRR (National Research Register), Science Citation Index and Current Controlled Trials]. The searches were undertaken in May 2007 and the MEDLINE search was updated in March 2009. The searches were not restricted by publication type, date of publication or language.

The inclusion criteria were as follows:

- *Population*: postmenopausal women with osteoporosis/osteopenia.
- *Intervention*: oral vitamin K (any dose).
- *Comparators*:
  - placebo or no treatment for bone health other than ensuring that the patient is replete of calcium and vitamin D.
  - the following drugs, which are licensed in the UK for the prevention or treatment of postmenopausal osteoporosis: alendronate, etidronate, risedronate and strontium ranelate.
- *Outcomes*: all-cause mortality; incident vertebral fracture; incident non-vertebral fracture; adverse effects; continuance; compliance, health-related quality of life; costs incurred.
- *Study design*: randomised controlled trials; economic evaluations.

Only randomised controlled trials (RCTs) that reported fracture outcomes were included in the review of clinical effectiveness; however, this criterion was relaxed for consideration of adverse events, allowing inclusion of observational studies or RCTs that did not report fracture outcomes.

The following studies were excluded: those that were considered methodologically unsound in terms of either study design or method used to assess fractures, or those that did not report results in the necessary detail; or those in which the participants were not vitamin D replete and/or had insufficient calcium intake.

Where appropriate, meta-analysis was carried out, using Review Manager software (REVMAN).

Number and quality of studies and direction of evidence

Five randomised controlled trials were identified that compared vitamin K with a relevant comparator in postmenopausal women with osteoporosis or osteopenia. The double-blind ECKO trial compared 5 mg of phylloquinone (vitamin K_1) with placebo in Canadian women with osteopenia but without osteoporosis. Four open-label trials used 45 mg of menatetrenone (vitamin K_2) in Japanese women with osteoporosis; the Osteoporosis Fracture (OF) study and that by Shiraki *et al*. compared menatetrenone with no treatment, the Yamaguchi Osteoporosis Prevention Study (YOPS) compared it with etidronate or no treatment, and the trial by Iwamoto compared it with etidronate or calcium.

The methodological quality of the ECKO trial was good. By contrast, all four trials of menatetrenone were poorly reported, making it impossible to exclude the possibility that their methodological quality was low; moreover, three were very small (< 100 women in each group).

Phylloquinone was associated with a statistically significant reduction in the risk of clinical fractures relative to placebo [relative risk (RR) 0.46, 95% confidence interval (CI) 0.22 to 0.99]; morphometric vertebral fractures were not reported. Although the smaller trials found that menatetrenone was associated with a reduction in the risk of morphometric vertebral fractures relative to no treatment or calcium, the much larger OF study found no evidence of a reduction in vertebral fracture risk. The three smaller trials found no significant difference between treatment groups in non-vertebral fracture incidence. OF study data relating to non-vertebral and clinical vertebral fractures have not been published.

Safety

In the ECKO trial, phylloquinone was not associated with an increase in adverse events; moreover, it was possible that it demonstrated anticancer efficacy. In the menatetrenone trials, the reporting of adverse events was generally poor; however, in the OF study, menatetrenone was associated with a significantly higher incidence of skin and skin appendage lesions.

Summary of benefits

Benefits have been measured in terms of quality-adjusted life-years (QALYs). Vitamin K provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the absolute risk of fracture.

Cost-effectiveness of identification and treatment strategies

No published economic evaluations of vitamin K were found. A mathematical model was thus constructed to estimate the cost-effectiveness of vitamin K_1; the efficacy data for other types of vitamin K were considered too poor to be included. Comparators were two bisphosphonates (alendronate and risedronate) and strontium ranelate. Vitamin K_1 and alendronate were seen to be markedly more cost-effective than either risedronate or strontium ranelate. The base-case results favoured vitamin K_1, but this relied on many assumptions, particularly on the efficacy of preventing hip and vertebral fractures.

Evaluation of further research

Calculation of the expected value of sampled information was conducted assuming a randomised controlled trial of 5 years' duration comparing alendronate with vitamin K_1. This showed that the costs incurred in obtaining updated efficacy data from a trial with 2000 women per arm, which would be used to influence future prescribing policy, were estimated to be a cost-effective use of resources.

Costs

It is unlikely that the present prescribing policy (i.e. alendronate as first-line treatment) would be altered, thus there would be no change in NHS expenditure. Even if vitamin K_1 was used, the acquisition prices of alendronate and vitamin K_1 are similar and thus there is unlikely to be a marked impact on NHS expenditure.

Conclusions/need for further research

There is currently large uncertainty over whether vitamin K_1 is more cost-effective than alendronate; further research is required. A calculation of the expected value of sampled information has shown that an RCT of 2000 women per arm would be a cost-effective use of resources.

Chapter 1
The aim of the review

The aim of the review was to address the question, 'What is the clinical and cost-effectiveness of vitamin K in preventing fractures in postmenopausal women at high risk of fracture?' The cost-effectiveness of vitamin K must be discussed with reference to the costs and clinical effectiveness of other licensed interventions in order to provide advice on the likely position of vitamin K within a treatment algorithm. Vitamin K has been explicitly compared with two bisphosphonates (alendronate and risedronate) and strontium ranelate.

The authors of the review have been involved with several evaluations of the clinical and cost-effectiveness of interventions for preventing fractures.[1–5] In the more recent work,[4,5] data on the risk of osteoporotic fracture were provided under an academic-in-confidence agreement; permission to use these data were not granted for this report and therefore a different methodology has been adopted for calculating fracture risk.

Chapter 2
Background

The internationally agreed definition of osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[6]

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 include vertebral compression fractures and fractures of the distal radius and the proximal femur (hip fracture). In addition, when the skeleton is osteoporotic, fractures occur more commonly at many other sites including the pelvis, proximal humerus, distal femur and ribs. The incidence of fracture is strongly related to age, with a steady increase in incidence as a woman ages.[7]

Fractures of the spine often go undetected; it is estimated that only one-third of fractures seen in trials in which morphometric criteria are used to establish the presence of a fracture come to clinical attention.[8] There is a good deal of uncertainty surrounding the impact of undetected 'morphometric' fractures on the quality of life of the sufferer, and any cost impacts that such fractures have.

Osteoporotic fractures occurring at the spine and the distal radius are associated with significant morbidity, but the most serious consequences arise in patients with hip fracture, which is associated with an increase in mortality in the year following the hip fracture.[9]

It has been estimated that the cost of treating osteoporotic fractures in female postmenopausal patients in the UK in 2000 was approximately £1.5–1.8 billion per annum.[10,11] It has been estimated that these costs will increase to £2.1 billion by 2010.[11] The key components of the costs associated with osteoporotic fractures are hip fractures and subsequent nursing home care that is required for a proportion of these patients.

This report is focused on postmenopausal women because of the deterioration of bone quality following the menopause.

Description of osteoporosis, osteopenia and severe (established) osteoporosis

The definition of osteoporosis based on bone mineral density (BMD) has been developed because BMD can be measured with precision and accuracy, allowing definitive diagnoses of osteoporosis. However, it is acknowledged that other factors such as abnormalities within the skeleton and risk of falls are also important in determining the risks of fracture. Nevertheless, 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 SDs from the average BMD of women of the same age as the patient.

Two thresholds of BMD have been proposed for Caucasian women based on the *T*-score.[12,13] The first, osteoporosis, denotes a value for BMD that is 2.5 SD or more below the young adult mean value (*T*-score –2.5 SD or less). The second, osteopenia, denotes a *T*-score that lies between –1 and –2.5 SD below the young adult mean value. These values refer to the use of dual X-ray absorptiometry at the lumber spine, hip (total hip or femoral neck) and the forearm. Other measurement methods, such as quantitative ultrasound or quantitative computerised tomography, or other sites, such as the calcaneus, do not produce comparable results.

The class of osteoporosis is further divided into patients with severe (or established) osteoporosis, which is defined as a *T*-score of –2.5 SD or less plus at least one documented fracture. In this report severe osteoporosis will be used to define

patients who have a *T*-score of –2.5 SD or less with a previous fracture. The term osteoporosis will be used to define patients with a *T*-score of –2.5 SD or less without a previous fracture.

Since the introduction of working definitions of osteoporosis, much attention has focused on their application to epidemiology, clinical trials and patient care. Several problems have emerged, however, largely because of 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, as this is the reference site for diagnosis because of the limitations of early dual X-ray absorptiometry machines.[14] Accordingly, 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.[15,16]

Epidemiological data

The prevalence of osteoporosis by age

Raw data were taken from a UK population-based study by Holt *et al.*[17] and used to calculate the relationship between *T*-score and age. The prevalence of osteoporosis within the UK has also been estimated from these data. This data set contained observations on 5713 women aged between 50 and 85 years and used the National Health and Nutritional Evaluation Study III (NHANES III) reference data for women aged 20–29 years.

The percentage of women with a *T*-score of –2.5 SD or less, as measured at the femoral neck, was recorded. These data are shown in *Figure 1*; there is a marked increase in the percentage with a *T*-score of –2.5 SD or less with age. The database taken from the Holt *et al.* study[17] had relatively few women aged between 80 and 84 years ($n = 40$). The confidence interval around the prevalence at this age is wide (*Figure 1*). Assuming, however, that the midpoint values are correct, and multiplying these prevalence rates by the respective population of England and Wales,[18] it is estimated that there are 0.95 million women suffering with osteoporosis. Assuming that the lower 95% confidence intervals are correct would result in a predicted 0.69 million women with osteoporosis; conversely, assuming that the upper 95% confidence intervals are correct would result in a predicted 1.22 million women with osteoporosis.

The average *T*-score at the femoral neck at each age band was calculated from the UK population data in the Holt *et al.* study.[17] A linear relationship was assumed and the *T*-score was assumed to be 2.0251–(0.0512×age in years). The assumed average *T*-score at the midpoint of each age band

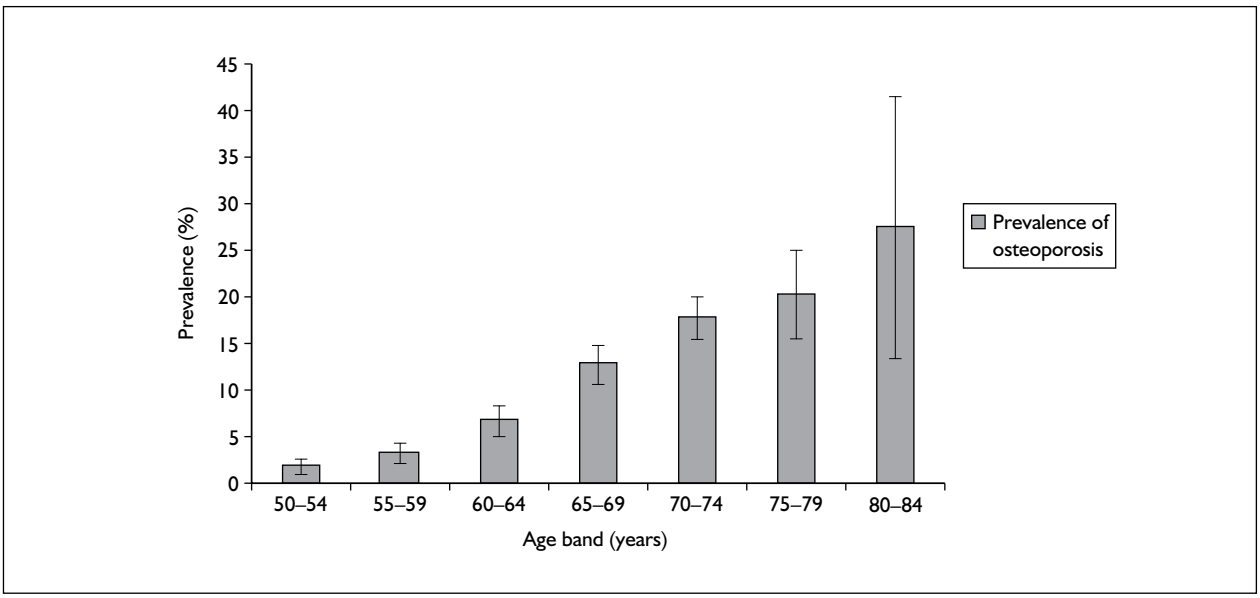

FIGURE 1 *The estimated prevalence of female osteoporosis by age band.*

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

Age (years)	Average UK *T*-score[17a]	*Z*-score at threshold of osteoporosis (*T*-score of –2.5 SD)[a]
50–54	–0.66	–1.84
55–59	–0.92	–1.58
60–64	–1.17	–1.33
65–69	–1.43	–1.07
70–74	–1.69	–0.81
75–79	–1.94	–0.56
80–84	–2.20	–0.3
85–89	–2.45	–0.05

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

is given in *Table 1*. It is seen that, above 85 years of age, the average *T*-score for women almost reaches the threshold for osteoporosis.

Fractures considered to be osteoporotic

Historically, four fracture sites were considered in estimating the cost-effectiveness of interventions to reduce fractures. These were the hip, spine, wrist and proximal humerus. Recent modelling work[4] has increased the number of sites included because of evidence that further sites are considered to be related to osteoporosis.[19] The additional fracture types included are fractures of the pelvis, humeral shaft, tibia, fibula, scapula, ribs and sternum and other femoral fractures.

Description of new intervention

Vitamin K is a fat-soluble vitamin that occurs naturally in two forms, K_1 and K_2. Vitamin K has also been synthesised in the forms K_3–K_7.

In most parts of the world, including Europe and the USA, the primary dietary source of vitamin K is vitamin K_1 (also known as phylloquinone).[20] Phylloquinone occurs naturally in a range of foodstuffs, especially green leafy vegetables.[21] The commercially prepared versions of vitamin K_1, phytonadione[22] and phytomenadione, are chemically identical to phylloquinone.

The term vitamin K_2 embraces a family of compounds known as the menaquinones. These are of microbial origin[23] and occur in nutritionally significant amounts only in meat, liver and some fermented foods, including cheese.[24] The richest known dietary source of vitamin K is natto, a product derived from fermented soya beans. Almost all of the vitamin K in natto takes the form of menaquinone-7 (MK-7).[25] Although natto is a traditional food in eastern Japan,[23] it is not popular elsewhere.[25] Vitamin K_2 is also synthesised in the colon, but absorption of this synthesised vitamin K is probably so poor as to make only a minor contribution to overall vitamin K status.[24] Menaquinone-4 (MK-4, also known as menatetrenone) is also produced synthetically.

Vitamin K_3 (menadione) is a synthetic form of vitamin K that is converted to menatetrenone (MK-4) in the body.[26] Vitamin K_4 (menadiol sodium diphosphate) is a synthetic water-soluble preparation for use in patients with fat malabsorption.[27]

Vitamin K: function

The first identified function of vitamin K was its role in blood coagulation. Because insufficiency results in a tendency to bleed as a result of the malfunction of vitamin K-dependent clotting factors,[28] it was defined as vitamin K-responsive hypoprothrombinaemia, measured clinically by the prothrombin time (the time it takes for blood to clot). Such 'classic' ('clinical') insufficiency is rare and severe.[29] Because neonates are relatively deficient in vitamin K it is recommended that they be given a single intramuscular injection of 1 mg of vitamin K_1 (as phytomenadione) at birth, to prevent vitamin K deficiency bleeding.[27] Because of its role in coagulation, vitamin K is contraindicated in patients on anticoagulant therapy as it may reduce its efficacy. However, it has been claimed that doses below 100 µg/day do not appear to cause problems in such patients.[26]

More recently, it has been recognised that vitamin K plays a role in the absorption of calcium into the bone.[27] Because of evidence that a low dietary intake of phylloquinone is associated with an increased risk of hip fracture in older women,[30,31] it has been suggested that vitamin K deficiency that is subclinical in terms of blood clotting may nonetheless be associated with the development of osteoporosis. Such deficiency is likely to be considerably more common than classic clinical deficiency measured by the prothrombin time.[29] However, a recent Danish observational study[32] of a cohort of perimenopausal women found no significant difference in BMD between the 5% with the lowest vitamin K_1 intake and the 5% with the highest vitamin K_1 intake at baseline (< 24.5 µg/day versus > 209 µg/day) or after 5 years (< 17 µg/day versus > 214 µg/day); the nested case–control study found no difference in fracture risk between the 5% with the lowest vitamin K_1 intake (< 46 µg/day) and the 5% with the highest vitamin K_1 intake (> 210 µg/day). The apparent association identified in epidemiological studies between a low dietary intake of phylloquinone and an increased risk of hip fracture may thus reflect the poor nutritional status of women with hip fracture rather than a specific effect of vitamin K deficiency on bone.[33,34]

Although vitamins K_1 and K_2 appear to have very similar actions in relation to haemostasis, they may have different roles in relation to bone function.[28]

Vitamin K: recommended daily intake

There is no precise UK recommended daily intake for vitamin K. COMA (the UK Department of Health's Committee on Medical Aspects of Food Policy) has suggested that a daily intake of 1 µg/kg body weight [approximately 64 µg/day for a 64-kg (10-stone) woman] is probably adequate for blood clotting,[35] and UK vitamin supplements intended for general consumption may contain up to 0.045 mg (45 µg) of vitamin K as either vitamin K_1 or vitamin K_2.[35] However, it has been suggested that dietary intakes that are sufficient to maintain normal blood coagulation may be suboptimal for bone health.[24] The US recommended daily dietary intake is somewhat higher than the suggested UK intake, at 90 µg/day of phylloquinone for women aged 19 years and over, a figure based on reported intakes in apparently healthy US population groups.[24] As there is currently insufficient evidence to differentiate between vitamin K_1 and vitamin K_2 requirements,[26] there is no UK or US recommended daily intake specifically for vitamin K_2. Although the majority of efficacy evidence for vitamin K has come from Japanese studies, it has not been possible to identify the Japanese recommended dietary intake for vitamin K.

The safe upper limit for vitamin K consumption is not clear. The safe maximal daily intake of vitamin K_1 has previously been claimed to be 32.5 mg,[36] but in 2003 the Expert Group on Vitamins and Minerals[35] concluded that there were insufficient data to establish a safe upper limit. However, it is claimed that intakes of up to 1 mg/day of vitamin K_1 and 45 mg/day of menatetrenone have been used with no apparent adverse effects in patients not requiring oral anticoagulation.[26] The Expert Group on Vitamins and Minerals[35] noted no toxicity related to oral vitamin K_1 or K_2, although toxicity was associated with high doses of vitamin K_3.

Because the body only stores enough vitamin K to meet its needs for a few days, these stores, unlike those of other fat-soluble vitamins, are rapidly depleted.[29] Deficiency may therefore occur within a short period either when dietary intake is insufficient or when the intestinal bacteria that synthesise vitamin K_2 are disrupted,[37] for instance after prolonged treatment with oral antibiotics. Deficiency may also occur in patients with fat malabsorption.[27] There is also evidence to suggest that, in women, oestrogen levels may influence vitamin K status regardless of diet; however, the mechanisms involved are currently not known.[34]

Vitamin K: actual daily intake in elderly women in the UK

Phylloquinone forms the main source of dietary vitamin K in Western countries, with a lesser contribution from the menaquinones. The fraction of the daily vitamin K requirement provided by menaquinones produced by bacteria in the bowel is unknown.[29]

Some research has sought to assess the extent to which elderly people in Britain achieve the guideline dietary intake of phylloquinone. In 1994–5, in a nationally representative sample of women aged 65 years and over living independently in mainland Britain, the geometric mean daily phylloquinone intake was 61 µg [95% confidence interval (CI) 57 to 64 µg], equivalent to 0.99 µg/kg body weight (95% CI 0.93, 1.05 µg/kg),[38] an intake very close to the UK recommended daily intake of 1 µg/kg body weight. However, average daily body weight-adjusted intakes decreased significantly with age and also varied by geographical location

TABLE 2 *Daily phylloquinone intake in British women living in the community and aged 65 years and over*[38]

	μg/day (geometric mean)	95% CI
Age group (years)		
65–74	66	61 to 71
75–84	57	52 to 63
85+	45	38 to 55
Region		
London and South East	74	66 to 83
Central, South West and Wales	61	56 to 66
Scotland and North	49	46 to 53

(*Table 2*). Overall, approximately half of the women studied had daily intakes below the guideline level of 1 μg/kg body weight.[38]

Some studies suggest that the absorption of vitamin K is increased when it is consumed with a meal containing fat. A small experimental study[39] in healthy volunteers found that absorption of phylloquinone (vitamin K_1) from boiled spinach was increased three-fold by the addition of butter, whereas another experimental study[40] in healthy young Japanese men found that, for optimum absorption, 15 mg of supplementary menatetrenone should be consumed with a meal containing 35 g of fat [approximately half the recommended daily fat intake (60 g) for a 20-year-old Japanese male]. However, the Expert Group on Vitamins and Minerals[35] has stated that the bioavailability of vitamin K_1 is not affected by the fat content of the accompanying meal.

Vitamin K: actual daily intake in elderly women in Japan

Because the evidence for the antifracture efficacy of menatetrenone comes entirely from Japanese studies, it is important to consider the extent to which the daily vitamin K intake of elderly women in Japan resembles that of elderly women in the UK. The traditional Japanese diet differs considerably from the British diet, as does the daily dietary vitamin K intake. Research has shown that the serum concentration of phylloquinone is somewhat higher in postmenopausal Japanese women than in postmenopausal English women (*Table 3*); this is independent of the habit of eating natto, a foodstuff that is very popular in eastern Japan but seldom eaten in western Japan. However, serum MK-7 is 14 times as high in postmenopausal women living in Tokyo as in English women, and this difference is largely attributable to natto intake.[28] As seen in *Table 3*, serum MK-7 is also over four times higher in Tokyo (eastern Japan) than in Hiroshima (western Japan), and in 1987 the incidence of hip fracture in women was lower in eastern Japan than in western Japan.[41]

Vitamin K: commercial preparations

Vitamin K is currently licensed within the EU for two indications:

- to prevent deficiency in people with fat malabsorption, using the water-soluble formulation, menadiol sodium phosphate, at a dose of about 10 mg/day[27]
- to prevent vitamin K deficiency bleeding in neonates (haemorrhagic disease of the newborn), using phytomenadione usually given at birth as a single intramuscular injection of 1 mg.[27]

Vitamin K is available for oral administration in five formulations:

- Phytonadione – A form of phylloquinone produced commercially by Merck and marketed as 5-mg tablets under the brand name Mephyton®. It is marketed for use in coagulation disorders, and the specified dosage (a single initial dose of 2.5–25 mg or, rarely, 50 mg, the frequency and size of subsequent doses depending on the patient's response) relates to that application only.[42] No UK price has been identified for this product.
- Phytomenadione – A synthetic form of phylloquinone used in nearly all vitamin

TABLE 3 *Serum concentration of vitamin K in postmenopausal women in England, Hiroshima and Tokyo*[23]

Location	Mean serum concentration of vitamin K ± SD	
	ylloquinone (ng/ml)	**MK-7 (ng/ml)**
England	0.497 ± 0.537	0.371 ± 0.204
Hiroshima (western Japan)	0.741 ± 0.581	1.221 ± 1.848
Tokyo (eastern Japan)	0.727 ± 0.461	5.268 ± 6.132

MK-7, menaquinone-7.

K-containing food supplements and multivitamins available in the Western world.[25,26] Phytomenadione is produced commercially by Roche and marketed as 10-mg tablets under the brand name Konakion®, at a price of £1.65 per 10-tablet pack.[43] Konakion is marketed for the treatment of haemorrhage or threatened haemorrhage associated with a low blood level of prothrombin or factor VII; the specified dosage (a single dose of 10–20 mg, repeated if necessary 8–12 hours later) relates to that application only.[44]

- Menatetrenone (MK-4) – A synthetic menaquinone almost exclusively used in Japan[25] where it is produced commercially by Eisai and marketed in 15-mg capsules under the brand name Glakay®.[45] As menatetrenone has a half-life in the circulation of 1–2 hours,[46] it is recommended that it be taken three times a day, giving a total daily dose of 45 mg.[45] The product information leaflet states that Glakay should be taken after meals because its absorption is decreased when taken on an empty stomach and that absorption is also decreased if the meal has a low fat content.[45] Menatetrenone is currently not permitted as a food supplement in the EU because there is no evidence for its independent role in health.[26] No UK price has been identified for this product.
- MK-7 – A natural menaquinone extracted from natto, which has only recently become commercially available.[25] As MK-7 has a half-life in the circulation of 3 days, it may be more effective than menatetrenone as a low-dose supplement.[46] MK-7 currently appears to be marketed in the UK only by Solgar, in 100-µg tablets; it is available online at a cost of £20.69 for 50 tablets.[47]
- Menadiol phosphate – Menadiol phosphate is produced by Cambridge Laboratories as menadiol sodium phosphate tablets, equivalent to 10 mg of menadiol phosphate.[27] It is marketed for the treatment of haemorrhage or threatened haemorrhage associated with a low blood level of prothrombin or factor VII, generally caused by obstructive jaundice (before and after surgery); the specified dosage (10–40 mg daily) relates to that application only.[48] The net price per 100-tablet pack is £48.25.[27]

The length of time for which these formulations are taken will vary according to the purpose for which they are being used. In principle, their use for osteoporosis prophylaxis could be lifelong.

Contraindications

Vitamin K is contraindicated in patients on anticoagulant therapy as it may reduce its efficacy. However, it has been claimed that vitamin K doses below 100 µg/day do not appear to cause problems in such patients.[26]

The product leaflet for Glakay capsules (menatetrenone) states that treatment should be discontinued should rash, redness, pruritus or other symptoms occur.[45]

Chapter 3
Clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

Systematic searches were undertaken to identify studies relating to the clinical effectiveness of vitamin K in preventing osteoporotic fractures. The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- hand searching of bibliographies of retrieved papers.

Sources searched

The electronic databases searched included MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, BIOSIS, CINAHL, DARE, NHS EED and HTA databases, AMED, NRR (National Research Register), Science Citation Index and Current Controlled Trials. The Food Standards Agency website was browsed. The searches were undertaken in May 2007; in addition, the MEDLINE search was updated in March 2009.

Keyword strategies

The search strategies included subject headings and free text terms, combined using Boolean logic, to identify all published and unpublished data relating to the prevention of fractures using vitamin K. The MEDLINE search strategy is presented in Appendix 1. Search strategies for the other databases are available on request.

Search restrictions

Searches were not restricted by publication type, date of publication or language.

Inclusion and exclusion criteria

Inclusion criteria

Participants

Postmenopausal women with osteoporosis/osteopenia [defined as BMD 1.5 SD or more below the young female adult mean value (*T*-score –1.5 SD or less) or a previous osteoporotic fracture].

Intervention

- Oral vitamin K (any dose).

Comparators

- Placebo or no treatment for bone health other than ensuring that the patient is replete of calcium and vitamin D.
- The following drugs, which are licensed in the UK for the prevention or treatment of postmenopausal osteoporosis: alendronate, etidronate, risedronate and strontium ranelate.

Although raloxifene and teriparatide are also licensed in the UK for the prevention or treatment of postmenopausal osteoporosis, they were excluded as comparators because of the restrictions placed on their use in the recent National Institute for Health and Clinical Excellence (NICE) guidance regarding the use of treatments for osteoporosis[49].

Outcome measures

The main outcome measures were:

- all-cause mortality
- incident vertebral fracture
- incident non-vertebral fracture
- adverse effects
- continuance
- compliance
- health-related quality of life
- costs incurred.

Only randomised controlled trials (RCTs) that reported fracture outcomes were included in the review of clinical effectiveness. However, this criterion was relaxed for consideration of adverse events, allowing inclusion of observational studies or RCTs that did not report fracture outcomes.

Study design

- RCTs.
- Economic evaluations.

Discussion of outcome measures

Vertebral fractures

Vertebral fractures may be symptomatic or asymptomatic. Symptomatic, or clinical, vertebral fractures cause either sufficient discomfort for

the patient to bring them to the attention of a health professional or a measurable loss of height. Their presence can be confirmed by radiography. Radiography can also identify asymptomatic fractures. Most studies of antiosteoporotic agents report radiographically identified vertebral fractures (also termed radiographic or morphometric); these will include symptomatic as well as asymptomatic fractures. However, some studies either report only clinical fractures or present separate data on clinical and radiographic fractures. Data from the Fracture Intervention Trial (FIT),[50] a large placebo-controlled trial of alendronate, suggest that, in postmenopausal osteoporosis, the relative risk (RR) of the two types of fracture is very similar.

None of the various different approaches that have been developed to identify radiographic vertebral osteoporotic fractures has been agreed to be the gold standard. The purely qualitative approach, which depends on the visual identification of abnormalities in vertebral shape or height, is a subjective method with poor inter- and intrarater reliability; however, unlike a purely quantitative method, when performed by an expert it can exclude vertebral abnormalities that are not osteoporotic in origin.[51] More recently, Jiang *et al.*[51] have developed an algorithm-based qualitative approach that aims to facilitate differentiation between osteoporotic fracture and deformity due to other causes. Quantitative methods are more objective and reproducible than qualitative methods but they may identify non-fracture deformities as fractures whilst failing to recognise mild end-plate fractures.[51] However, the number of false positives may be reduced if the definition of incident fracture requires a 20% or greater reduction in anterior, central or posterior vertebral height.[52] The semiquantitative method developed by Genant *et al.*[53,54] grades each vertebra according to the visually apparent degree of reduction in vertebral height and area, irrespective of the type of deformity, but also gives careful attention to changes in vertebral shape, enabling non-fracture deformities to be excluded whilst end-plate fractures that are not associated with a 20% reduction in vertebral height can be identified.[55] The semiquantitative method is more objective and reproducible than the qualitative method and has better specificity and sensitivity than the quantitative method because it reduces the number of false positives while identifying mild deformities that the quantitative method would exclude.[55] However, some researchers claim that the semiquantitative method can be difficult to apply accurately and that it overestimates fracture prevalence by failing to differentiate adequately between true fractures and non-fracture deformities.[51,56]

Non-vertebral fractures

Traditionally, most studies of antiosteoporosis interventions have reported only those non-vertebral fractures that are so-called fragility fractures, defined as low trauma fractures (e.g. those sustained by falling from standing height or less). However, more recently, the prospective Study of Osteoporotic Fractures[57] found that decreases in BMD increase the risk of fracture occurring as a result of severe trauma such as motor vehicle accidents, and therefore recommended that traumatic fractures should be included as outcome measures in osteoporosis trials.

Adverse events

Randomised controlled trials whose main focus is the efficacy of the study intervention have limited ability to assess drug toxicity because they are generally not powered to reliably detect rare, though potentially serious, adverse drug reactions and because their follow-up period is not long enough to permit the detection of either adverse drug reactions widely separated in time from the original use of the drug or delayed consequences associated with long-term therapy.[58] In addition, their populations may not be wholly typical of the target population, as they tend to exclude older participants and those with comorbidities. Moreover, they do not always measure all potential side effects.[59] For this reason, although studies reporting survival and adverse effects were included in the systematic review only 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. A systematic search was therefore carried out in MEDLINE to identify evidence of the adverse effects of vitamin K therapy in osteoporotic patients in the form of RCTs designed specifically for this purpose and other types of studies that are important in identifying drug-related adverse events: retrospective analyses of large databases (e.g. prescription-event monitoring studies), cohort studies (including postmarketing surveillance studies), case–control studies, cross-sectional surveys and case reports.

Continuance and compliance

The efficacy of a therapy is clearly affected by the extent to which patients take it in the intended manner. This has two aspects:

- continuance: the length of time for which a patient continues to take a prescribed medication (sometimes termed persistence)
- compliance: the extent to which a patient takes the medication each day in accordance with the prescribed dosage regimen.

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, occasionally missing doses or taking extra doses; such partial compliance may be erratic or may be consistent but different from what the physician prescribed.[60] It has been suggested that partial compliance (defined 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 omissions of single doses or of 2 or more consecutive days' doses.[61]

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

- patient recall (e.g. self-reported questionnaire)
- pill counts
- self-recorded diaries
- electronic devices that record the date and time of opening of the drug containers
- direct measurements of therapeutic response, such as blood tests
- repeat prescriptions.

However, none of these methods is ideal in terms of determining whether or when the patients actually took the medication; direct measurements such as blood tests may be confounded by an unknown degree of variation in therapeutic response, whereas the remainder depend on the reliability of self-reporting or the assumption that dispensed medication has actually been used by the patient.[62] 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.[63] Moreover, a study of the proportion of medication taken would not necessarily identify partial compliance that involved either extra doses or deviations from the prescribed time of dose. In a random sample of patients participating in a controlled trial of fluvastatin versus placebo,[61] electronic monitoring found that, although mean compliance as measured by the number of doses taken was found to be 94% (range 54–110%), mean compliance as measured by the number of days on which the correct number of doses was taken was only 81% (range 36–100%), and mean compliances to the prescribed morning and evening dosing schedules (i.e. within ±6 hours) were only 71% (range 23–100%). Thus, compliance measured by pill counts is likely to overestimate the actual degree of compliance with medication.

Unsurprisingly, continuance and compliance with a medication are related to a number of the properties of that medication, including its tolerability, its convenience of administration, the patient's perception of its safety, and quality of life while on treatment.[64] Thus, compliance decreases as the complexity, cost and duration of the regimen increase. The risk of non-continuance or non-compliance with prescribed medication is particularly high in patients with asymptomatic chronic diseases or risk factors that require long-term preventive medication[64] – in other words, patients with conditions such as osteopenia, or osteoporosis without previous fracture. Because treatment brings no immediately apparent benefits to such patients, they are less well motivated to comply long term, and find any minor side effects less acceptable.[65]

Continuance and compliance are clearly important in assessing the actual, rather than theoretical, efficacy of a medication. It is recognised that, for a number of reasons, continuance at least is likely to be substantially better in clinical trials than in real life. Therefore, as with adverse effects, we did not exclude the use of relevant evidence from other sources to supplement that drawn from the studies under review.

Exclusion criteria

The following publication types were excluded from the review:

- non-randomised studies (except for adverse effects or continuance and compliance)
- animal models
- preclinical and biological studies
- narrative reviews, editorials, opinions
- reports published as meeting abstracts only when insufficient methodological details were reported to allow critical appraisal of study quality.

Systematic reviews of primary studies were also excluded from the review but were read in case

they led to the identification of additional relevant trials.

In addition, studies were excluded if:

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

Sifting

The references identified by the literature searches were sifted in three stages. They were screened for relevance first by title and then by abstract. Those papers that seemed from their abstracts to be relevant were then read in full, as were those for which abstracts were not available. At each step, studies that did not satisfy the inclusion criteria were excluded.

Data extraction strategy

Data were extracted by one reviewer using a customised data extraction form based on that proposed by the NHS Centre for Reviews and Dissemination.[66] When multiple publications of the same study were identified, data were extracted and reported as a single study. Any disagreements were resolved by discussion.

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

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

Quality assessment strategy

The methodological quality of all trials that met the inclusion criteria was assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination[66] (see Appendix 2). In addition, the quality of identification of incident fractures was assessed using the criteria proposed by Gillespie *et al.*[67] When a study was reported in more than one publication, its quality was assessed on the basis of the combined data from all relevant publications.

It is recognised that the quality assessment tool inevitably assesses the reported quality, and not necessarily the true methodological quality, of each study.

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.[68,69]

Meta-analysis strategy

Studies that met the review's entry criteria were eligible for inclusion in the meta-analysis if this was appropriate (i.e. if the study populations, interventions and outcomes were comparable) and if they reported fracture incidence in terms of the number of subjects suffering fractures, as only this will enable the calculation of the RR of subjects in the intervention group developing a new fracture or fractures compared with subjects in the control group. Studies that reported only the number of fractures in each group, or the proportion of subjects in each group who suffered fractures, could not be included in the meta-analysis 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 software (REVMAN).[70] Both fixed- and random-effects models were used, and heterogeneity was explored through consideration of the study populations, methods and interventions, by visualisation of the results and, in statistical terms, using the chi-squared test for homogeneity and the I^2 statistic.

Relative risks for individual studies have also been calculated using Review Manager.

Results

Quantity and quality of research available

Number of studies of clinical efficacy identified

The electronic literature searches identified 1078 potentially relevant articles. Of these, 14 articles related to five trials that compared vitamin K with a relevant comparator in postmenopausal women with osteoporosis or osteopenia (*Figure 2*).

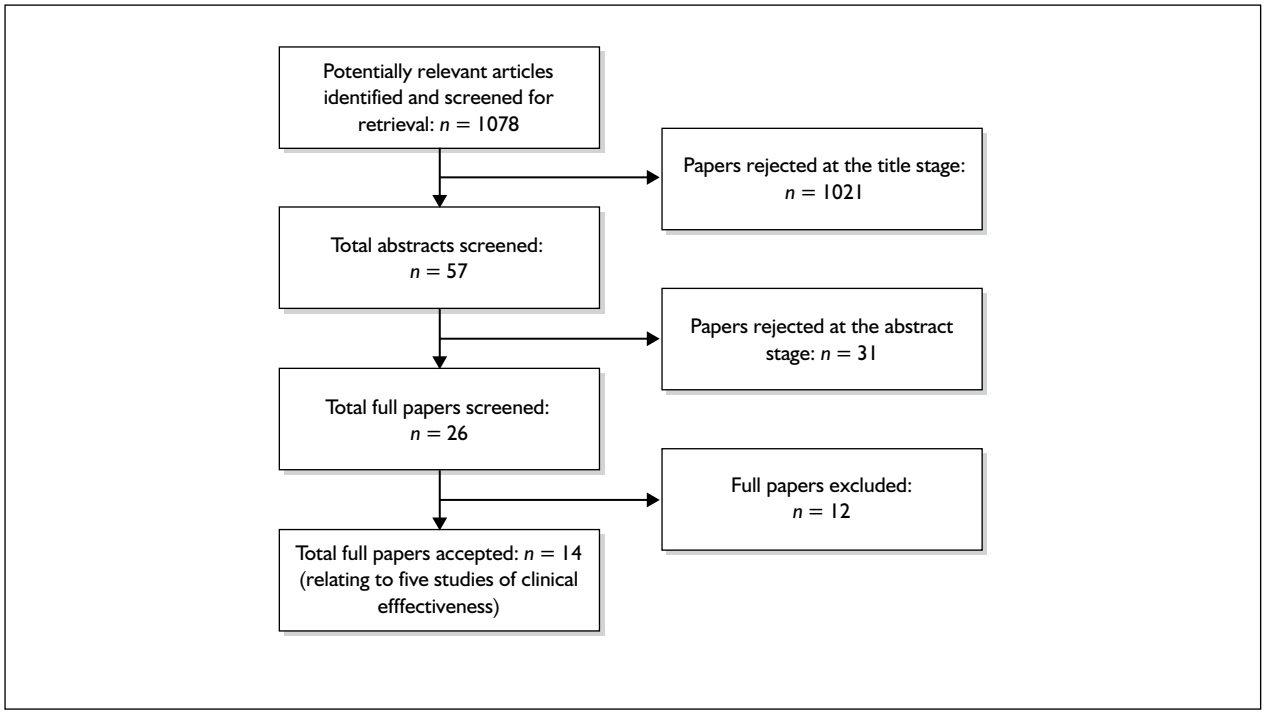

FIGURE 2 *Clinical effectiveness: summary of study selection and exclusion – electronic literature searches.*

Number and type of studies included

A total of five individual RCTs met the review inclusion criteria. The various publications relating to these studies are listed in Appendix 3.

Number and type of studies excluded, with reasons

As may be seen, a substantial number of the references identified by the electronic searches related to studies that did not meet the inclusion criteria and were thus excluded as part of the sifting process. Details are therefore given only of those references that were excluded at the full paper stage. These references are listed in Appendix 4 together with the reasons for their exclusion.

Quantity and quality of research available

Phylloquinone (vitamin K_1)

Only one study of phylloquinone met the review's inclusion criteria. This was the ECKO study,[71] a double-blind placebo-controlled trial that used a daily dose of phylloquinone of 5 mg, nearly 60 times the US recommended daily dietary phylloquinone intake of 90 µg/day for adult women.[24] The study population of postmenopausal women with osteopenia but without osteoporosis was predominantly (88%) European Canadian (i.e. Caucasian). The daily dietary calcium and vitamin D intakes of all participants were assessed and supplements were given as required to bring these to 1500 mg and 800 IU respectively.[71]

The ECKO trial was originally planned as a 2-year study. However, because of interest in the long-term safety and antifracture efficacy of vitamin K, participants enrolled before 15 March 2004 were subsequently invited to continue in a 2-year extension. In total, 325 participants who had completed the first 24 months were invited to participate in this extension, and 261 (80%) agreed. However, because the extension study terminated before 66% (172/261) of those who had been enrolled had completed it, only 17% (73/440) of the original study participants completed the full 4 years.[71]

For further details of study design and reporting quality see Appendix 4.

Menatetrenone (vitamin K_2)

Four trials of menatetrenone met the review's inclusion criteria: these were the studies by Iwamoto *et al.*[72] and Shiraki *et al.*,[73,74] the Osteoporosis Fracture (OF) study[75] and the Yamaguchi Osteoporosis Prevention Study (YOPS).[76] All were open-label trials that had as their population postmenopausal women with osteoporosis. All were carried out in Japan and,

as none commented on the ethnicity of the study populations, probably all participants, but certainly the majority, were likely to be of Japanese ethnic origin. The trial by Shiraki *et al.* was originally planned as a 2-year study,[73] but subsequently an extension study[74] was carried out for 3 years, thus apparently bringing the total study period to 5 years.

Three trials (OF study,[75] Shiraki *et al*. study[73,74] and YOPS[76]) essentially compared menatetrenone with no treatment. Two of these trials stated that calcium was given to both the intervention and control groups. The dose of calcium used in the OF study was not specified.[75] The Shiraki *et al.* trial originally gave participants a daily dose of 150 mg of elemental calcium,[73] although the later extension study[74] used a dose of 200 mg/day. The trial by Iwamoto *et al.*[72] strictly encouraged all participants (apparently including those randomised to calcium) to consume 800 mg of calcium and 400 IU of vitamin D a day in their meals. The YOPS trial[76] made no mention of the use of calcium in any of the treatment groups.

In addition, two trials, the Iwamoto trial[72] and the YOPS trial,[76] compared menatetrenone alone with etidronate alone, and the Iwamoto trial compared menatetrenone alone with calcium alone. The YOPS trial also compared menatetrenone with hormone replacement therapy (HRT), calcitonin and alfacalcidol; these comparisons are not reported here.

All of the trials used a daily dose of 45 mg of menatetrenone (although this was not clear from the published data relating to the OF study, clarification was obtained from Eisai UK[77]). Although there is no recommended dietary intake for menatetrenone, 45 mg appears to be a high dose.

Menatetrenone is available in the form of Glakay capsules, which contain no more than 175 mg of hydrogenated oil,[45] substantially less than the 35 g of fat said to be required for the optimum absorption of menatetrenone.[40] However, none of the trials specified that participants were advised to consume the study medication with a meal containing fat.

Three of the four trials were published as journal articles. However, the extension study of Shiraki *et al.*[74] was only published in abstract form, whereas the results of the OF study[75] were only reported in a press release.

For further details of study design and reporting quality see Appendix 4.

Assessment of effectiveness

Phylloquinone (vitamin K_1)

Phylloquinone: antifracture efficacy

The ECKO trial[71] reported only clinical fractures. These included all fragility and non-fragility fractures except those of the fingers and toes. Phylloquinone was associated with a significant reduction in the risk of such clinical fractures (*Table 4*). As the trial was carried out in women with osteopenia, not osteoporosis, relatively few fractures were reported.

The study was not powered to identify a significant reduction in the risk of clinical fragility fractures (defined as low trauma fractures such as those sustained by falling from standing height).

Phylloquinone: adverse effects

In the ECKO trial,[71] no serious adverse events were attributed to phylloquinone therapy. Indeed, it was suggested that phylloquinone might have anticancer effects as only three women in the phylloquinone group developed cancer compared with 12 in the placebo group (RR 0.26, 95% CI 0.07 to 0.90). The incidence of nausea and vomiting was similar in the intervention and placebo groups (5.1% versus 4.5%, $p = 0.77$).

The MEDLINE search identified no large, long-term studies of the safety of phylloquinone therapy in the treatment of osteoporosis, and no postmarketing surveillance data could be identified. The Expert Group on Vitamins and Minerals[35] noted no toxicity related to oral vitamin K_1, although a review by Vermeer *et al.*[26] referred to unpublished preliminary studies which suggested that vitamin K_1 supplementation in doses higher than 1 mg/day might contribute to periodontal disease.

Phylloquinone: health-related quality of life

In the ECKO trial, health-related quality of life was not significantly different between the intervention and placebo groups.

Phylloquinone: continuance and compliance

In the ECKO trial, 91.2% of participants randomised to phylloquinone completed the first 2 years of the study, compared with 90.6% in the placebo group, suggesting relatively high continuance with study medication in both groups. However, 25% of eligible women in the phylloquinone group who were invited

TABLE 4 *Phylloquinone in postmenopausal osteopenia: all clinical fractures*

Study	Dose	Numbers in each group suffering clinical fractures
ECKO trial 2008[71]	5 mg/day	All clinical fractures: Phylloquinone: 9/217 (4.2%) Placebo: 20/223 (9.0%) RR: 0.46 (95% CI 0.22 to 0.99) Clinical fragility fractures: Phylloquinone: 4/217 (1.8%) Placebo: 11/223 (4.5%) RR: 0.41 (95% CI 0.13 to 1.29)

to participate in the study extension refused to continue, compared with 15% in the placebo group.[71] The reasons for their refusal were not reported.

The ECKO trial assessed compliance by counting leftover pills at follow-up visits; participants who took 80% or more of the study medication were considered compliant.[71] Compliance at different time periods is presented in *Table 5* and, as may be seen, is higher in the placebo group. The difference is particularly marked at 4 years, even though participants had been given the opportunity to refuse to participate in the study extension, and refusal was substantially higher in the phylloquinone group than in the placebo group.

Menatetrenone (vitamin K_2)

Menatetrenone: antifracture efficacy

Vertebral fracture All four trials reported vertebral fracture data (*Table 6*). However, the extension study of Shiraki *et al.*[74] reported the number of fractures rather than the number of women suffering those fractures and thus the RR of fracture for that period could not be calculated.

The two trials that compared menatetrenone with cyclical etidronate found no difference between the two interventions in relation to vertebral fracture risk (*Figure 3*). However, it should be noted that both studies would have been substantially underpowered to demonstrate a difference in efficacy between two active interventions.

Of the trials that compared menatetrenone, with or without calcium, with no additional active treatment, only one, that by Shiraki *et al.*,[73] reached statistical significance. In this trial, menatetrenone plus calcium was associated with a reduction in the risk of radiographic fractures relative to calcium alone. In two other trials, Iwamoto *et al.*[72] and YOPS,[76] the point estimates also favoured menatetrenone but neither trial was large enough to achieve statistical significance. However, interim analyses from the substantially larger OF study[75] found no difference in the risk of vertebral fracture between women randomised to menatetrenone plus calcium and those randomised to calcium alone (*Table 6*).

Meta-analysis of data from all four trials suggests that menatetrenone is not associated with a significant reduction in the risk of vertebral fracture compared with no active treatment (*Figure 4*). However, this meta-analysis demonstrates substantial statistical heterogeneity, as indicated

TABLE 5 *Compliance with phylloquinone (data from the ECKO trial[71])*

Time point	Phylloquinone	Placebo
2 years	82.5%	83.9%
3 years	84.9%	89.9%
4 years	82.4%	93.3%

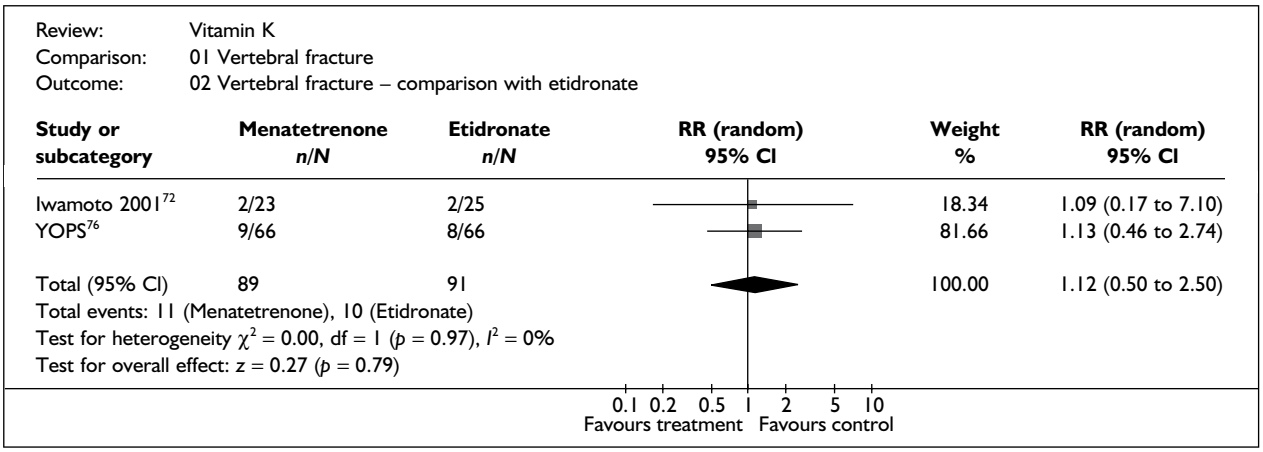

FIGURE 3 *Menatetrenone vs etidronate: vertebral fracture.*

by the chi-squared test for heterogeneity, with its very low p-value of 0.01, and the moderately high I^2 statistic of 71.4%, which measures the percentage of variation that is due to heterogeneity rather than chance.[78] Meta-analysis of data from the three earlier trials indicates that this heterogeneity is due to the inclusion of the OF study (*Figure 5*); without data from this trial menatetrenone appears to be associated with a statistically significant reduction in the risk of radiographic vertebral fracture. This highlights the extent to which the results of the OF study differ from those of the other studies,

TABLE 6 *Menatetrenone in postmenopausal osteoporosis or osteopenia: vertebral fracture data*

Study	Dose	Fracture definition	Number in each group suffering vertebral fracture
Iwamoto 2001[72]	45 mg/day	A decrease of at least 20% in any vertical height ratio; or central/anterior or central/posterior height less than 0.8; or anterior/posterior height less than 0.75	Menatetrenone: 2/23 (8.7%) Etidronate: 2/25 (8.0%) Calcium: 6/24 (25.0%) RR menatetrenone vs etidronate: 1.09 (95% CI 0.17 to 7.10) RR menatetrenone vs calcium: 0.35 (95% CI 0.08 to 1.55)
OF study 2005[75]	45 mg/day[77]	Not specified	Menatetrenone + calcium: 227/1619 (14.0%) Calcium: 223/1638 (13.6%) RR: 1.03 (95% CI 0.87 to 1.22)
Shiraki 2000,[73] 2002[74]	45 mg/day	2000 data: semiquantitative; ≥ 20% decline in any of the three vertebral heights compared with baseline 2002 data: clinical fractures only	2000: Menatetrenone + calcium: 13/91 (14.2%) Calcium: 30/99 (30.3%) RR: 0.47 (95% CI 0.26, 0.85) 2002: Number of fractures: Menatetrenone + calcium: 33 Calcium: 54
YOPS 2004[76]	45 mg/day	A decrease of at least 20% in one of the ratios of vertebral height in intact vertebrae, or a decrease of at least 4 mm in vertebrae fractured at baseline; also semiquantitative assessment	Menatetrenone: 9/66 (13.6%) Etidronate: 8/66 (12.1%) No treatment: 17/66 (25.8%) RR menatetrenone vs etidronate: 1.13 (95% CI 0.46 to 2.74) RR menatetrenone vs no treatment: 0.53 (95% CI 0.25 to 1.10)

prompting exploration of the possible reasons for this difference and consideration of which results are more likely to represent the true antifracture efficacy of menatetrenone. Such an exploration can only be conjectural because of deficiencies in the published data relating to all four trials.

The OF study appears to differ from the other three trials in terms of its population (*Table 7*). All four trials took as an inclusion criterion the presence of osteoporosis diagnosed using the Japanese diagnostic criteria (see Appendix 5, *Table 31*). Despite this, the OF study appears to have recruited participants at substantially lower risk of vertebral fracture than did the smaller studies; the fracture rate in the control group of the OF study, at under 14%, is less than half the mean fracture rate (28%) seen in the control groups of the smaller trials (*Table 6*). Because the OF study has not published data relating to the baseline characteristics of its population, it is not possible to determine whether it recruited a lower proportion of patients with pre-existing fractures than did the smaller trials. However, it seems unlikely that the difference in the OF study results can be attributed to hypothetical differences in the study populations; data from the FIT trial fracture[79] and non-fracture[80] arms indicate that an intervention with antifracture efficacy will result in a very similar RR of vertebral fracture in populations at higher and lower risk of fracture.

Alternatively, the lower fracture rate seen in the control group of the OF study may be due not to a difference in the study populations but to the use of a different definition of vertebral fracture. Whereas the other trials stated that they reported radiographic fractures, the OF study did not provide a fracture definition; it is therefore possible that only clinical fractures have been reported. However, this seems unlikely as the OF study describes its primary end point as 'new incidence of vertebral fracture', in contrast to its secondary end point, 'new incidence of clinical fracture' of any sort, including vertebral fracture.[75] Moreover, although the reporting of only clinical vertebral fractures would have resulted in lower absolute fracture rates, evidence from the FIT trial[50] suggests that it should not have had a noticeable effect on the RR of fracture.

Because the results of the smaller trials are systematically different from those of the larger OF study, it is possible that the difference in antifracture efficacy may relate to differences in methodological quality, most probably relating to the methods of randomisation and allocation concealment. All four trials were poorly reported, making it impossible to exclude the possibility of low methodological quality, but it is perhaps more likely that the three smaller trials were of lower quality than the larger one.

Finally, the heterogeneity between the trials may derive from publication bias. Small trials are particularly vulnerable to the play of chance, and it is impossible to exclude the possibility that, in addition to the published studies that favour menatetrenone, there may be a number of small unpublished trials whose results are either neutral or unfavourable to menatetrenone. This conjecture is strengthened by the fact that the considerably

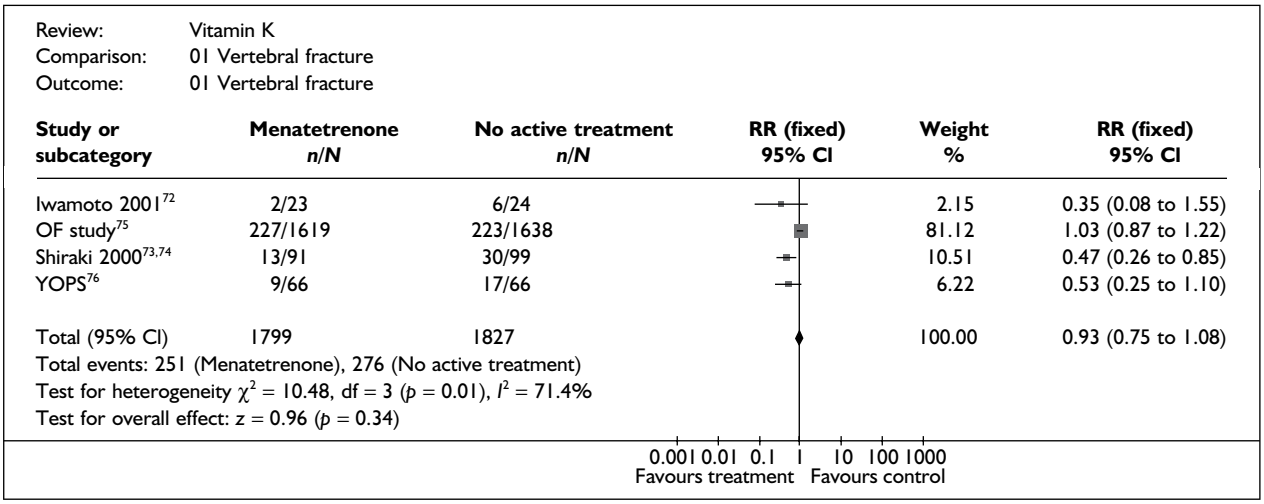

FIGURE 4 *Menatetrenone vs calcium or no additional active treatment: vertebral fracture risk – meta-analysis using fixed-effects model.*

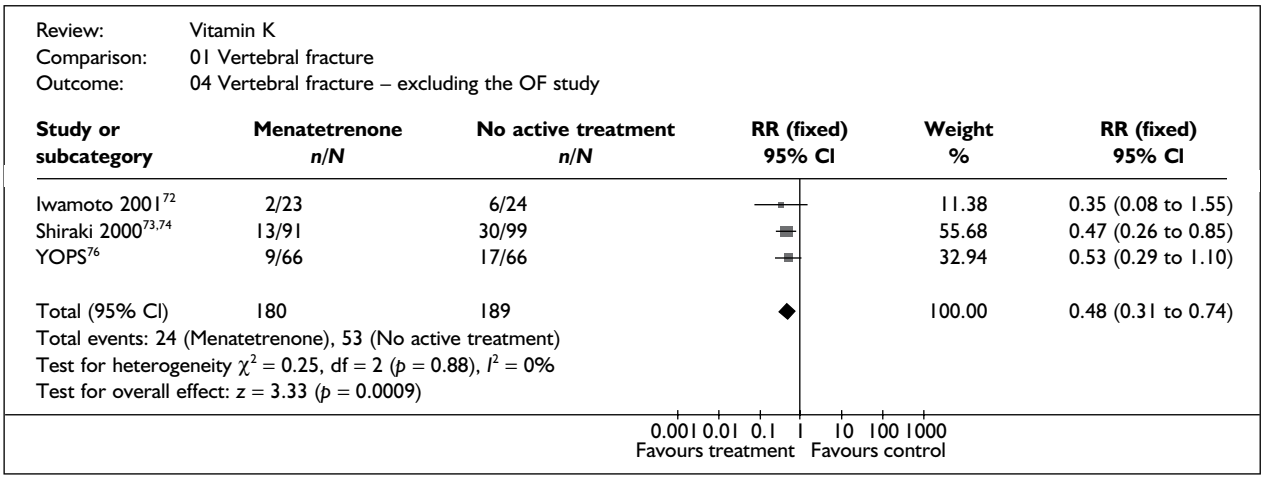

FIGURE 5 *Menatetrenone: vs calcium or no additional active treatment, excluding the OF study:[75] vertebral fracture risk.*

larger OF study, which yielded non-significant results, has not been published in journal form. The number of studies is too small to allow publication bias to be assessed using a funnel plot.

Thus, there seems no reason why the OF study should be excluded from the meta-analysis on the basis of clinical heterogeneity and, indeed, it could be argued that its results should be prioritised above those of the smaller trials as being less vulnerable to the play of chance. However, if data from all four trials are combined in a meta-analysis, conservatively using the random-effects model, which gives considerably less weight to the larger OF study than does the fixed-effects model, menatetrenone is still not associated with a statistically significant reduction in vertebral fracture risk (RR 0.63, 95% CI 0.36 to 1.11; *Figure 6*).

Vertebral fracture: post-hoc subgroup analyses Post hoc subgroup analysis undertaken by the OF study analysts[75] found that menatetrenone was associated with a statistically significant reduction in vertebral fracture in women with five or more fractures at baseline (*Figure 7*). This result should be treated with caution because post hoc subgroup analyses do not represent true randomised comparisons. Moreover, in this particular instance, the subgroup was extremely small, representing only 4% of those originally enrolled in the study.

The OF study analysts[75] also claimed that menatetrenone was associated with less height

TABLE 7 *Menatetrenone: population*

Study	Percentage of study population with prevalent vertebral fractures at study entry: Menatetrenone	Percentage of study population with prevalent vertebral fractures at study entry: No active treatment	Percentage of group receiving no active treatment suffering incident vertebral fractures	Definition of incident vertebral fracture
Iwamoto 2001[72]	30.4	29.2	25.0	Decrease of ≥ 20% in any vertical height ratio
Shiraki 2000[73]	38.7	35.8	30.3	20% decline in any of the three vertebral heights
YOPS 2004[76]	30.3	30.3	25.8	Decrease of ≥ 20% in any vertical height ratio
OF study 2005[75]	Not specified	Not specified	13.6	Not specified

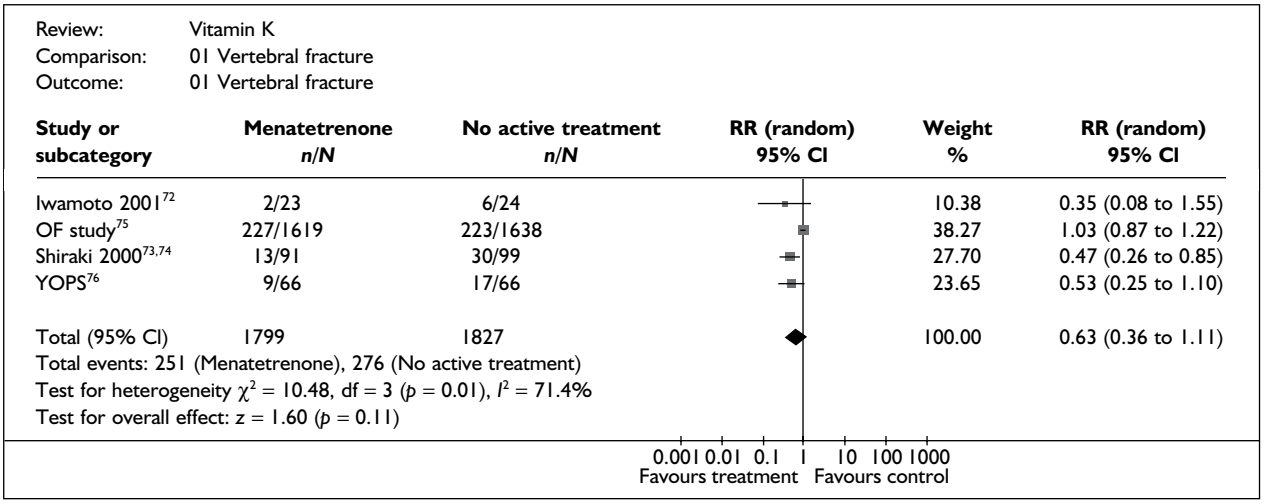

FIGURE 6 *Menatetrenone vs calcium or no additional active treatment: vertebral fracture risk – meta-analysis using random-effects model.*

loss than no treatment in women aged 75 years and older, women more than 30 years past the menopause and women who had at least five vertebral fractures at study entry. These claims should again be treated with caution because they derive from post hoc subgroup analyses. Moreover, the underlying data were not presented, making it impossible to assess either the proportion of participants included in the first of the two subgroups or the magnitude of the treatment effect.

Non-vertebral fracture Three trials reported non-vertebral fracture data (*Table 8* and *Figure 8*); however, none was powered to identify a statistically significant difference in the incidence of non-vertebral fracture. In 2002, Shiraki reported only the number of fractures,[74] not the number of participants suffering a fracture, and therefore it was not possible to calculate a RR. The OF study took as its secondary outcome measure the incidence of all new clinical fractures of the upper forelimb, femur, radius and vertebrae[81] but stated that these data would not be analysed until after completion of the 12-month observational follow-up period.[75] Although almost 3 years have elapsed since Eisai announced the intermediate results of the OF study, the clinical fracture data do not appear to have been released, raising the suspicion that menatetrenone did not reduce the risk of fracture.

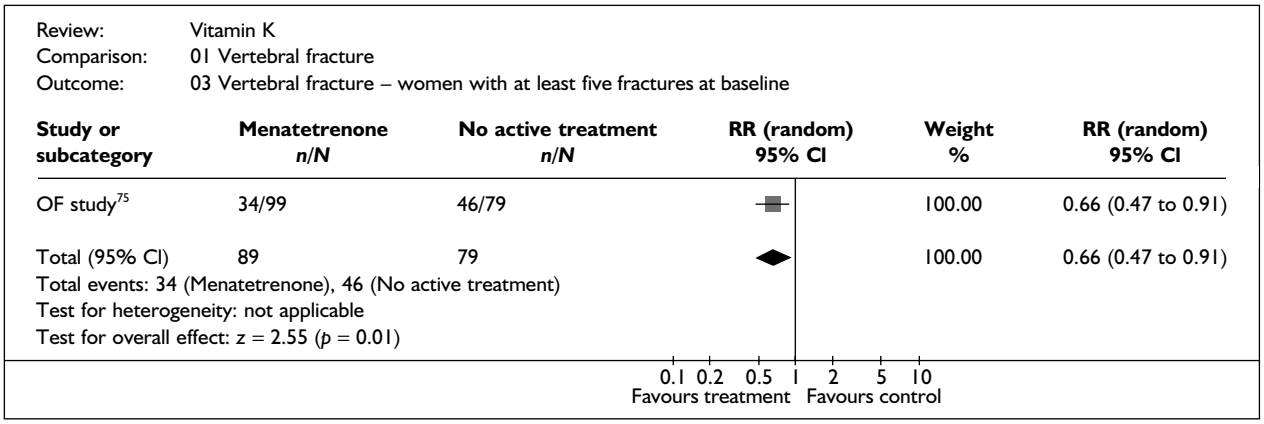

FIGURE 7 *Menatetrenone vs no additional active treatment in women with at least five vertebral fractures at study entry: vertebral fracture.*

TABLE 8 *Menatetrenone in postmenopausal osteoporosis or osteopenia: all non-vertebral fractures*

Study	Dose	Number in each group suffering non-vertebral fracture
Iwamoto 2001[72]	45 mg/day	Menatetrenone: 0/23
		Etidronate: 0/25
		Calcium: 0/24
		RR menatetrenone vs etidronate: not estimable
		RR menatetrenone vs calcium: not estimable
Shiraki 2000,[73] 2002[74]	45 mg/day	2000:
		Menatetrenone + calcium: 1/91 (1.1%)
		Calcium: 5/99 (5.1%)
		RR: 0.22 (95% CI 0.03 to 1.83)
		2002:
		Number of long bone fractures:
		Menatetrenone: 4
		Control: 10
		RR not calculable as number of patients with fracture not reported
YOPS 2004[76]	45 mg/day	Menatetrenone: 0/66
		Etidronate: 1/66 (1.5%)
		No treatment: 3[a]/66 (4.5%)
		RR menatetrenone vs etidronate: 0.33 (95% CI 0.01 to 8.04)
		RR menatetrenone vs no treatment: 0.14 (95% CI 0.01 to 2.71)

a There were said to have been three fractures among women in this group and it is therefore possible that one woman may have suffered more than one fracture.

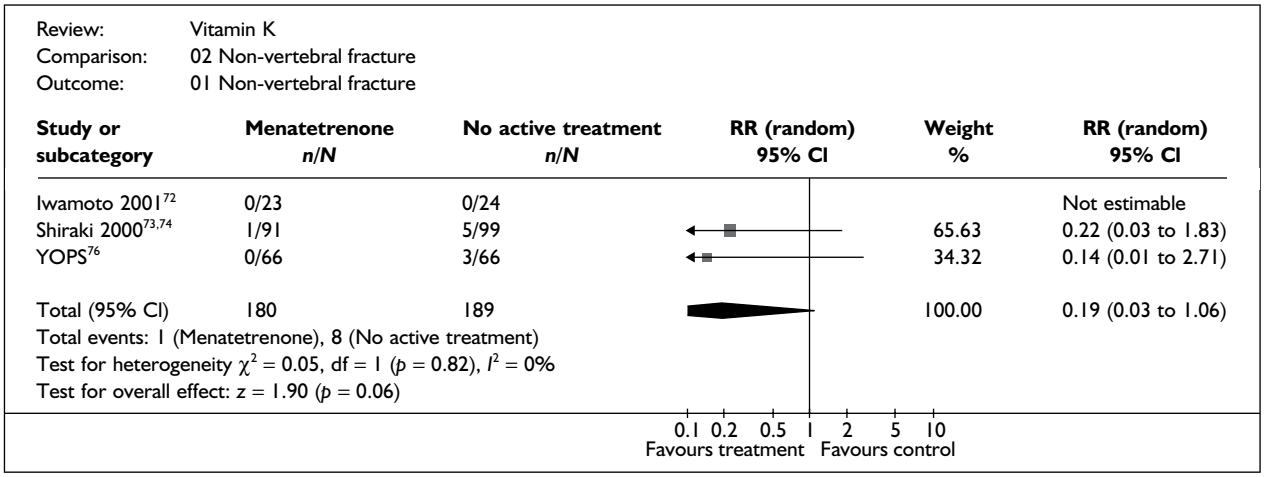

FIGURE 8 *Menatetrenone vs calcium or no additional active treatment: non-vertebral fracture risk.*

TABLE 9 *Menatetrenone in postmenopausal osteoporosis or osteopenia: hip fracture data*

Study	Dose	Number of women in each group suffering hip fracture
Iwamoto 2001[72]	45 mg/day	Menatetrenone: 0/23
		Etidronate: 0/25
		Calcium: 0/24
		RR menatetrenone vs etidronate: not estimable
		RR menatetrenone vs calcium: not estimable
Shiraki 2000[73]	45 mg/day	Menatetrenone + calcium: 0/91
		Calcium: 2/99
		RR: 0.22 (95% CI 0.01 to 4.47)
YOPS 2004[76]	45 mg/day	Menatetrenone: 0/66
		Etidronate: 0/66
		No treatment: 1/66
		RR menatetrenone vs etidronate: not estimable
		RR menatetrenone vs no treatment: 0.33 (95% CI 0.01 to 8.04)

Hip, wrist and other non-vertebral fractures Three trials reported hip fracture data; however, none was big enough to yield a statistically significant result (*Table 9*), nor did their combined results achieve significance (*Figure 9*).

Three trials reported wrist or forearm fractures (*Table 10*). None reported fractures of the humerus. Again, none of the trials was big enough to yield a statistically significant result, nor did their combined results achieve significance (*Figure 10*).

Menatetrenone: adverse effects

In the included trials of menatetrenone, reporting of adverse events was generally poor. The OF study[75] noted a significantly higher incidence of skin and skin appendage lesions in patients receiving menatetrenone (0.5 per 100 patient-years compared with 0.1 in the control group, $p < 0.001$).

Although the MEDLINE adverse events search identified no large, long-term studies of the safety of menatetrenone therapy in the treatment of postmenopausal osteoporosis or osteopenia, it

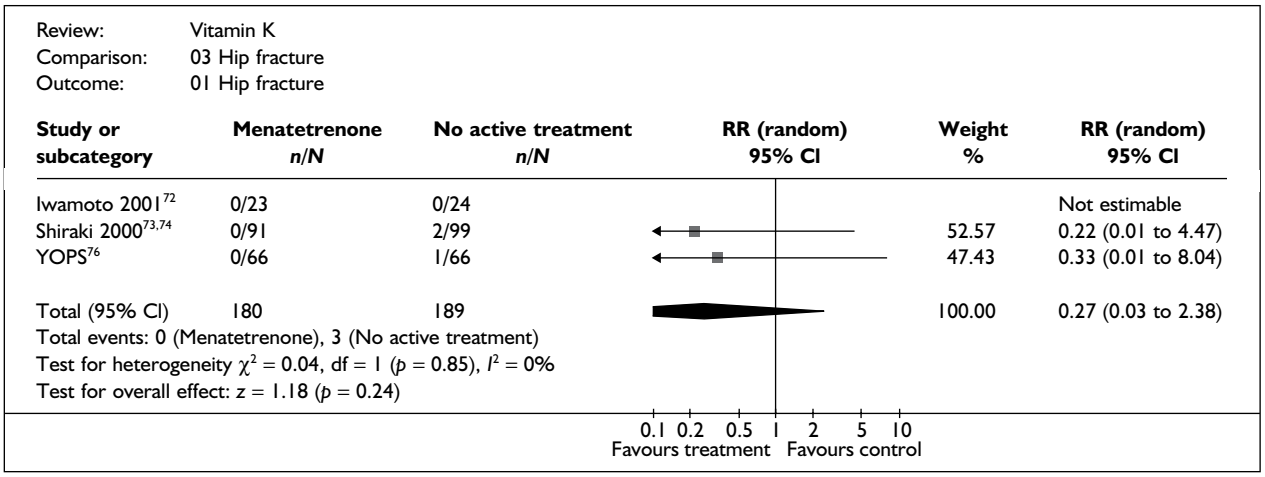

FIGURE 9 *Menatetrenone vs calcium or no additional active treatment: hip fracture risk.*

TABLE 10 *Menatetrenone in postmenopausal osteoporosis or osteopenia: wrist or forearm fracture data*

Study	Dose	Number of women in each group suffering wrist or forearm fracture
Iwamoto 2001[72]	45 mg/day	Menatetrenone: 0/23
		Etidronate: 0/25
		Calcium: 0/24
		RR menatetrenone vs etidronate: not calculable
		RR menatetrenone vs calcium: not calculable
Shiraki 2000[73]	45 mg/day	Menatetrenone + calcium: 1/91
		Calcium: 2/99
		RR: 0.54 (95% CI 0.05 to 5.90)
YOPS 2004[76]	45 mg/day	Menatetrenone: 0/66
		Etidronate: 1/66
		No treatment: 2[a]/66
		RR menatetrenone vs etidronate: 0.33 (95% CI 0.01 to 8.21)
		RR menatetrenone vs no treatment: 0.20 (95% CI 0.01 to 4.09)

a It is possible that both of these fractures occurred in the same woman.

identified two relatively small studies[82,83] of the effect of menatetrenone therapy on haemostatic activity in patients with osteoporosis or osteopenia. These suggested that menatetrenone, at a dose of 45 mg/day, did not induce a thrombotic tendency in such patients.

The Expert Group on Vitamins and Minerals[35] noted no toxicity related to oral vitamin K_2, and the review by Vermeer *et al.*[26] stated that menatetrenone had been used in Japan on a large scale and as yet no adverse side effects had been reported. However, the product leaflet for Glakay capsules[45] stated that adverse reactions were reported in 81 of 1885 patients (4.3%) taking the product (*Table 11*).

Menatetrenone: health-related quality of life

Only one study of menatetrenone reported health-related quality of life. The OF study[75] claimed that, in the first 12 months of the study, walking, and the degree and duration of back pain at rest, improved more in women who received menatetrenone and calcium than in those who received calcium alone. However, as the data underlying this claim were not presented, the improvements cannot be quantified.

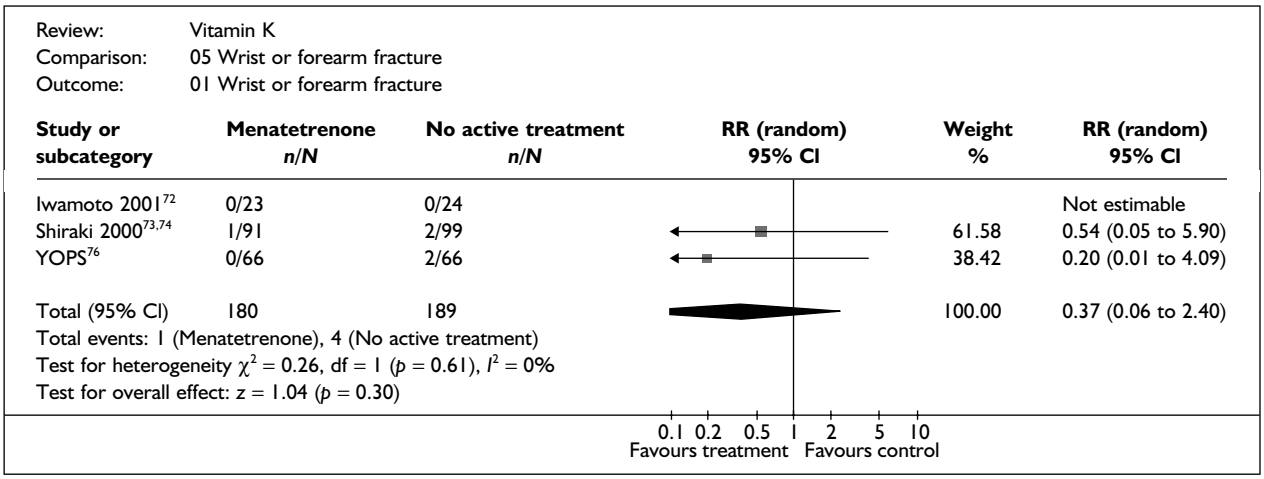

FIGURE 10 *Menatetrenone vs calcium or no additional active treatment: wrist or forearm fracture risk.*

TABLE 11 *Glakay capsules (menatetrenone): adverse reactions*[45]

	≥ 0.1% to 5%	< 0.1%	Incidence unknown
Gastrointestinal	Stomach discomfort, abdominal pain, nausea, diarrhoea, dyspepsia	Thirst, anorexia, glossitis, constipation	Vomiting, stomatitis
Hypersensitivity	Rash, pruritus, redness		
Psychoneurological	Headache	Light-headedness, numbness	Dizziness
Cardiovascular		Increase in blood pressure	Palpitations
Hepatic	Elevation of AST (GOT), ALT (GPT) and γ-GPT, etc		
Urinary	Elevation of BUN, etc		Urinary frequency
Other	Oedema, eye abnormalities		Malaise, arthralgia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

Moreover, it is not clear whether such data were only collected for the first 12 months of the study or whether they were collected for the full 36 months but only reported for the first 12 months; the latter would suggest that no difference between the groups in relation to these factors was seen following the first 12 months.

Menatetrenone: continuance and compliance

None of the trials of menatetrenone provided information on compliance with study medication. However, two trials provided information on the proportion of participants who completed follow-up for the planned length of the study (*Table 12*).

Discussion

The evidence summarised in the previous sections suggests that phylloquinone is associated with a significant reduction in the risk of clinical fractures in postmenopausal women with osteopenia but without osteoporosis, despite the fact that its benefits are likely to have been underestimated by the use of an osteopenic population rather than an osteoporotic population at higher risk of fracture. However, there is no evidence to suggest that menatetrenone is associated with a significant reduction in fracture risk in postmenopausal women with osteoporosis. Because there is no recommended daily intake for menatetrenone, it is not possible to directly compare the 45-mg dose used in the menatetrenone trials with the 5-mg dose of phylloquinone used in the ECKO trial, although superficially the dose of menatetrenone would seem to be considerably larger than that of phylloquinone. Moreover, because Japanese women are generally smaller than Caucasian women, Japanese studies of interventions for postmenopausal osteoporosis generally use half of the dose used in Western populations[84] (so, in the trials reviewed here, both Iwamoto *et al.*[72] and YOPS trial[76] use a 200-mg dose of etidronate compared with the 400-mg dose used in Western trials such as those by Storm *et al.*[85] and Watts *et al.*[86]). Thus, the 45-mg dose of menatetrenone used in the Japanese trials would presumably equate to a 90-mg dose in Western populations, 18 times

TABLE 12 *Proportion of participants completing the study protocol*

Study	Duration of study	Proportion of participants completing study protocol
Shiraki 2000[73]	2 years (data not available for extension study)	Menatetrenone + calcium: 92%
		Calcium: 87%
YOPS 2004[76]	2 years	Menatetrenone: 95%
		Etidronate: 94%
		No treatment: 91%

the weight of phylloquinone used in the ECKO trial. This suggests that the failure of the combined menatetrenone trials to demonstrate a statistically significant reduction in vertebral fracture risk is unlikely to result from underdosing. However, it should be noted that the population of the ECKO trial was one-tenth that of the OF study, and consequently its results are more subject to the play of chance.

Asian women in general appear to have lower BMD than white women but similar vertebral fracture rates and lower hip fracture rates. This discrepancy may result from differences in bone structure or geometry and/or, in the case of hip fractures, a reduced risk of falling or a better ability to protect themselves in case of a fall.[87] It may also be related to the use of dual energy X-ray absorptiometry to calculate BMD; this method underestimates BMD in small bones and overestimates it in large bones. As any differences in fracture rates between Asian and white women may derive from differences in hereditary factors and in lifestyle factors such as calcium intake, it is not clear to what extent data obtained from Japanese populations are relevant to Western populations.[26]

Chapter 4
Economic analysis

The assessment group undertook a systematic literature review to identify any economic evaluations of vitamin K. No relevant papers were found and thus, to our knowledge, this report is the first assessment of the cost-effectiveness of vitamin K. We assess the cost-effectiveness of vitamin K compared with no treatment, two bisphosphonates (alendronate and risedronate) and strontium ranelate, at combinations of age and *T*-score, assuming that a BMD scan has already been undertaken and thus the *T*-score is known without cost. Previous modelling work[4] has estimated the likely combinations of age and clinical risk factors at which BMD scanning would be cost-effective; this modelling work was updated following a fall in the price of alendronate, the intervention that appeared most cost-effective, from £301 to £54 per annum,[5] and further updating of this work is beyond the remit of this project. 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. It is noted that some of the parameters used in previous modelling work[5] may have become outdated. These have been updated when appropriate in producing the results for this report. Any changes in parameters between the previously published work using an alendronate price of £54 per annum and this report are detailed within the text and are additionally summarised later in this chapter (see Summarising changes within the parameters used in this report and in preceding work).

Methods for economic analyses

The assessment group has constructed a peer-reviewed model to estimate the cost-effectiveness of osteoporosis interventions.[88] The most recent work undertaken[4,5] used academic-in-confidence data that were used in the development of the FRAX tool.[89] Permission to re-use the academic-in-confidence data for this project was not granted. As such, an alternative model for predicting the risks of fracture was developed based on age, BMD and previous fracture history. The results produced by the model were compared, and recalibrated when appropriate, with the data provided in the recent work[5] to try and ensure that the results were relatively consistent.

The key inputs to the 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 Chapter 2, other fracture types are subsumed into these groups, but for reasons of brevity we will refer only to the four main fracture sites.

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

The cost per QALY of vitamin K treatment has been evaluated against a no treatment option to provide information on whether vitamin K can be given cost-effectively in the absence of other osteoporosis interventions. Incremental analyses against alendronate, risedronate and strontium ranelate have also been conducted to provide information on the likely placement of vitamin K within a treatment algorithm.

As the results were being calculated it was apparent that vitamin K_1 was potentially a cost-effective treatment for the prevention of osteoporotic fractures. The expected net benefit of sampling (ENBS) of conducting an RCT that compared alendronate and vitamin K_1 was estimated. Such analysis will provide data on whether such a trial would be an efficient use of resources and, if so, on the number of patients that would need to be recruited to maximise the ENBS.

This section is divided into the following subsections:

- the structure of the model, which will discuss the formulation of the appraisal model and the modelling assumptions made
- the costs associated with each event contained within the model
- the utility multipliers associated with each event contained within the model
- comparison of the results produced using the new model with those produced by previous work
- changes in the parameters used for this evaluation compared with those used in previous evaluations
- methodology for calculating the ENBS of an RCT comparing vitamin K with alendronate.

The structure of the cost-effectiveness model

The individual patient model

The model used to calculate cost-effectiveness ratios is an updated version of the previously reported Sheffield Health Economic Model for Osteoporosis (SHEMO).[4,88,90] This model deviated from approaches previously used, which have been based on cohort analyses using the standard techniques of decision analysis and state transition models.[91,92]

The basic design of SHEMO is similar in many ways to the conventional state transition models used in the area of osteoporosis, in which 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 as individual women pass through the model one at a time. The model simulates for each patient whether or not an event occurs in the forthcoming year that would impact on the costs and utility associated with the woman.

The full patient history is recorded and factors such as previous fractures and current residential status can therefore be used 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 is reached. This process is repeated until the chosen number of women has been simulated. The rationale for using the individual patient approach is that it provides more accuracy and flexibility than a cohort approach, which is bounded by a limited number of transition states.[4,90] A diagram of the model structure is provided in *Figure 11*.

The exact values of $p2$: $p14$ will be determined by 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.

The basic probabilities for moving from transition state to transition state have been taken from epidemiological data, as described later in this chapter. Once a fracture is sustained within the model the risk is increased in accordance with the data reported by Klotzbuecher *et al.*,[93] as described later in this chapter.

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

When a patient moves into a transition state this affects their quality of life. It has been assumed that there will be a QALY multiplier effect within the first year and a separate QALY multiplier that will apply 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, only the first year reduction

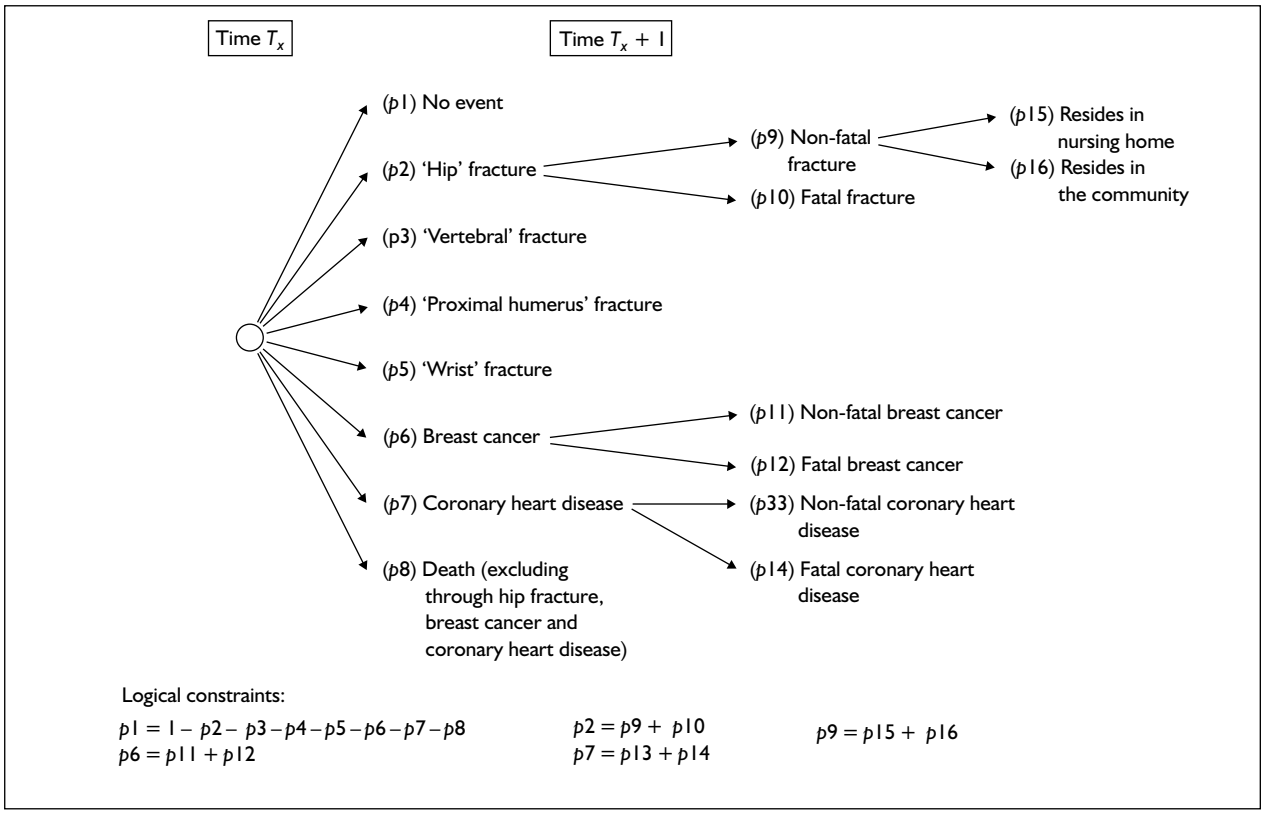

FIGURE 11 *The structure of the individual patient model.*[90]

in quality of life will be taken into consideration, using similar logic to that employed for costs. 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 to the first, or a second vertebral fracture. However, because of insufficient data the approach of assuming no extra residual QALY loss from a second incident was taken. As in the explanation given when discussing costs, the inclusion of more than one fracture in some states may be slightly unfavourable to the intervention.

It has been assumed that, for a year in which death occurs, the QALYs gained are half those for the previous year, costs incurred are equal to half of the ongoing annual costs, and only half of the drug acquisition cost is paid.

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 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 each intervention the RRs were sampled from the relevant meta-analysis of efficacy undertaken.

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

The time horizon of the individual patient model was constrained to a 10-year period because of the likely treatment effects being confined within this period, the 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.

Diseases for which possible links with osteoporosis treatments may exist, such as Alzheimer's disease,

venous thrombolic events and cancer, were excluded from this cost-effectiveness analysis.

The construction of a meta-model

Gaussian process modelling was used to transform the results of the individual patient model into a meta-model that allowed instantaneous calculation of the incremental costs and QALYs associated with an input parameter configuration.[88] 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.

Subsequent adjustments to the results produced by the meta-model

Limiting the time horizon of the model to 10 years will underestimate the effect of mortality, particularly in younger women, which has been shown to markedly impact on the cost-effectiveness ratio.[1–5] The benefits of reduced mortality beyond the initial 10-year time horizon have been estimated. The methodology for estimating the QALYs gained through prevented mortality is explained in Appendix 6.

The discount rates used for the individual patient model[2,4] were 6% per annum for costs and 1.5% per annum for utility in accordance with the prevailing NICE rates at the commissioning of the initial project. In the interim period the discount rates have been set to 3.5% per annum for both costs and utility[94] and therefore the results need to be adjusted to take the discount rate change into consideration. The summated discounted value of 10 single units over 10 years is 7.36, 8.32 and 9.22 when using discount rates of 6%, 3.5% and 1.5% respectively. These values were used to adjust the model outputs, with QALYs for each scenario multiplied by 0.90 (8.32/9.22) and costs associated with fracture multiplied by 1.13 (8.32/7.36). Intervention costs (drug costs, GP visits and BMD scans) that were assumed to be incurred only in the first 5 years were multiplied by 1.07 to reflect the shorter time horizon of such costs, using the discounted values of five single units over 5 years. Although the methodology used for altering the discount rates is likely to introduce some inaccuracies, as the costs and QALYs will not be equally spread across the 10-year period (as the intervention is used only in the initial 5-year period), it is a pragmatic solution and is not expected to markedly change the conclusions.

Each treatment option has also been assigned GP costs in addition to drug acquisition costs. Following (NICE Osteoporosis) Guideline Development Group (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 one-third of women below 75 years of age requiring an additional GP appointment per annum. It was also assumed that no follow-up BMD scans would be required.

Compliance has been modelled at 50% in line with published estimates.[95] Women who are non-compliant are assumed to incur the costs of 3 months of treatment whilst receiving no benefit.

The individual patient model assumed a 5-year treatment period and a residual benefit that declined linearly to zero over a 5-year period. For vitamin K, which has a short duration in the body, a 5-year residual benefit was not deemed appropriate and it was assumed that any protective benefit would cease upon discontinuation of treatment. Analyses of the results from the individual patient model were undertaken to determine the effect of a decrease in residual benefit from 5 years to 0 years. Multiplicative factors were estimated that would be applied to the incremental costs (excluding intervention costs) and incremental QALYs associated with 5 years of residual benefit. For women with a *T*-score of –2.5 SD, these factors ranged from 0.73 for costs and 0.67 for QALYs at 50 years of age to corresponding values of 0.78 and 0.75 at 75 years of age.

The incidence of hip, vertebral, wrist and proximal humerus fractures by age

Data on the incidence of hip, vertebral, wrist and proximal humerus fractures were taken from a large-scale Scottish study.[7] Exponential distributions have been applied to these distributions to smooth the data. The distributions are shown in *Figures 12–15*; all R-squared values are greater than 0.90, showing that these are good fits. These distributions are also plausible as the rates do not decrease as a woman ages. The summarised risks are provided in *Table 13* and *Figure 16*.

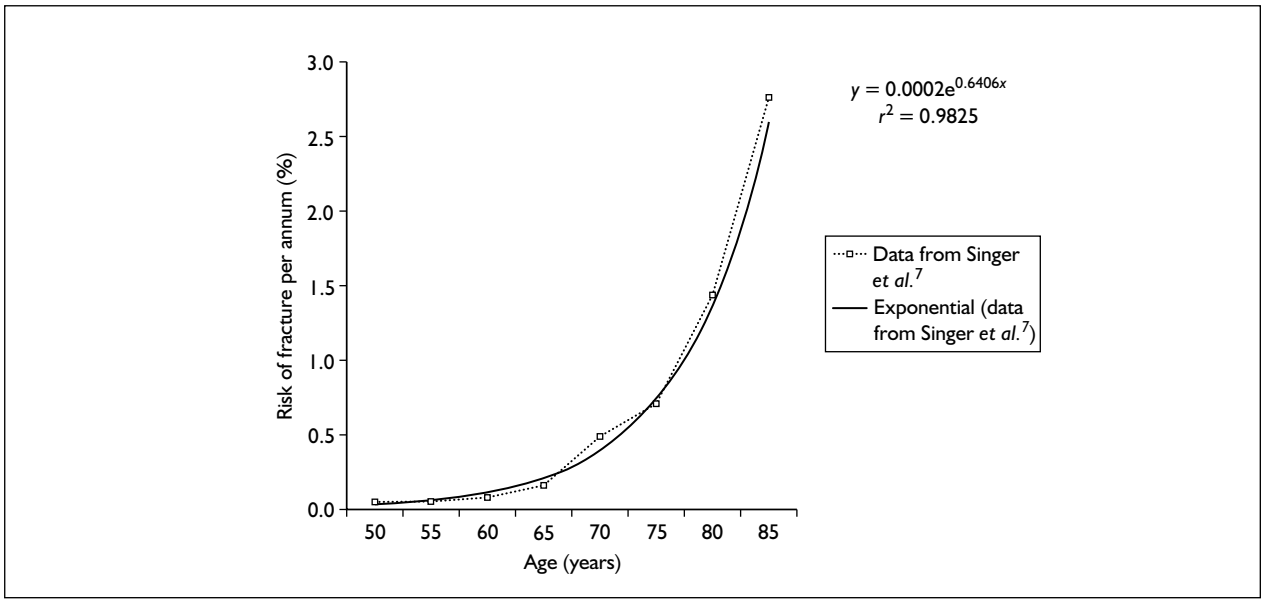

FIGURE 12 *The goodness of fit when replacing the raw data for hip fracture[7] with a statistical distribution.*

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

As detailed in Stevenson *et al.*,[4] other fracture sites considered were incorporated into the four main fracture types in order to use the previously calculated meta-model.[88] The earlier modelling work[4] used the raw data without adjustment to estimate the increase in the expected numbers of fractures at each site. For this report it was decided to smooth these data by fitting statistical distributions, which were used to estimate the increased fracture risk. The goodness of each fit between a statistical relationship and the raw data is shown in *Figures 17–19*. Whereas the increase against age was presumed to be linear for hip and proximal humerus fracture, the best fit for increasing the number of wrist fractures was seen to be parabolic. The estimated increase in fracture risk at each age is given in *Table 14*. This would adjust the average risk of fracture for the female

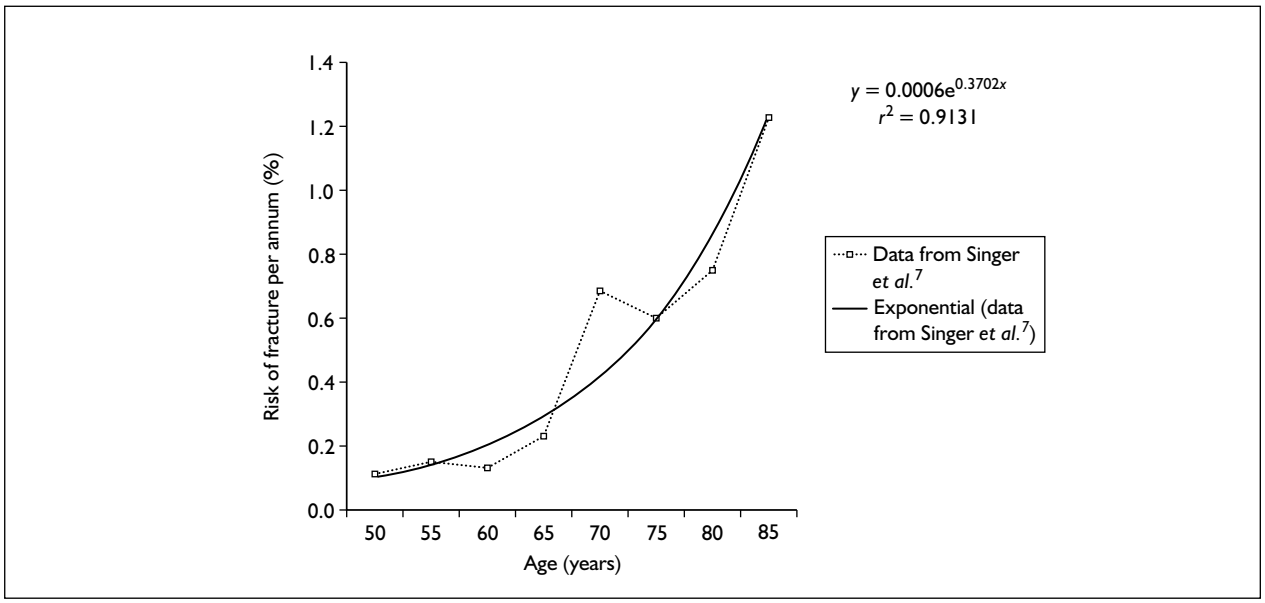

FIGURE 13 *The goodness of fit when replacing the raw data for vertebral fracture[7] with a statistical distribution.*

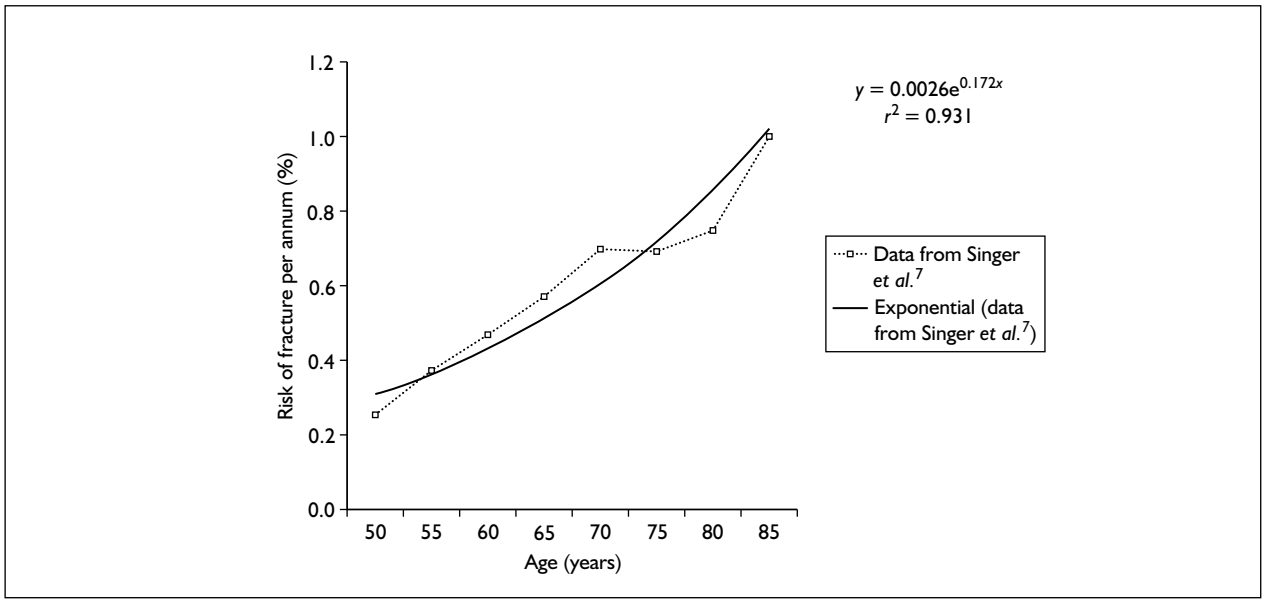

FIGURE 14 *The goodness of fit when replacing the raw data for wrist fracture[7] with a statistical distribution.*

population in the UK at each age to those given in *Table 15* and *Figure 20*.

The increased risk of fracture following a previous fracture

There is a breadth of published literature, meta-analysed in Klotzbuecher *et al.*,[93] which indicates that an initial fracture greatly increases the risk of subsequent fractures independently of BMD. The results from Klotzbuecher *et al*.[93] are summarised in *Table 16*. These data were used in the meta-model[88] that forms the foundation for the cost-effectiveness analyses.

The meta-model assumed that the risk of secondary fracture at the proximal humerus is equivalent to that of the pooled non-spinal fractures category reported by Klotzbuecher *et al.*[93] It was also assumed that the proximal humerus had the predictive power equal to that of the 'other' category reported by Klotzbuecher *et al.*[93] There have been no studies on the future effect that hip fractures have upon wrist fractures. As a conservative estimate this risk was set at 1.4,

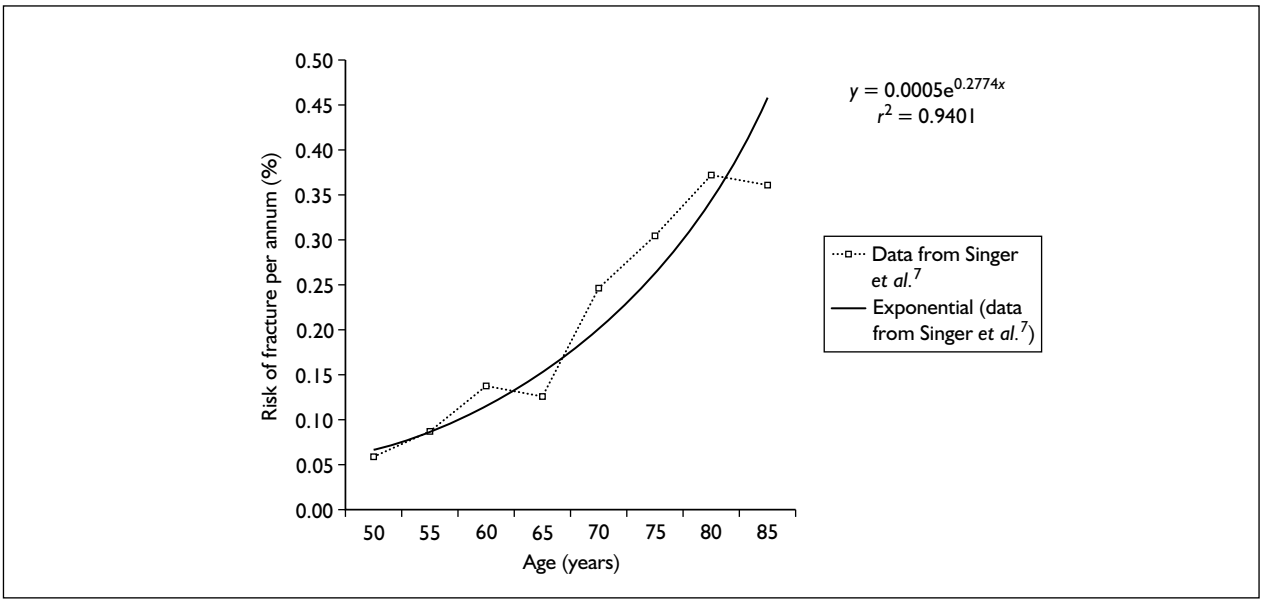

FIGURE 15 *The goodness of fit when replacing the raw data for proximal humerus fracture[7] with a statistical distribution.*

TABLE 13 *The female population risk of hip, vertebral, proximal humerus and wrist fractures estimated from the smoothed Singer* et al. *data*[7]

Age (years)	Probability of hip fracture	Probability of vertebral fracture	Probability of proximal humerus fracture	Probability of wrist fracture
50–54	0.03%	0.09%	0.31%	0.07%
55–59	0.06%	0.13%	0.36%	0.09%
60–64	0.11%	0.19%	0.43%	0.12%
65–69	0.20%	0.28%	0.51%	0.15%
70–74	0.38%	0.40%	0.61%	0.20%
75–79	0.73%	0.59%	0.72%	0.26%
80–85	1.38%	0.85%	0.86%	0.35%
85–89	2.62%	1.23%	1.02%	0.46%

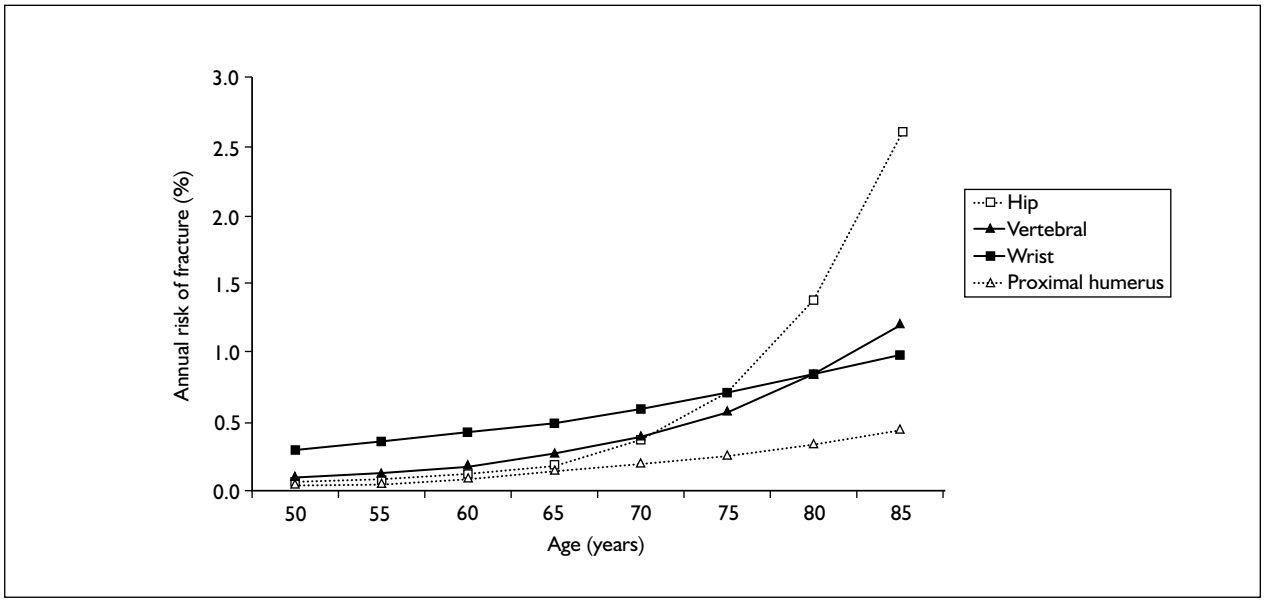

FIGURE 16 *The annual female population risk of hip, vertebral, proximal humerus and wrist fractures estimated from the smoothed Singer* et al. *data.*[7]

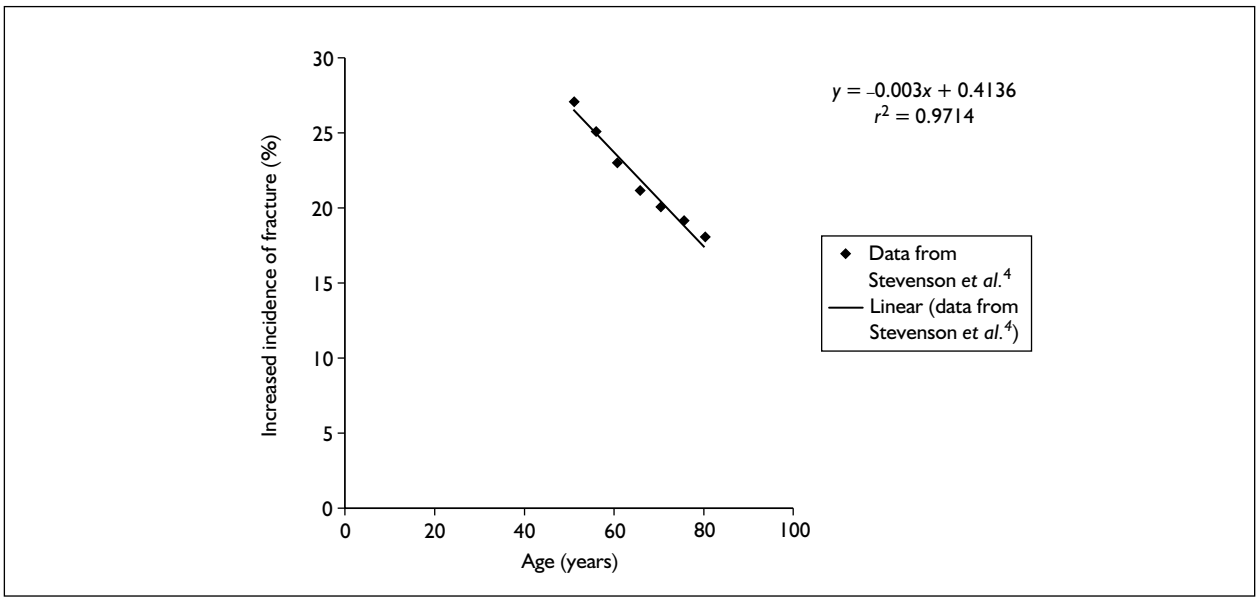

FIGURE 17 *The goodness of fit when replacing the increased incidence of hip fracture type as detailed in Stevenson* et al.[4] *with a statistical distribution.*

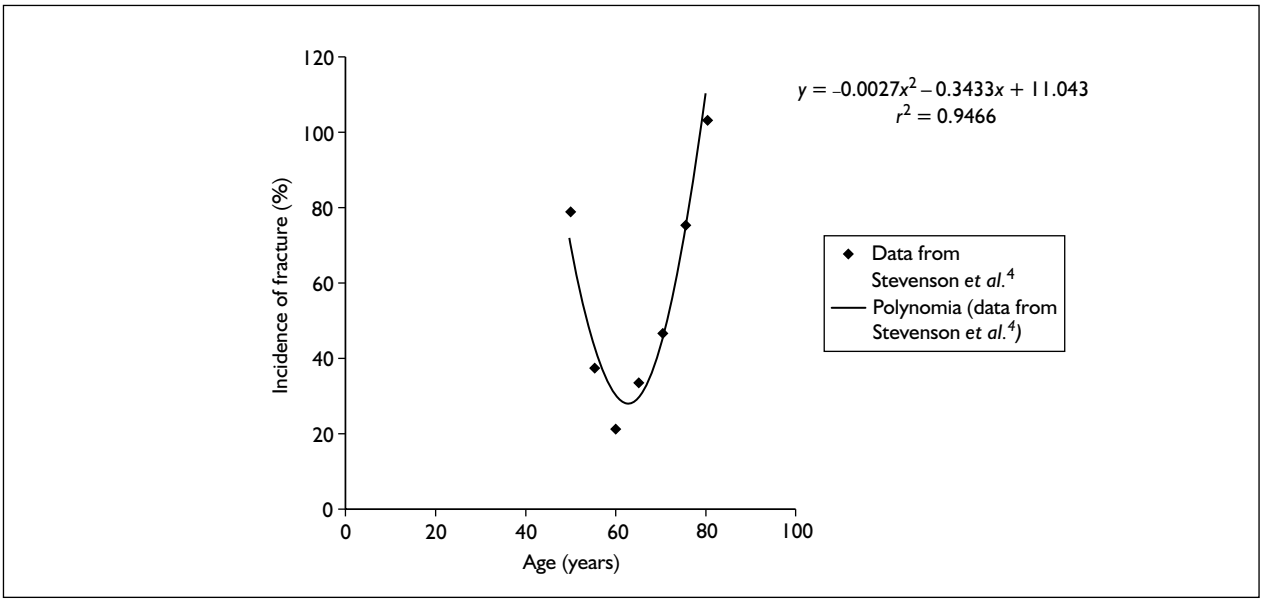

FIGURE 18 *The goodness of fit when replacing the increased incidence of wrist fracture type as detailed in Stevenson* et al.[4] *with a statistical distribution.*

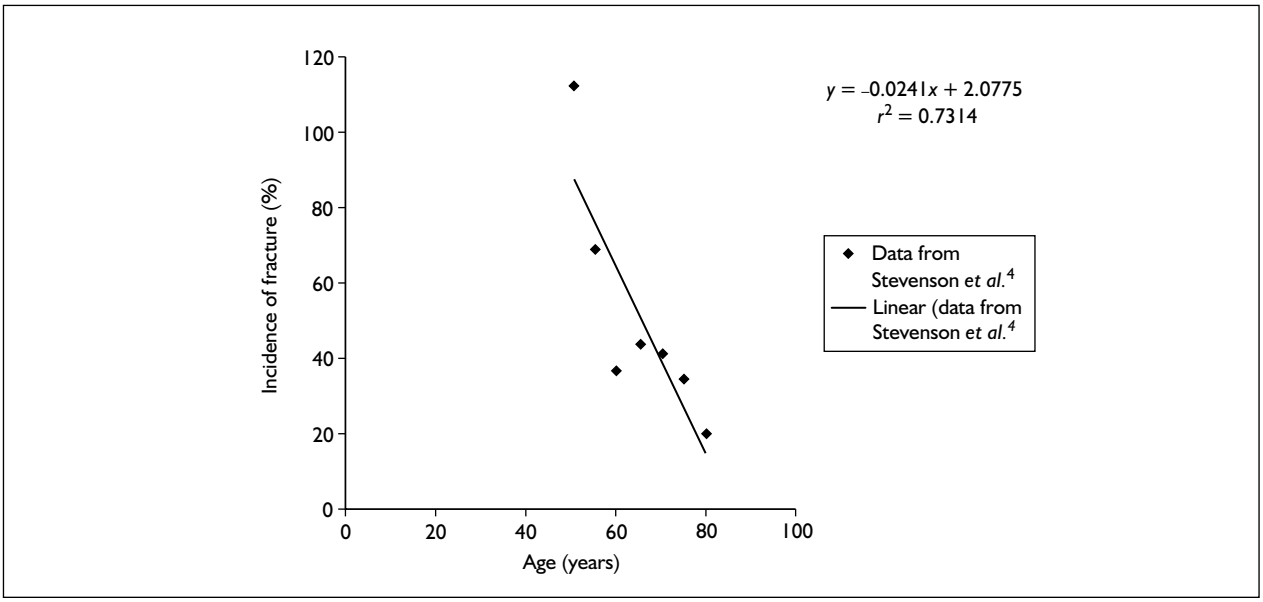

FIGURE 19 *The goodness of fit when replacing the increased incidence of proximal humerus fracture type as detailed in Stevenson* et al.[4] *with a statistical distribution.*

equivalent to the lowest RR 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, if a woman has both previous hip and wrist fractures, the RR adjustment for a subsequent vertebral fracture would be 2.5 (from the hip fracture) rather than 1.9 (from the wrist fracture). The RR adjustment for a subsequent wrist fracture would be 3.3 (from the wrist fracture) rather than 1.4 (from the hip fracture).

Klotzbuecher *et al.*[93] did not adjust these values for the effects of BMD as most of the studies incorporated within the meta-analysis did not adjust for it; those studies that controlled for baseline BMD reported that adjusting for BMD reduced the magnitude of the association, although the reduction was slight. Thus, any errors due to

TABLE 14 *The increase in incidence of hip, wrist and proximal humerus fractures to incorporate fractures at other sites, as used in the model*

Age (years)	Increase in hip fracture incidence to incorporate pelvis and other femoral fractures	Increase in proximal humerus fracture incidence to incorporate tibia and fibula fractures	Increase in wrist fracture incidence to incorporate rib, sternum, clavicle and scapula fractures
50–54	26%	87%	63%
55–59	25%	75%	33%
60–64	23%	63%	17%
65–69	22%	51%	14%
70–74	20%	39%	24%
75–79	19%	27%	48%
80+	17%	15%	86%

Note that the incidence of vertebral fractures was not increased.

TABLE 15 *The female population risk of hip, vertebral, proximal humerus and wrist fractures estimated from the smoothed Singer* et al. *data[7] and incorporating other osteoporotic fractures*

Age (years)	Probability of hip fracture	Probability of vertebral fracture	Probability of proximal humerus fracture	Probability of wrist fracture
50–54	0.04%	0.09%	0.50%	0.12%
55–59	0.07%	0.13%	0.48%	0.15%
60–64	0.13%	0.19%	0.50%	0.19%
65–69	0.25%	0.28%	0.58%	0.23%
70–74	0.46%	0.40%	0.75%	0.28%
75–79	0.87%	0.59%	1.07%	0.34%
80–85	1.62%	0.85%	1.59%	0.40%

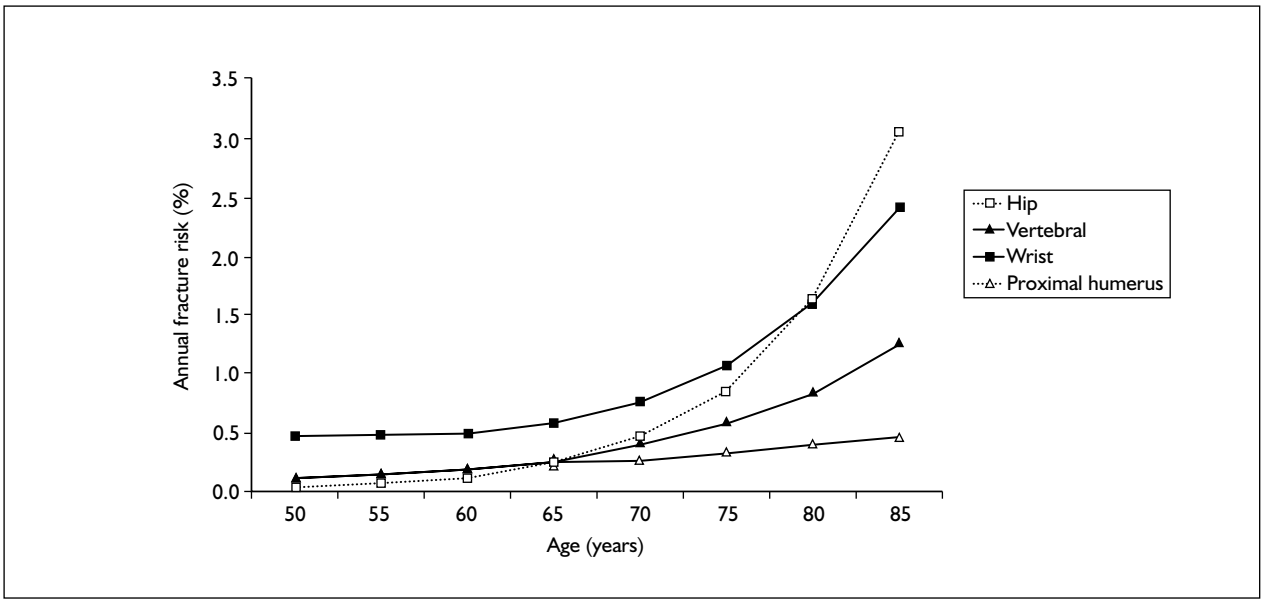

FIGURE 20 *The average annual female population risk of hip, vertebral, proximal humerus and wrist fractures estimated from the smoothed Singer* et al. *data[7] and incorporating other osteoporotic fractures. ph, proximal humerus; vert, vertebral.*

TABLE 16 *The relative risk of subsequent fracture following an initial fracture*

	Location of subsequent fractures			
Previous 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 Klotzbuecher *et al.*[93]

double counting the effects of BMD are likely to be small.

Previous modelling work[2] has assumed that the initial risk of fracture for a woman following a previous fracture is double that of a woman of identical age and BMD who has not sustained a fracture. This assumption was investigated when the mathematical model developed was calibrated. The section below, Comparison and calibration of the model against previously published work, details the methodology used; it appears that increasing the initial risk of a woman who has sustained a fracture by 50% compared with a woman of identical age and BMD who has not sustained a fracture produces a more accurate estimation. The reduction in increased risk may be explained by the fact that there is some interaction between BMD and previous fracture history.

The increased risk of fracture for patients with low bone mass

BMD status is a significant factor in estimating the risk of fracture for a patient. Work conducted by Marshall *et al.*[15] assessed the increased probability of fracture associated with a *Z*-score of –1 when measured at the femoral neck. The point estimates of this increased risk of fracture are presented in *Table 17*. Data for proximal humerus were assumed to equal data reported by Marshall *et al.*[15] for all fractures.

The equations presented in Marshall *et al.*[15] are of the form (relative risk) raised to the power of –*Z*-score difference, hence the increased risk of a vertebral fracture for patients with a *Z*-score of –2 would be 3.24 times (1.8^2). The increased risk would be 4.19 times ($1.8^{1.5}$) for a patient with a *Z*-score of –1.5.

More recent work undertaken by Johnell *et al.*[16] has shown that the increased risk of hip fracture in relation to *Z*-score is age dependent. (*Table 18*) These newer data have been used in the model. It is noted that, for the ages at which the majority of osteoporosis trials have been conducted (70–80 years), the increased risks per *Z*-score are similar for Marshall *et al.*[15] and Johnell *et al.*[16]

TABLE 17 *Increased risk of fracture associated with a Z-score of –1, as reported by Marshall* et al.[15]

Fracture site	**Increased risk of fracture per *Z*-score**
Hip	2.6
Vertebral	1.8
Wrist	1.4
Proximal humerus[a]	1.6

a Assumed equal to the value for all fractures.[15]

TABLE 18 *Increased risk of hip fracture associated with a Z-score of –1, as reported by Johnell* et al.[16]

Age (years)	**Increased risk of hip fracture per *Z*-score**
50–54	3.68
55–59	3.35
60–64	3.07
65–69	2.89
70–74	2.78
75–79	2.58
80–84	2.28
85–90	1.92

Although it is also likely that there is a correlation between the increased risks per *Z*-score of fracture at the vertebrae, proximal humerus and wrist, such a relationship is unknown and we have assumed that the values reported by Marshall *et al.*[15] are constant with age.

Calculating the risk of fracture for populations with average BMD and without a previous fracture

The increase in fracture associated with a previous fracture and low BMD is reported compared with the risk in women without fracture and with average BMD. To accurately estimate the fracture risk for patients with low BMD and/or previous fracture, the risk for women with average BMD and without previous fracture needs to be calculated. Use of average population values would overestimate the number of fractures because these average figures already contain a subset of females with osteoporosis and/or previous fractures. So that the overall average risk equals that reported in epidemiological studies when subgroups of women with low BMD and previous fracture are included, the risk for women with average BMD and no previous fracture must be reduced below the average population risk.

The percentage reduction by age group is influenced by two factors. At younger ages there will be relatively few osteoporotic and severely osteoporotic women (see *Figure 1*). However, the *Z*-score required to reach an absolute *T*-score of 2.5 SD is greater in younger women (see *Table 1*), which will increase the influence of the osteoporotic women on the risk of fracture for women with average BMD values compared with more elderly women (see *Table 17*). This is more pronounced for hip fracture for which a relationship between age and the increased risk per *Z*-score has been established (see *Table 18*). As the number of osteoporotic women and the increased risk due to *Z*-score adjust the risk of fracture in women with average BMD in different directions, the magnitude of the reduction between the average population risk and that of a woman with average BMD at different age bands cannot be predicted intuitively.

The estimated fracture risks for a woman with average BMD and without previous fracture are shown in *Table 19*. The methodology behind these calculations is given in Appendix 7.

It is seen that for vertebral, wrist and proximal humerus fractures, which have relatively low increases because of *Z*-score differentials (*Tables 17* and *18*), the increased proportion of women with osteoporosis dominates the effect due to the greater *Z*-score between average BMD and a *T*-score of –2.5 SD. As the cohort age increases the percentage reductions compared with the average values increase.

For hip fracture, which has a relatively high risk of fracture in relation to *Z*-score at younger ages (*Table 18*), the percentage reduction values are large even at younger ages and no clear trend is observed.

These data from *Table 19* will be used within the model and multiplied as appropriate to take into account the extra risks for the assumed BMD value and prevous fracture status for each patient.

TABLE 19 *The estimated fracture risk by age for a woman with average BMD and no previous fracture. The percentage reduction in fracture incidence compared with the average for all women in that age band is contained in parentheses*

Age band (years)	Fracture site (including fractures grouped with the main site)			
	Hip	Vertebral	Wrist	Proximal humerus
50–54	0.02% (37%)	0.08% (9%)	0.48% (4%)	0.12% (7%)
55–59	0.04% (40%)	0.11% (15%)	0.44% (8%)	0.13% (12%)
60–64	0.07% (44%)	0.15% (22%)	0.43% (14%)	0.15% (18%)
65–69	0.13% (48%)	0.20% (29%)	0.47% (19%)	0.17% (24%)
70–74	0.21% (54%)	0.26% (37%)	0.56% (26%)	0.19% (32%)
75–79	0.42% (52%)	0.36% (39%)	0.75% (30%)	0.22% (35%)
80–84	0.81% (50%)	0.49% (42%)	1.06% (34%)	0.25% (38%)
85–89	1.62% (47%)	0.68% (45%)	1.52% (37%)	0.28% (41%)

Fracture risk at the threshold for osteoporosis

Table 20 and *Figure 21* give the estimated fracture risk at each site by age for women at the threshold of osteoporosis (*T*-score –2.5 SD). No data on the fracture risks for patients with severe osteoporosis have been given, as the risks would be dependent upon the site of the previous fracture, as detailed in *Table 6*. As the population age increases, the risk at the threshold for osteoporosis may become lower than that of the average population (compare *Tables 19* and *20*). This is due both to the large proportion of women with severe osteoporosis and to the small differential between the average population BMD and the *T*-score of –2.5.

It is seen that at a *T*-score of –2.5 SD the risk of hip fracture greatly increases from 70 years of age. The rate of proximal humerus fractures remains fairly stable regardless of age, whereas that of vertebral fractures exhibits a relatively steady increase as the woman ages. The risk of a 'wrist' fracture initially decreases (as the influence of tibia and fibula fractures wanes) but this effect is overridden by the large natural increase in wrist fractures that are estimated to occur in the elderly.

Mortality following fracture

There is a risk of mortality following a fracture, which is dependent on the site of the incident fracture.

Mortality following hip fracture

Excess mortality is well described after hip fracture. In the first year following hip fracture, the relative mortality risk varies in women from 2 to greater than 10 depending on age.[96] However, case–control studies that adjust for prefracture morbidity indicate that a substantial component can be attributed to comorbidity.[97,98]

The data used in the cost-effectiveness model are taken from unpublished data from the second Anglian audit of hip fracture,[99] 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.[100] It was estimated that 33% of deaths 1 year after hip fracture were totally unrelated to the hip fracture, 42% were possibly related and 25% were 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.[99] An estimate of this can be inferred from the graph in Parker and Anand,[100] 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 attributable 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 21*. No data were available for the age band 50–59 years and it was assumed that, as suggested by Swedish data,[96] this value was one-third that of the rate between 60 and 69 years.

TABLE 20 *The estimated annual fracture risk by age for a woman with a T-score of –2.5 and no previous fracture*

Age band (years)	Fracture site (including fractures grouped with the main site)			
	Hip	Vertebral	Wrist	Proximal humerus
50–54	0.26%	0.25%	0.88%	0.27%
55–59	0.29%	0.29%	0.75%	0.28%
60–64	0.33%	0.33%	0.68%	0.29%
65–69	0.40%	0.37%	0.67%	0.29%
70–74	0.48%	0.41%	0.73%	0.28%
75–79	0.71%	0.49%	0.90%	0.28%
80–84	1.04%	0.58%	1.17%	0.28%
85–89	1.67%	0.70%	1.55%	0.29%

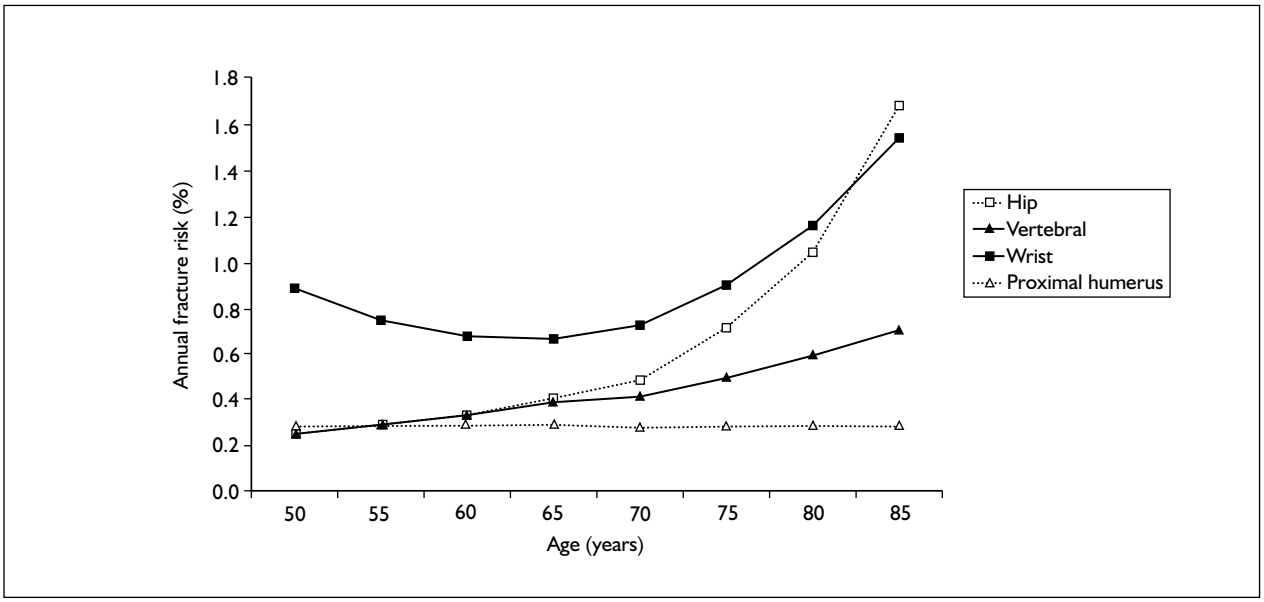

FIGURE 21 *The estimated annual fracture risk by age for a woman with a* T*-score of –2.5 and no previous fracture. ph, proximal humerus; vert, vertebral.*

TABLE 21 *Percentage of hip fractures that result directly in mortality*

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

Mortality following vertebral fracture

Several studies have shown an increase in mortality following vertebral fracture.[8,101–103] In one study,[8] women with one or more vertebral fractures had a 1.23-fold greater age-adjusted mortality rate (95% CI 1.10 to 1.37). This study used morphometric rather than clinical definitions of vertebral fracture. In contrast, other studies that examined mortality after vertebral fracture using clinical criteria have shown more marked increases in mortality. In one study from Australia,[101] vertebral fractures in women were associated with an age-standardised risk of 1.92 (95% CI 1.70 to 2.14) and, in another study,[103] the risk was more than eightfold higher. A study on clinical fractures from the UK[102] compared mortality in women with osteoporosis (and no fracture) with mortality in women with osteoporosis and a previous vertebral fracture. The hazard ratio was 4.4 (95% CI 1.85 to 10.6) and was used for the present model.

The pattern of mortality after clinical vertebral fracture is non-linear, suggesting, as is the case for hip fracture, that a fraction of deaths would not have occurred in the absence of a fracture. Using the patient register for hospital admissions in Sweden, 28% of all deaths associated with vertebral fracture were judged to be causally related.[104] 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.[8,103,105] For humeral fractures we conservatively assumed a twofold increase in mortality and that 28% of deaths associated with humeral fractures are causally related.[104]

For pelvis and other femoral fractures we have assumed a mortality rate equal to that for hip fractures. 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 fractures, no excess mortality was assumed.

Death due to causes other than fracture

These data have been taken from 1999 interim life tables.[106] These data could not be updated as they were used within the individual patient model that formed the meta-model. It is unlikely that life expectancy has changed markedly over the last decade and thus it is expected that little bias has been introduced.

Several studies[107,108] have shown an increased mortality associated with low BMD of similar magnitude derived from measurements at the radius or heel. At the radius, the increase in RR was 1.22 per SD decrease in BMD adjusted for age,[107] 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 authors are not aware of any relevant data that have been published since.

The mortality rates of the general female population and for those women at the threshold of osteoporosis are shown in *Table 22*. The general population mortality rates have not been adjusted to take into account those women who are osteoporotic, meaning that these death rates are likely to be slight overestimates. As these apply to all interventions it is unlikely that this will bias results between interventions but will be slightly unfavourable to all interventions.

A study[109] has suggested that there may be no link between BMD and excess mortality. This link was examined in a previous assessment report[2] and was shown to make little difference to the results, with a marginally unfavourable effect towards the intervention. As such, the increase in mortality associated with osteoporosis has been retained, as this was used within the individual patient model that provided data for the meta-model.

Entry into nursing home following an osteoporotic fracture

It was assumed that only fractures of the hip or pelvis or other femoral fractures could result in nursing home entry. Data were sought to estimate what percentage of women who suffer a hip fracture move from living in the community into nursing home accommodation. The mathematical model used tracks the living status of individual patients, rather than assuming a constant percentage as has been used in some models;[110] this second methodology would allow nursing home costs to be incorrectly allocated to women already residing in such care. The model also allows the risks of entering a nursing home to be dependent on age. Models that use an average value for all

TABLE 22 *The mortality rate 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	0.24%	0.34%
55–59	0.39%	0.54%
60–64	0.65%	0.85%
65–69	1.13%	1.40%
70–74	1.86%	2.19%
75–79	3.07%	3.43%
80–84	5.28%	5.60%
85–89	9.18%	9.27%

ages, such as that of Burge *et al.*,[11] would be likely to significantly overestimate the proportion of younger patients with a hip fracture who enter a nursing home as the data set would be dominated by older patients.

Data from the second Anglian audit of hip fracture[99] were used in the model. These data are shown in *Table 23*. It is assumed that women who enter a nursing home will remain there for the remainder of their lives.

A recent estimate of the costs associated with osteoporotic fractures assumed that 10% of all women with a hip fracture would reside in a nursing home for the remainder of their lives.[11] This figure looks plausible within the age range of 70 years and above but appears, as expected, to be too high for those aged 50–69 years. Data from Kanis *et al.*[111] used values ranging from 7% for 50- to 59-year-olds to 23% for those aged 90 years or over, but it is not stated how applicable these values are to the UK. 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 who subsequently have to reside in a nursing home are unlikely to be included within the audit. However, this may be balanced by the fact that a significant proportion of patients who sustain a hip fracture may already reside in a nursing home; Johnell *et al.*[112] report that 22% of patients with a hip fracture were admitted from a nursing home or a hospital.

The health state values associated with osteoporosis used within the model

The utilities used in this model are those detailed in Stevenson *et al.*,[4] which were heavily influenced by work undertaken by Kanis *et al.*[104] This comprehensive study provided a coherent source of health state utility multipliers for all of the fracture types. A utility multiplier is combined multiplicatively with the general population utility to provide an estimate of the utility for patients in that state, and results in the absolute disutility becoming less as a person ages and their underlying utility lower. The baseline values used in these analyses are taken from Kind *et al.*[113]

The utilities reported by Kanis *et al.*[104] 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. The only case for which the utility data did not match closely was for tibia and fibula fractures (multiplier of 0.926) compared with proximal humerus fractures (multiplier of 0.973) in the second year. To prevent the disutility of tibia and fibula fractures being underestimated we have calculated a weighted mean using the incidences of tibia and fibula fractures relative to proximal humerus fractures at each age.[7] This varies the utility multiplier in the second year for proximal humerus, tibia and fibula fractures from 0.949 at 50–54 years to 0.966 at 80 years and over.

One deviation from the data of Kanis *et al.*[104] was that the fractures grouped as similar to wrist were not assumed to affect utility in the second year, which was an assumption contained in the individual patient model.[90] A utility multiplier of 0.999 is reported in Kanis *et al.;* this is very slightly unfavourable to the intervention. The utility data used within the model are shown in *Table 24*.

It is noted that we are using a greater disutility for vertebral fracture in the initial year than that in previous work for NICE,[5] which increased the value to that associated with hip fracture (0.792). We have used the values reported by Kanis *et al.*[104] for consistency, acknowledging that the adjustment requested by the NICE appraisal committee was arbitrary.

TABLE 23 *The percentage of women who move from the community to a nursing home following a hip fracture*

Age band (years)	Percentage of women
50–59	0%
60–69	4%
70–79	4%
80–89	12%
90+	17%

Cost data used in the treatment model

This report is based on the costs calculated by Stevenson and Davis[114] and uses Healthcare Resource Group (HRG) costs with the inclusion of home help costs as used in a NICE assessment.[4] The calculations are replicated in Appendix 11. A summary is provided in *Table 25* with the values inflated from 2006 prices to 2008 prices by using a factor of 8%, as appears reasonable based on

TABLE 24 *Utility data used within the model*

Fracture type	Utility in first year following fracture	Utility in second year following fracture
Spine (clinical)	0.626	0.909
Hip	0.792	0.813
Wrist	0.977	1.000
Proximal humerus	0.794	Dependent upon age, ranging from 0.949 to 0.966

All taken from Kanis *et al.*[104] except for wrist fracture in the second and subsequent years, which is an assumption.

historic inflation indices.[115] The ongoing cost of pharmaceutical treatment following a vertebral fracture was maintained at £222 per annum.

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 a significant impact on the cost-effectiveness ratios but will slightly favour no treatment over interventions with beneficial effects on fracture.

The costs presented have been divided, when 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 cost of a visit to a GP has been estimated at £30.[115] The cost of a BMD scan has been estimated at £34 in 2001/2 prices;[2] this has been assumed to be £48 in 2008 prices with reference to published inflation indices.[115]

The costs of the interventions

Women receiving bisphosphonates, vitamin K or strontium ranelate should also be prescribed calcium plus vitamin D supplements if their dietary intake is insufficient. It is assumed that all women have adequate vitamin and calcium D intakes and that only the intervention is prescribed. The costs per annum are shown in *Table 26* and come from the *British National Formulary* (BNF) when available.[43]

The price of vitamin K_1 at 5 mg per day is not listed in the BNF[43] although 10-mg formulations are listed. No evidence has been found on the effects of 10 mg of vitamin K daily and it has been assumed that the efficacy in fracture prevention is equivalent to that of the 5-mg formulation.

Vitamin K_2 is not listed in any formulation, probably because of the fact that menatetrenone is currently not permitted as a food supplement in the EU because there is no evidence for its independent role in health.[26]

The duration and efficacy of treatment and associated adverse events

The treatment duration for bisphosphonates and strontium ranelate has been maintained at 5 years; however, there is evidence which suggests that, for bisphosphonates, courses of 10 years may be cost-effective.[117]

The treatment duration for vitamin K is unknown as it is not listed in the BNF[43] as a treatment for osteoporosis. We have assumed that a 5-year course will be undertaken. Data on the fall time of vitamins are also unknown; we have used 5 years in the base case but adjust this to an immediate loss of effect (i.e. a fall time of 0 years) in sensitivity analyses.

The efficacy data for each intervention used within the model

As detailed, a systematic review of the clinical efficacy of vitamin K has been conducted. The efficacies for strontium ranelate and for bisphosphonates have been updated and are contained in Appendices 9 and 10 respectively. These differ slightly from those reported in Stevenson *et al.*[4] For all interventions we assume that the efficacy for all non-vertebral fractures is applicable for 'wrist' and 'proximal humerus' fractures. Data for vitamin K_1 came from an

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TABLE 25 *The cost (£) of each event, by age and by initial and subsequent years, used within the model (2008 prices)*

	50–54 years		55–59 years		60–64 years		65–69 years		70–74 years		75–80 years	
State	**First-year costs**	**Subsequent annual costs**	**First-year costs**	**Subsequent annual costs**	**First-year costs**	**Subsequent annual costs**	**First-year costs**	**Subsequent annual costs**	**First-year costs**	**Subsequent annual costs**	**First-year costs**	**Subsequent annual costs**
Hip fracture[a]	6152	–	6152	–	6152	–	6940	–	7290	–	7290	–
Hip fracture[a,b]	34,385	25,447	34,385	25,447	34,385	25,447	35,183	25,813	35,499	26,179	35,499	26,179
Death due to hip fracture	8666	–	8666	–	8666	–	8666	–	8666	–	8666	–
Vertebral fracture	2525	222	2525	222	2525	222	2525	222	2981	222	2981	222
Wrist fracture[c]	868	–	981	–	1067	–	1085	–	1545	–	1353	–
Proximal humerus fracture[d]	2545	–	2416	–	2268	–	2097	–	2770	–	2436	–

a Assumed applicable for pelvis and other femoral fractures.
b Leading to nursing home admission.
c Assumed applicable for rib, sternum, clavicle and scapula fractures.
d Assumed applicable for tibia, fibula and humeral shaft fractures.
For sources of data see main text and Appendix 11.

TABLE 26 *The cost for each intervention per annum*

Intervention	Assumed dosage	Cost per annum (£)
Alendronic acid (non-proprietary)	70 mg once weekly	51.00
Risedronate sodium (Actonel®)	5 mg once daily	249.15
Risedronate sodium (Actonel®)	35 mg once weekly	264.80
Strontium ranelate (Protelos®)	2 g once daily	333.94
Vitamin K_1 (Konakion®)	10 mg once daily[a]	60.27
Vitamin K_2	Not in the BNF[43] – see text for comment	

a This is double the dose used in the RCT[116] – see text for more discussion.

exclusively osteopenic population and have been assumed to be applicable to women with osteoporosis.[71]

All data have been calculated using a random-effects model. We have used efficacy for the prevention of all clinical fractures rather than clinical fragility fractures when both data were presented to be consistent between interventions (*Table 27*).

These RRs were assumed applicable regardless of whether the risk of fracture was conferred by age, gender, *T*-score or previous fracture status. It is noted that there are no specific fracture data at the hip or the vertebrae for vitamin K_1. As these fractures are associated with relatively large costs and disutilities, if the efficacy of vitamin K_1 was substantially different this would affect the cost–utility results produced.

A decision was taken not to model vitamin K_2 for a number of reasons. This intervention is currently not permitted as a food supplement in the EU because there is no evidence for its independent role in health.[26] The price of the intervention is unknown and the fracture efficacy data had wide confidence intervals, all of which spanned unity. The only large ($n > 1500$ patients per arm) RCT reported a RR of 1.01 for vitamin K_2 compared with calcium or no active intervention, which may be disproportionally weighted because of the assumption of a random-effects model and the presence of a number of small ($n > 100$ per arm) RCTs.

Two scenarios for vitamin K_1 were modelled: the base-case scenario and an exploratory analysis assuming that vitamin K_1 had no effect at the hip or vertebrae.

Because of limited data on the efficacy of interventions for fracture in the very elderly, it has been assumed that the results for women aged 75–79 years would approximate those for women aged 80 years and older, which is in line with previous modelling work.[4]

Adverse events associated with treatment

We have assumed that the adverse events associated with bisphosphonates are equal to those reported in Stevenson and Davis.[114] These result in a QALY loss per woman over a 5-year treatment period ranging from 0.0016 at 50 years of age to 0.0013 at 75 years of age. The NICE appraisal committee requested that these values be increased by a factor of 10 in the base case for some analyses;[5] however, the authors believe that the utility detriment had already been overestimated and did not need to be increased further. Strontium ranelate is associated

TABLE 27 *The assumed relative risks of fracture for each intervention in women with osteoporosis*

	Vertebral fracture	'Hip' fracture	All other fractures
Vitamin K_1	0.46 (95% CI 0.22 to 0.99)	0.46 (95% CI 0.22 to 0.99)	0.46 (95% CI 0.22 to 0.99)
Vitamin K_2	0.63 (95% CI 0.36 to 1.11)	0.27 (95% CI 0.03 to 2.38)	0.19 (95% CI 0.03 to 1.06)
Alendronate/risedronate	0.58 (95% CI 0.50 to 0.67)	0.72 (95% CI 0.58 to 0.88)	0.82 (95% CI 0.74 to 0.90)
Strontium ranelate	0.63 (95% CI 0.56 to 0.71)	0.89 (95% CI 0.67 to 1.18)	0.86 (95% CI 0.75 to 0.98)

with a different set of adverse events but was assumed to have the same disutility as that used for bisphosphonates, values that have been previously used.[5]

We have assumed that there are no adverse events associated with vitamin K treatment.

Summarising changes between parameters used in this report and those used in preceding work

Work has previously been undertaken for NICE on the cost-effectiveness of bisphosphonates and strontium ranelate,[5] with the results used in calibration and discussion of the parameters that predict fracture risk. *Table 28* summarises the changes that have been made in calculating the cost-effectiveness ratios in this report with respect to this previous work.

Comparison and calibration of the model against previously published work

Recent modelling work[4,5] undertaken using SHEMO for NICE and the National Coordinating Centre for Health Technology Assessment used data regarding the risks of fracture that were provided under an academic-in-confidence agreement. These data were not permitted to be used for this report and, as previously described, the model has reverted to estimating the risks of fracture based on age, gender and *T*-score alone, with increases in risks associated with clinical risk factors (including previous fracture).

Analyses have been carried out to compare the results of the new model with those of the model that used academic-in-confidence data. The most recent work[5] incorporating the current price of alendronate could not be used for the comparison as different efficacies were used for some of the clinical risk factors. Instead the results are compared with previous work in which the price of alendronate was £173 per annum.[119] With the exception of the underlying risks of fracture, which have now been calculated using age, gender, *T*-score and previous fracture status, and a slight adjustment in the costs, because of different proportions of additional fractures (see *Table 4*), the input parameters were identical. These results are shown in *Figures 22* and *23*. It is seen that the change in cost per QALY in relation to age is less pronounced in the new model compared with the model using academic-in-confidence data, with similar results being obtained for women aged 70 years and older with a *T*-score of –2.5 SD to –3.0 SD (*Figure 22*). This is favourable to the interventions as the cost per QALY in the younger patients has been underestimated.

Additional analyses were undertaken to determine an appropriate level of increased fracture risk when a previous fracture has been sustained.

The new model was rerun using four different ratios for the initial fracture risk due to a previous fracture. These were increases of 25%, 50%, 75% and 100%. The results produced by these factors were compared with the results for women with a previous fracture and a *T*-score of –2.5 SD to –3.0 SD.[119] These data are depicted in *Figure 23*. It is seen that increases of 100% and 75% underestimate the cost per QALY at all ages, whereas an increase of 25% overestimates the cost per QALY at all ages. An increase of 50% appears the most appropriate as it produces similar results in those aged 70 years and over. This factor still underestimates the cost per QALY in younger ages, which will be favourable to the interventions.

The expected net benefit of sampling of a proposed RCT comparing alendronate and vitamin K_1

The rationale for conducting an RCT

Both alendronate and vitamin K_1 are relatively cheap compared with risedronate and strontium ranelate, with the former group priced below £61 per annum and the latter group priced at more than £250 per annum (*Table 26*). Both alendronate and vitamin K_1 have relatively good midpoint estimates for efficacy at preventing fracture (*Table 27*), although the evidence base for alendronate is much stronger because of the large number of RCTs conducted with bisphosphonates and the wide confidence intervals for vitamin K. Given these mid-point efficacy estimates, it is thus not surprising that, as detailed later, the most cost-effective intervention using standard cost per QALY thresholds[94] appears to be either vitamin K_1 or alendronate.

TABLE 28 *Changes between previous modelling work and that undertaken in this report*

Parameter	Change	Reason	Further description
Discount rate (per annum)	From 6% for costs and 1.5% for benefits to 3.5% for both costs and benefits	Recommendation from NICE	See Epidemiological data used in the model
Efficacy of bisphosphonate/strontium ranelate	Adjustment in the assumed efficacy	New evidence	Appendix 9 and Appendix 10
Effect of adverse events for bisphosphonates	From 10 times that reported in a systematic review[118] to that reported in the systematic review	We do not believe that the multiplying factor of 10 adopted by the NICE appraisal committee is justifiable	See Adverse events associated with treatment
Cost of a GP consultation	Increased from £18 to £30	New evidence	See Epidemiological data used in the model
Cost of a BMD scan	Increased from £34 to £48	New evidence	See Epidemiological data used in the model
Utility in the initial year of a vertebral fracture	Reduced from 0.792 to 0.626	The NICE appraisal committee did not believe that vertebral fractures could cause a greater utility loss than hip fractures in the initial year of fracture. This is not supported by clinicians on the NICE GDG and the data from published literature were used	See The structure of the cost-effectiveness model
Cost of fractures	Inflated to 2008 prices	New evidence	See Epidemiological data used in the model
The adoption of a different set of predictive values for estimating the risk of fractures	Calculating the risk of fracture based on age, gender, *T*-score and previous fracture status alone	Permission was not granted to use the academic-in-confidence data previously used	See The increased risk of fracture following a previous fracture, The increased risk of fracture for patients with low bone mass, Calculating the risk of fracture for populations with average BMD and without a previous fracture and Fracture risk at the threshold for osteoporosis
The underlying rate of fractures	We have smoothed the underlying fracture rates of Singer *et al.*[7] and the increases associated with the four main fractures to incorporate other fracture types	The results of Singer *et al.*[7] would have been associated with noise, which would affect the data collected. Our methodology of smoothing the data will hopefully provide more coherent answers	See The incidence of hip, vertebral, wrist and proximal humerus fractures by age
The efficacy of bisphosphonates is assumed to be the same, independent of the constituents of risk	The efficacy of bisphosphonates is constant for all levels of risk. On the request of the NICE appraisal committee previous work[5] used, differential efficacies depending on the risk factors used to calculate absolute risk	As permission to use the academic-in-confidence data previously used was not granted, differentiating between different constituents of risk was not possible	See Methods for economic analyses

GDG, (NICE Osteoporosis) Guideline Development Group.

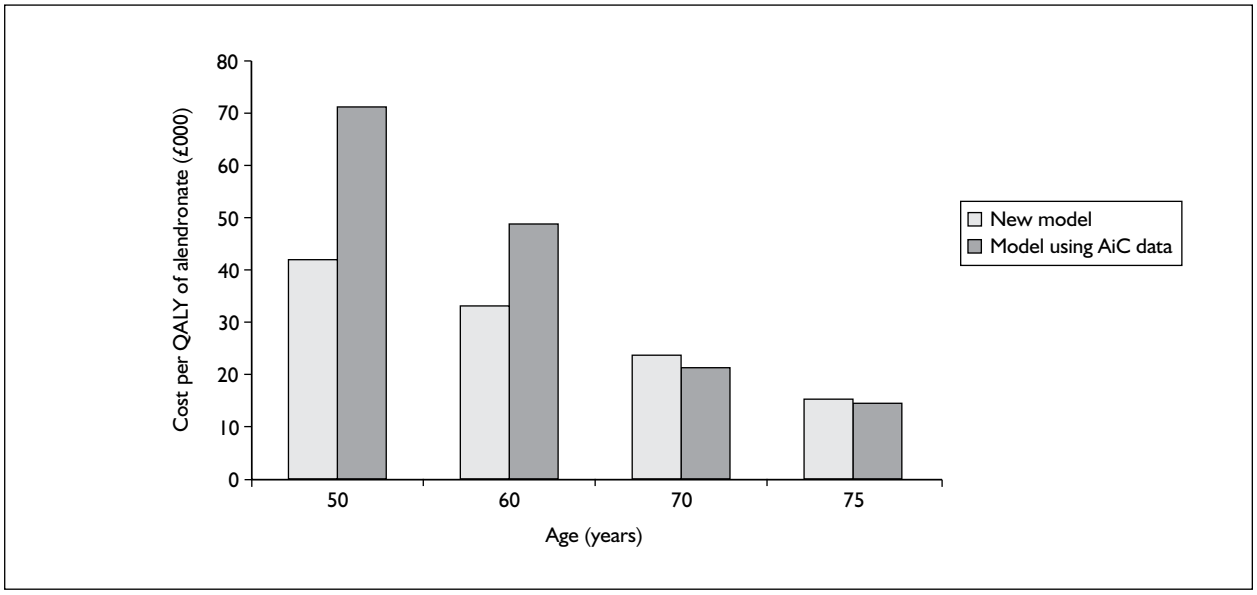

FIGURE 22 *Comparing the results under the new model and those when using the academic-in-confidence data allowed for previous modelling work assuming that women have no additional clinical risk factors and a* T*-score of –2.5 SD to –3.0 SD. AiC, academic-in-confidence.*

To address the uncertainty in the decision regarding which treatment to prescribe, an RCT directly comparing alendronate and vitamin K_1 would be beneficial, although there has been no previous work undertaken on whether such a trial would be cost-effective. We employ expected value of sample information (EVSI) techniques. The method is fully described elsewhere[120–122] and has recently been employed to determine the cost-effectiveness of an RCT to look at the long-term efficacy of bisphosphonates;[117] it will be summarised in this report.

A major unknown in the knowledge base is the uncertainty around the efficacy of vitamin K_1 in preventing fractures. An RCT of vitamin K_1 against calcium alone would provide these data but may be unethical as patients allocated to the

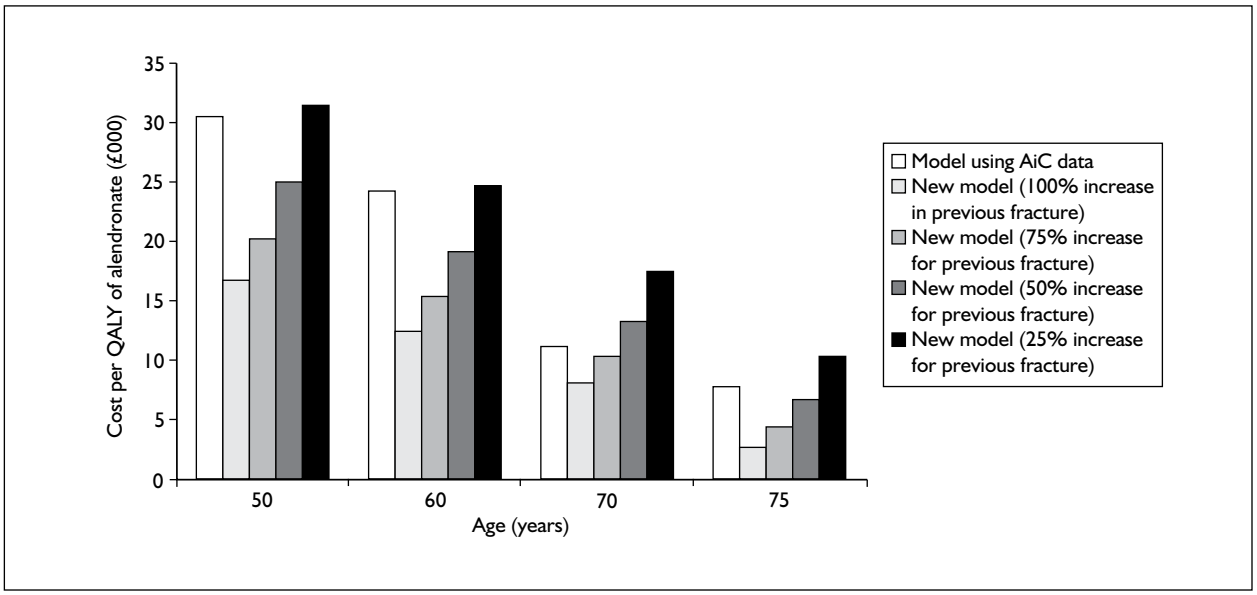

FIGURE 23 *Comparing the results under the new model and those when using the academic-in-confidence data allowed for previous modelling work assuming that women have no additional clinical risk factors except for a previous fracture and a* T*-score of –2.5 SD. AiC, academic-in-confidence.*

calcium arm would be denied alendronate, which, as shown later, is estimated to be cost-effective in postmenopausal women. Thus, ethically an RCT should compare vitamin K_1 directly against alendronate. The information that would be provided by the RCT would be the number of patients who fracture at each site in the two arms of the study. This would allow a RR of fracture at each site to be computed for alendronate compared with vitamin K_1. Note that as there is not a 'no treatment' arm the RCT would not provide any direct additional data on the efficacy of either alendronate or vitamin K_1 against no treatment.

The analyses undertaken assume that the proposed RCT would have a duration of 5 years and that an equal number of patients would be randomised to the alendronate and vitamin K_1 arms. It is recommended that within the proposed trial it is ensured that women are replete of calcium as is standard in trials of osteoporosis interventions.

Simulating the prior expectation of the comparative efficacy of alendronate and vitamin K_1

To undertake EVSI a prior expectation of the RR of fracture for alendronate compared with vitamin K_1 is required. This was obtained at each fracture site by sampling 1000 RRs for alendronate compared with no treatment and 1000 RRs for vitamin K_1 compared with no treatment (*Table 27*). The RRs for each intervention were combined to form 1000 estimates of the RR of alendronate compared with vitamin K_1. Note that this assumes independence between the efficacy of alendronate and the efficacy of vitamin K_1.

A statistical distribution was fitted to the generated RRs of alendronate compared with vitamin K1. *Figure 24* shows the underlying simulated data on the RR of alendronate compared with vitamin K_1 at the hip and the statistical distribution fitted. *Figures 25* and *26* give corresponding data for vertebral and the combined wrist and proximal humerus fractures respectively. A summary of the assumed distribution is provided in *Table 29*.

Calculating the expected value of sample information

The optimal decision given current information is that which yields the greatest expected net benefit,[123] defined as max t Eθ NB(t, θ) where t represents the treatments being compared (t = 1,2, … T), θ a multivariate probability distribution based on current evidence and NB(t, θ) the net benefit of treatment t associated with θ. Undertaking an RCT will provide additional data on a subset of the unknown parameters θI (in this example the RR of alendronate compared with vitamin K_1 in preventing fracture at each site) but no direct evidence on the complimentary parameters denoted $\theta I\ c$, for example the disutility

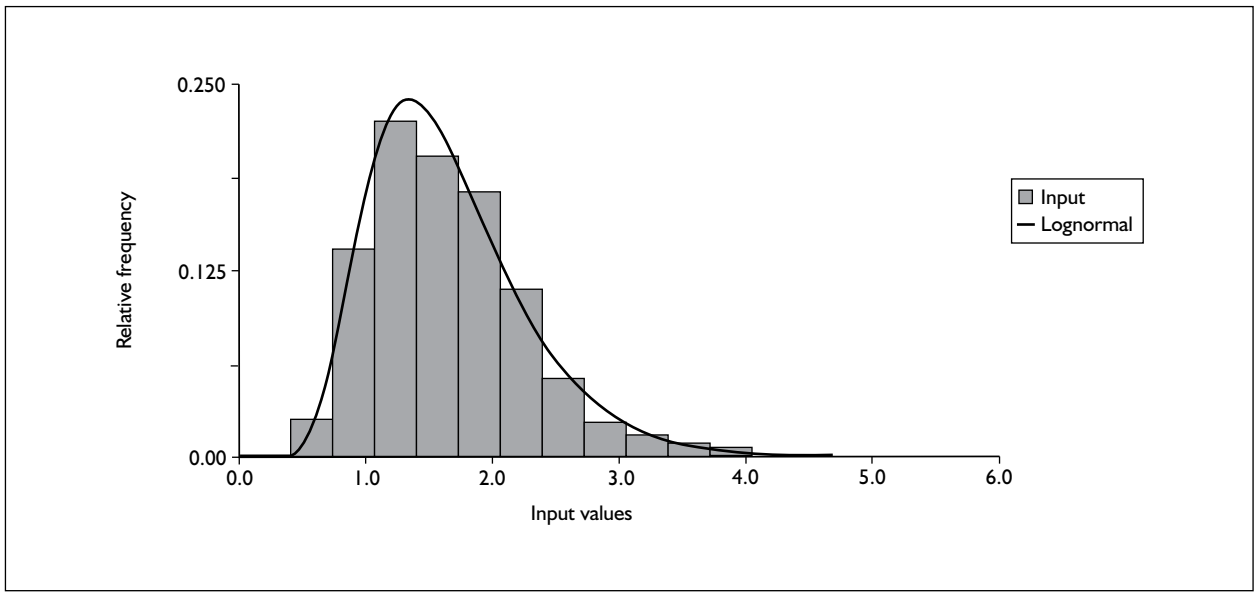

FIGURE 24 *The fitted distribution for the relative risk of alendronate compared with vitamin K_1 for hip fracture.*

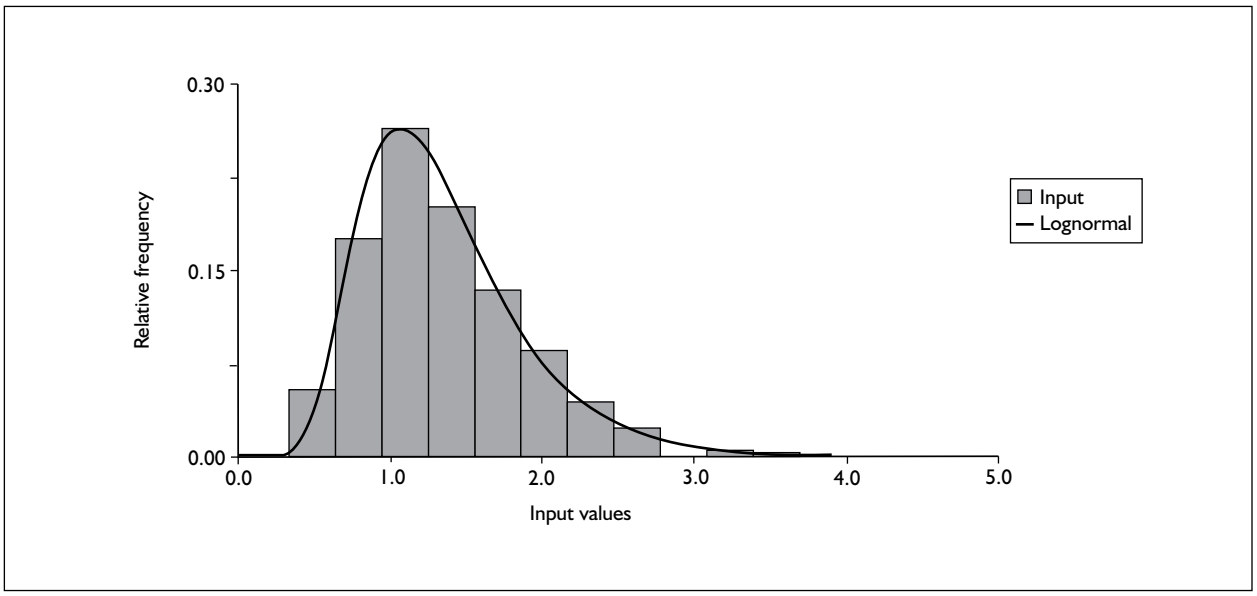

FIGURE 25 *The fitted distribution for the relative risk of alendronate compared with vitamin K_1 for vertebral fracture.*

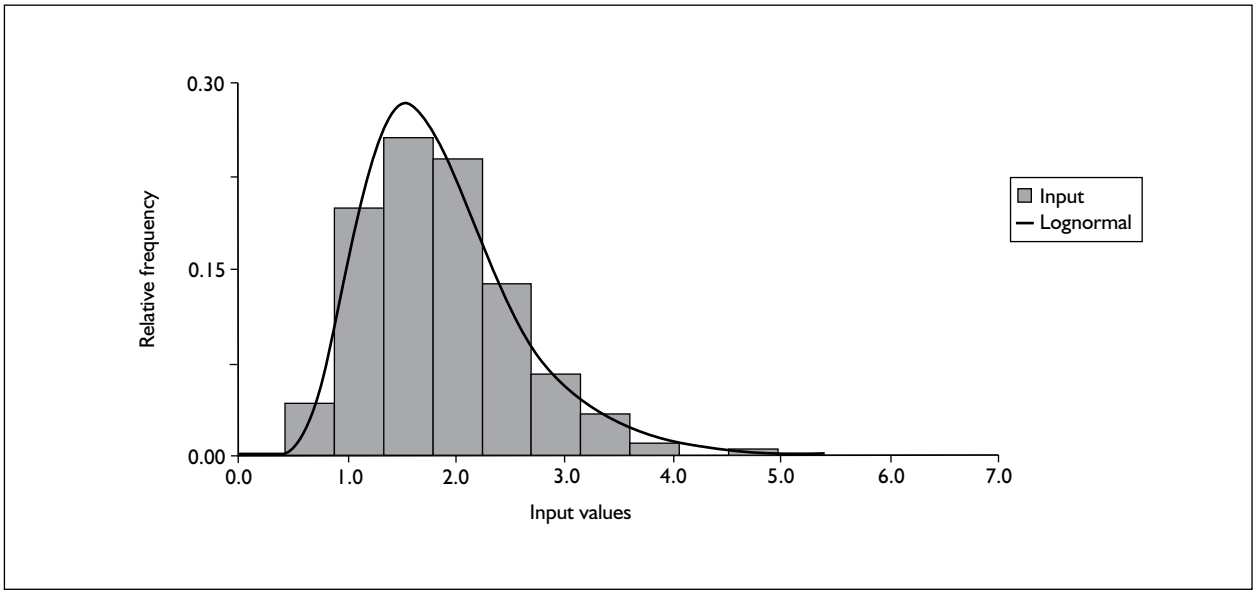

FIGURE 26 *The fitted distribution for the relative risk of alendronate compared with vitamin K_1 for wrist and proximal humerus fracture.*

TABLE 29 *The summarised prior distribution of the relative risk of alendronate compared with vitamin K_1*

Site	Distribution	Mean (SD) of the log of the value
Hip	Log-normal	0.4463 (0.3821)
Vertebral	Log-normal	0.2287 (0.3941)
Wrist and proximal humerus	Log-normal	0.5558 (0.3924)

of a hip fracture. Calculation of EVSI involves simulating the collection of data samples and for each simulated sample data set examining the potential effect on the decision between treatment options. The data collected, which will be affected by both the underlying uncertainty in the parameters and the lack of precision associated with finite sample sizes, are denoted $X\theta_I$ and a posterior distribution of $\theta_I, \theta_I{}^c \mid X\theta_I$ is calculated, which synthesises the prior distribution with the information produced by the RCT. Further 'inner level' Monte Carlo sampling then quantifies the effect of the simulated data obtained from the RCT on the decision, that is, whether the RCT would produce evidence to change the decision from that which is estimated to be optimal given current information. The optimal decision following data collection is the treatment option $t_{optimal|X\theta_I}$, which maximises the expected net benefit $[\max_t E(\theta_I, \theta_I{}^c \mid X\theta_I) NB(t, \theta_I, \theta_I{}^c)]$. From this, the expected net benefit, given the updated data, of the treatment that was optimal using current information $[E(\theta_I, \theta_I{}^c \mid X\theta_I) NB(t_{baseline}, \theta_I, \theta_I{}^c)$, where $t_{baseline}$ is that which maximises $E\theta\, NB(t, \theta)]$ is subtracted to provide the additional expected net benefit obtained by making a decision after obtaining the sample data set $X\theta_I$. It is noted that when updating the data does not change the optimal decision the EVSI for that value of $X\theta_I$ is zero. The expected EVSI for the RCT is calculated as the average EVSI across all sampled data sets $X\theta_I$. That is:

$$EVSI = E_{X\theta I}([\max_t E_{(\theta_I, \theta_I{}^c \mid X\theta_I)} NB(t, \theta_I, \theta_I{}^c)] - [E_{(\theta_I, \theta_I{}^c \mid X\theta_I)} NB(t_{baseline}, \theta_I, \theta_I{}^c)])$$

For this case study, the process of simulating the number of fractures expected in a proposed RCT of specified size, updating the prior distribution and calculating which is the better treatment duration from an inner probabilistic sensitivity analysis (PSA) process was undertaken for each of the 1000 parameter configurations previously used in calculating the better duration of treatment given current information. This produced a range of 1000 different simulated results for the specified trial design. To estimate the likely number of fractures in each arm the likely fracture risks of women recruited to the RCT needed to be estimated. It was assumed that the risks of those recruited would be equivalent to the risks associated with women aged 70–74 years with a *T*-score of –3 SD but no previous fracture, which are 0.93%, 0.84%, 0.80% and 0.31% per annum for vertebral, hip, wrist and proximal humerus fractures respectively.

Estimating the number of fractures in the RCT

For simplicity, we consider only trials with equal numbers of women, denoted n, in the two arms. The number of fractures simulated to occur in each arm of an RCT was estimated using a normal distribution with a mean equal to n multiplied by the probability of having a fracture, and variance equal to n multiplied by the product of the probability of fracture and the probability of not fracturing. The simulated trial results provide the number of people who fracture in the alendronate arm (x_1) and the number of people who fracture in the vitamin K_1 arm (x_2).

Updating the prior distribution with the data from the RCT to form a posterior distribution

The prior distributions of the RR of alendronate compared with vitamin K_1 were seen to be log-normal, thus the natural log of the RR of alendronate compared with vitamin K_1 is distributed normally with a mean m_1 and a variance of v_1. We approximate the distribution of the log RR from the hypothetical RCT by a normal distribution with mean z, where z is the log RR of alendronate compared with vitamin K_1, and variance s, where $s = (n - x_1)/(n.x_1) + (n - x_2)/(n.x_2)$. Note that this approximation has used an estimate of the true sampling variance based on the data x_1 and x_2, and so uncertainty in the sampling variance has been ignored. The posterior distribution of the log of the RR of alendronate compared with vitamin K_1 is then approximately normal, with mean m_2 and variance v_2 given by $v_2 = 1/(1/v_1 + 1/s)$ and $m_2 = v_2 \times (m_1/v_1 + z/s)$. Note that, as the number of women in the RCT increases, the posterior distribution becomes less sensitive to the choice of prior distribution and moves closer to that observed from the RCT.

An illustrative example of forming a posterior distribution

An illustrative example is provided using the prior distribution of the RR of alendronate compared with vitamin K_1 for vertebral fractures (*Table 27*). The natural log of the prior distribution of the RR of alendronate compared with vitamin K_1 is distributed normally with a mean of 0.2287 and a variance of 0.1553. It is assumed that we sample a 'true' log RR of alendronate compared with vitamin K_1 of 0.3; however, due to lack of precision from a finite sample size, this value of the log RR

of alendronate compared with vitamin K_1 may not be observed. For illustrative purposes we assume that a simulated RCT of 1000 women produced 25 vertebral fractures in the alendronate cohort and 20 vertebral fractures in the vitamin K_1 cohort {thus exhibiting a RR of alendronate compared with vitamin K_1 of 0.2231 [log (25/20)] rather than the 'true' value of 0.3}. The distribution of z is thus estimated to be normally distributed with a mean of 0.2231 and a variance of 0.0880 [(1000–20)/(1000×20) + (1000–25)/(1000×25)]. The posterior distribution of the natural log of the RR of alendronate compared with vitamin K_1 would then be estimated to be normal with a variance of 0.0561 [1/(1/0.1553 + 1/0.0880)] and a mean of 0.2251 [0.0561×(0.2287/0.1553 + 0.2231/0.0880)]. Monte Carlo sampling would be based on this distribution to provide estimates of the log RR of alendronate compared with vitamin K_1. These values would be used in a standard PSA to determine which of the two treatments was optimal.

Transforming the posterior distribution into RRs compared with no treatment for alendronate and vitamin K_1

Our mathematical model has been constructed whereby the efficacy of an intervention compared with no treatment is used to calculate the incremental costs and QALYs associated with treatment. The posterior distribution is for the log RR of alendronate compared with vitamin K_1. This must be converted into a RR for each intervention compared with no treatment. To do this it is assumed that the RRs for alendronate compared with no treatment are correct, because of the large number of patients (almost 5000 per arm) recruited to the bisphosphonate RCTs. In the PSA, the RR of alendronate is sampled and the RR of vitamin K_1 compared with no treatment is directly derived from a sampled RR of alendronate compared with vitamin K_1 and a RR of alendronate compared with no treatment. For example, if alendronate was sampled to have a RR of 0.8 compared with no treatment and a RR of 2 compared with vitamin K_1 then the RR of vitamin K_1 compared with no treatment would be estimated to be 0.4 (0.8/2).

Calculating the optimal decision following the RCT data

Given the simulated data from the RCT and the resulting posterior distribution of the natural log of the RR of alendronate compared with vitamin K_1, the optimal decision was re-evaluated using PSA and the expected net benefit of the optimal decision obtained. This expected net benefit was compared with the expected net benefit of the optimal decision based on prior information alone. The average of the increase in mean net benefit across all 1000 simulated trial results gives the estimated EVSI. To calculate if the RCT is a cost-effective use of resources two further sets of data are needed: how much the RCT will cost and how many patients will benefit from the additional information.

The costs of recruiting to the RCT

The cost of running the proposed RCT has been assumed to be £1000 per recruit (Clinical Trials Research Unit, ScHARR, University of Sheffield, 2007, personal communication) with additional intervention acquisition costs of £111.27 (£51 + £60.27) per annum. Although in reality there will be fixed costs and some form of economies of scale to be exploited, this value appears to be a reasonable approximation to the costs of successfully funded bids in the UK.

The expected number of women who will benefit from the increased knowledge

Estimating the number of women who may benefit from the extra research is more complicated. *Table 40* in Appendix 7 reports that an estimated 20.9% of women aged 70–74 years are osteoporotic; as the number of women in this age range is estimated to be 1,130,516[124] this would equate to approximately 236,000 women who could benefit from the better information regarding the relative efficacy of alendronate and vitamin K_1. Assuming that one of these interventions is likely to remain the mainstay of treatment for 10 years and with an assumed 50,000 women becoming eligible for treatment per year, this would equate to an estimated 736,000 women who would benefit, which has been rounded up to 1,000,000 to account for patients over 75 years of age or under 70 years of age who may also be eligible. It is believed that compliance with osteoporosis interventions is in the region of 50%[95] and, thus, the estimated number of women who could benefit from an RCT assessing the relative efficacy of alendronate and vitamin K_1 is approximately 500,000. This value is adjusted to 200,000 and 1,000,000 in sensitivity analyses.

The scenarios undertaken

Two scenarios were run, the first using a cost per QALY threshold of £20,000 and the second using a cost per QALY threshold of £30,000. In both scenarios RCTs were evaluated assuming that 1000, 2000, 5000 or 10,000 women were recruited per arm. Sensitivity analyses were undertaken on the number of women who would benefit from the better data and the underlying fracture risks of those recruited within the trial.

Chapter 5
Results

Results for women with and without a previous fracture

The results from the cost-effectiveness analyses are provided in detail in Appendix 11, with summary values provided in *Figures 27–30*. Note that, for ease of interpretation, when an intervention dominates no treatment the value in the figure has been shown as zero.

Conclusions from the analyses given current information

The following conclusions can be drawn from the cost-effectiveness analyses undertaken:

1. Vitamin K_1 shows potential to be a cost-effective treatment for preventing fractures. Incremental analyses suggest that it is the most cost-effective intervention if the efficacy data are assumed applicable at the hip and vertebrae. However, the results for alendronate are similar, as shown by the cost-effectiveness acceptability curves in Appendix 11.
2. If vitamin K_1 is not effective at preventing fractures at the hip or vertebrae then it does not appear to be a cost-effective intervention. As such, robust data on the efficacy of vitamin K at these fracture sites are urgently needed.
3. Both vitamin K_1, assuming efficacy at the hip and vertebrae, and alendronate are relatively much more cost-effective than either risedronate or strontium ranelate. Vitamin K_1 is estimated to have a cost per QALY of below £20,000 in all osteoporotic women aged 50 years and older.
4. The results for women with a *T*-score of –2.5 SD and a previous fracture are relatively similar to those for women with a *T*-score of –3.0 SD and no previous fracture.

Although the analyses have shown that vitamin K_1 is potentially the most cost-effective intervention when the efficacy data are assumed to be applicable to all sites, caution must be applied when interpreting the results. In the absence of vitamin K_1 the most cost-effective treatment is alendronate, a bisphosphonate, which is a class of drugs that has been evaluated in numerous RCTs, approaching 5000 patients per arm. In contrast, vitamin K_1 has

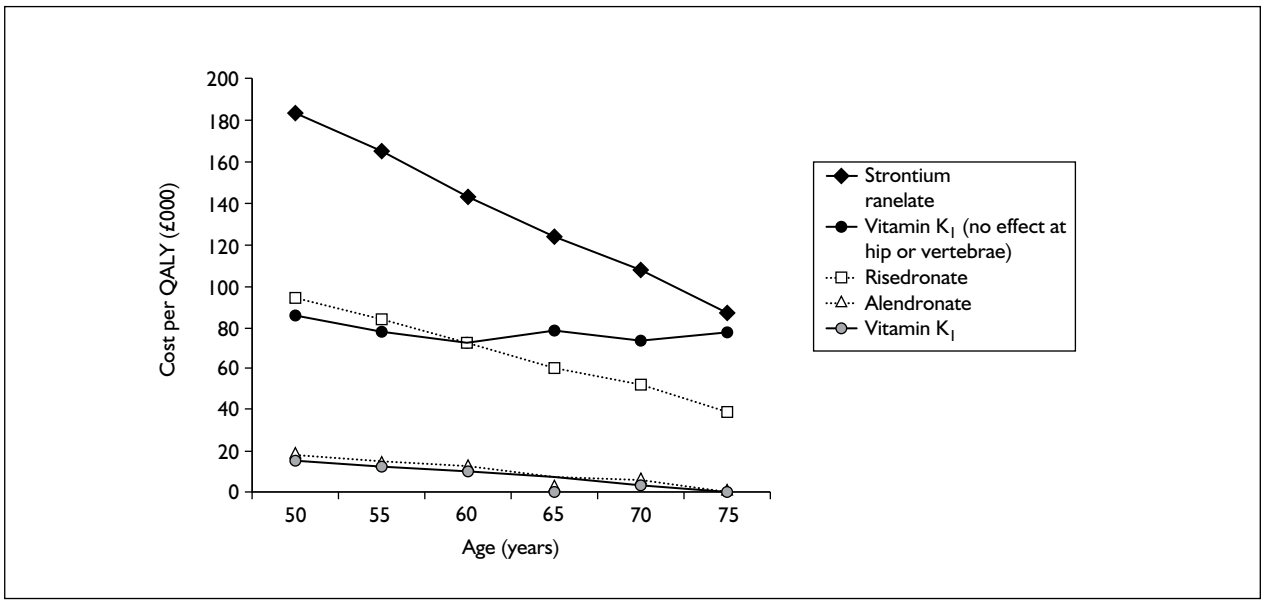

FIGURE 27 *The cost-effectiveness of osteoporosis interventions compared with no treatment in women with a T-score of –2.5 SD and without a previous fracture.*

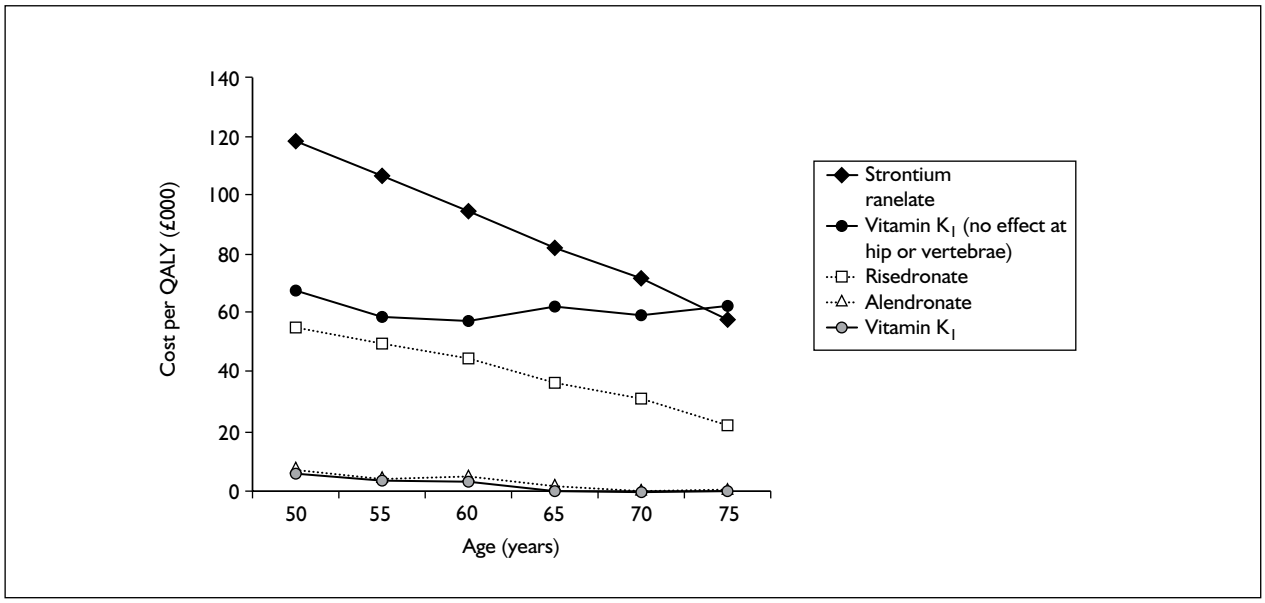

FIGURE 28 *The cost-effectiveness of osteoporosis interventions compared with no treatment in women with a* T*-score of –3.0 SD and without a previous fracture.*

been evaluated in only one RCT, the ECKO study,[71] in which there were less than 250 patients per arm, with the efficacy not detailed by fracture site. Although the small patient numbers are reflected in the wide confidence intervals, the low midpoint results in vitamin K_1 appearing to be the most cost-effective intervention. Were data to become available which showed that the efficacy at the hip and vertebrae were lower than that reported for all fractures (excluding fingers and toes), the cost-effectiveness results could substantially alter, as shown in *Figures 27–30*. Observational data from Denmark[32] found no association between dietary vitamin K_1 intake and fracture risk, although it should be noted that the reported dietary intakes (median 67 µg/day at baseline and 60 µg/day at year 5) were considerably lower than the 5-mg daily dose used in the ECKO study.

For this reason we have undertaken EVSI analyses to determine if an RCT of alendronate versus vitamin K_1 would represent an efficient use of

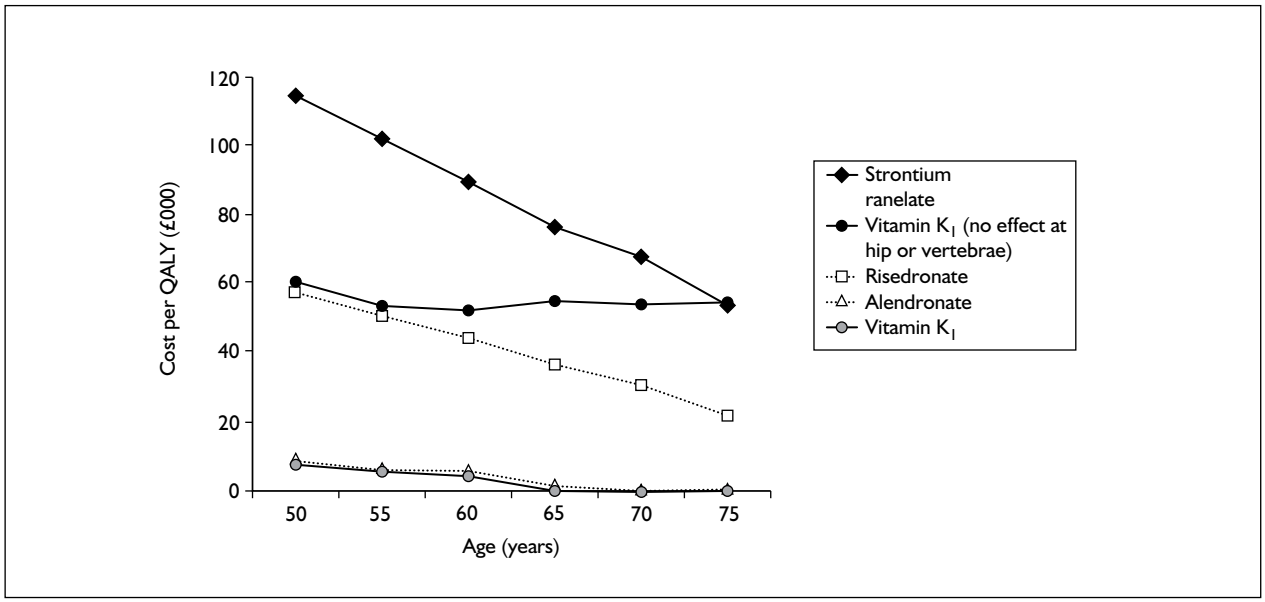

FIGURE 29 *The cost-effectiveness of osteoporosis interventions compared with no treatment in women with a* T*-score of –2.5 SD and with a previous fracture.*

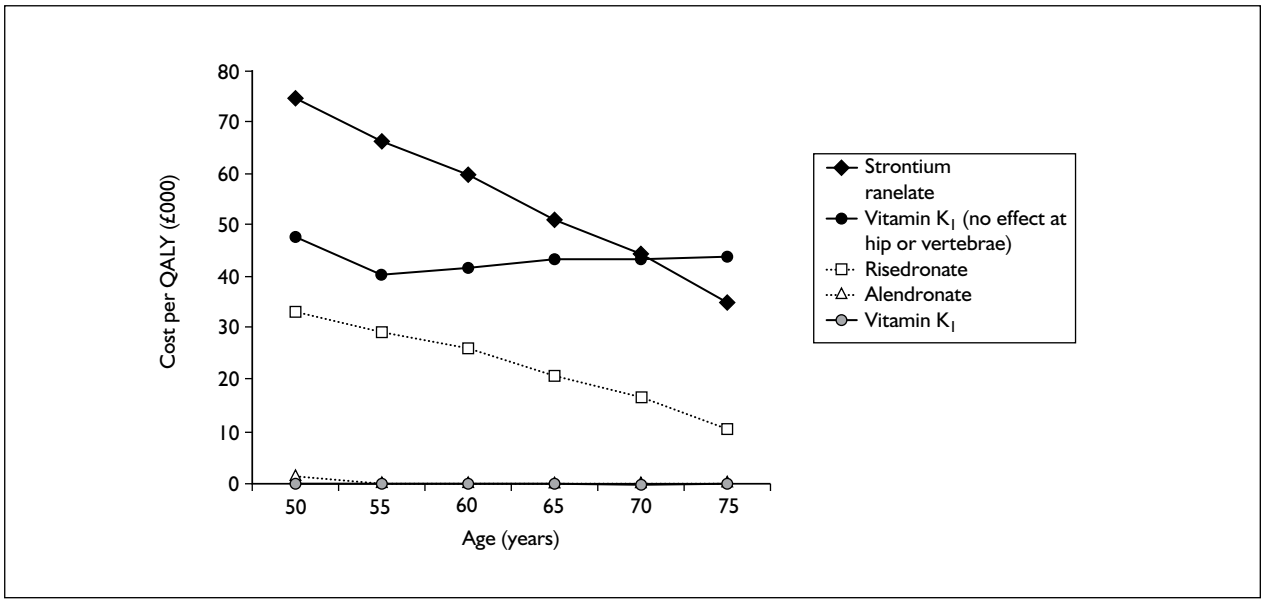

FIGURE 30 *The cost-effectiveness of osteoporosis interventions compared with no treatment in women with a* T*-score of –3.0 SD and with a previous fracture.*

resources, compared with a decision to prescribe all osteoporotic women with vitamin K_1.

Results of the EVSI analyses

Two scenarios were examined, which differed in the cost per QALY threshold used (£20,000 or £30,000). In all cases it was assumed that the efficacy data from the ECKO study[71] were applicable at all fracture sites. The results are presented graphically in *Figures 31* and *32*. In both figures the expected EVSI is given, which is seen to decline as the marginal addition of patients provides less information (i.e. moving from 1000 to 2000 patients per arm is expected to provide more benefit than moving from 9000 to 10,000 patients as at 9000 patients the uncertainty in the relative efficacies will have been substantially reduced). The costs of the trial are linear. The ENBS, which is the

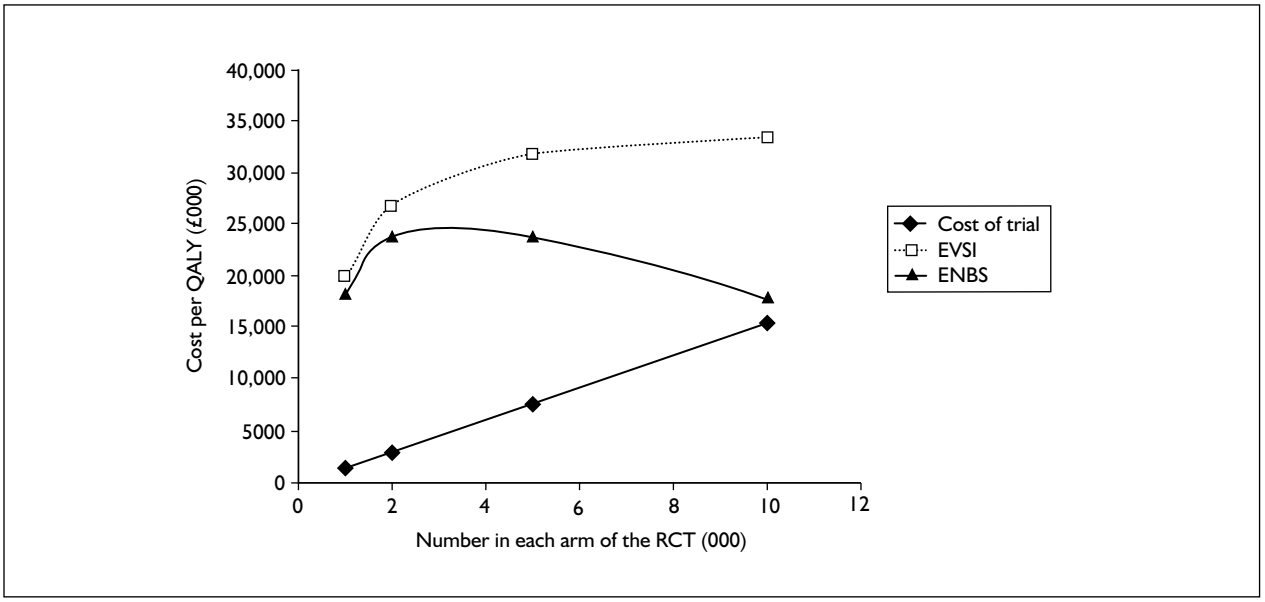

FIGURE 31 *The expected net benefit of sampling (ENBS) assuming a £20,000 cost per QALY threshold. EVSI, expected value of sample information.*

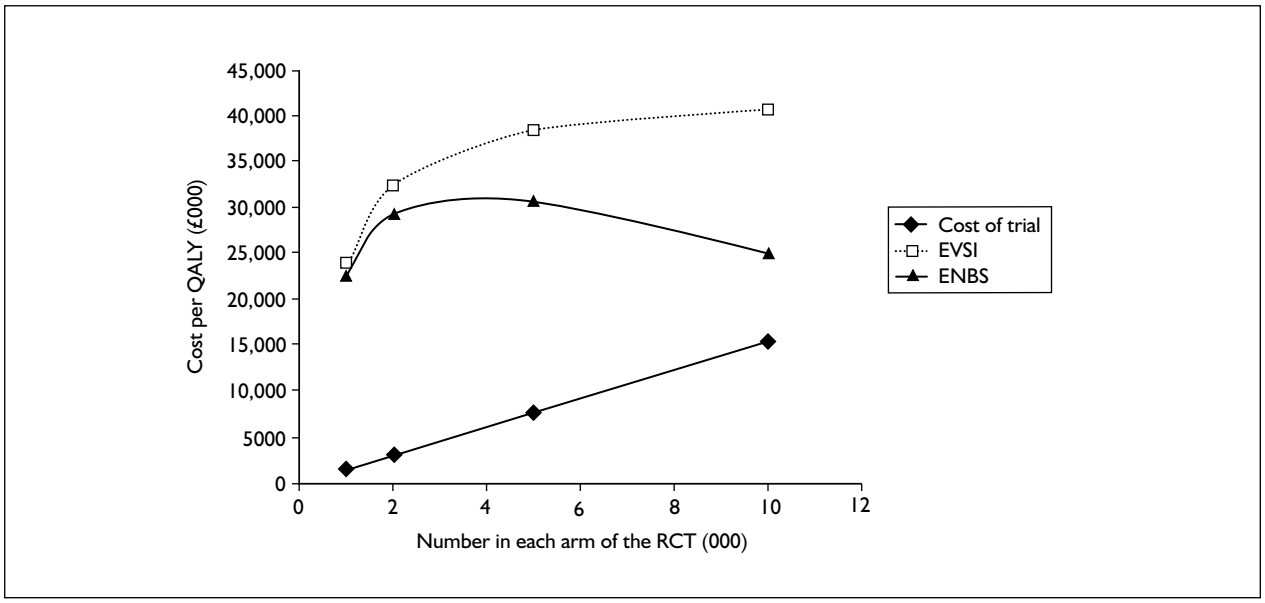

FIGURE 32 *The expected net benefit of sampling (ENBS) assuming a £30,000 cost per QALY threshold. EVSI, expected value of sample information.*

EVSI minus the costs of the trial, is curved, with the optimal number of patients per arm shown by the turning point. It is seen that in both scenarios an RCT of 2000 women per arm appears to be optimal.

Sensitivity analyses undertaken for the EVSI analyses

A number of sensitivity analyses were undertaken. Changing the number of patients who would benefit from the data collected to 1,000,000 rather than 500,000 resulted in the optimal trial size from among those evaluated becoming 5000 women per arm. However, there was little difference in the ENBS produced between trial sizes of 2000 women per arm and 5000 women per arm, with the average increase being 1%. If the number of women assumed to benefit was decreased to 250,000 then 2000 women per arm remained the optimal number from among those evaluated. Similarly, increasing the cost of recruiting a patient to a trial to £2000 did not change the conclusion that 2000 women per arm was optimal amongst those trial sizes evaluated.

When the assumed fracture risks were reduced to those of a 70-year-old woman without a previous fracture and with a *T*-score of –2.5 SD the optimal size OF study arm from among those evaluated remained at 2000 women at a cost per QALY threshold of £20,000, but rose to 5000 women at a cost per QALY threshold of £30,000. However, there was little difference in the ENBS produced between trial sizes of 2000 women per arm and 5000 women per arm, with the average increase being 2%.

When the risks were changed to those of a 70-year-old woman with a *T*-score of –3.5 SD and without a previous fracture, a trial size of 2000 patients per arm remained optimal amongst the trial sizes evaluated, for both scenarios. From the sensitivity analyses undertaken it appears that an RCT of 2000 patients per arm would continually provide data that were cost-effective to obtain.

Chapter 6
Discussion

Vitamin K_1 has the potential to be a cost-effective intervention for preventing osteoporotic fractures, as it is likely to have a relatively inexpensive acquisition cost and a low RR of fracture prevention. However, this conclusion is heavily dependent on the efficacy of the intervention at the hip and the spine. At present there has been only one RCT of vitamin K_1,[116] which has reported efficacy in the reduction of fractures as one group rather than at different sites. Analyses assuming that this efficacy is applicable at all sites indicate that vitamin K_1 would be the most cost-effective intervention. However, supplementary analyses that took an extreme position that vitamin K_1 had no effect on hip or vertebral fractures indicated that alendronate, the cheapest bisphosphonate, would be more cost-effective in this scenario. Data are urgently needed on the efficacy of vitamin K_1 at individual sites. It is noted that vitamin K_1 in the preparation used in the RCT is not currently available in the UK, although preparations at double this dose do exist. We have used the price of the higher-strength formulation but indicate that the price of 5 mg of vitamin K_1 is likely to be different to that used in this evaluation.

Expected value of sampling information has been conducted, which shows that an RCT comparing alendronate with vitamin K_1 and recruiting 2000 patients per arm would represent a cost-effective use of resources and would allow a more informed decision to be made over which drug, alendronate or vitamin K_1, is the more cost-effective. Although this analysis necessarily made assumptions regarding the likely efficacy of both drugs compared with no treatment the choice of 2000 women per arm consistently produced high ENBS. It has been assumed that clinicians and osteoporotic women are sufficiently in equipoise between the benefits of alendronate and vitamin K_1 to allow an RCT to be conducted, although it is recognised that some clinicians may have strong prevalent opinions on the relative merits of the two interventions. The authors note that the uncertainty in the efficacy of vitamin K_1, particularly in Western women, will not be resolved unless an RCT is undertaken, and that it would be ethically more appropriate to provide alendronate rather than placebo in the comparator arm.

The model constructed for this analysis differed from that used in recent NICE appraisals[4,5] (*Table 28*). However, comparison of the results produced by the two modelling approaches shows that the cost per QALY ratios are unlikely to be substantially changed by the alternative methodology; however, it is noted that the cost-effectiveness ratios produced in this report may be favourable to the intervention for younger women (50–60 years of age).

Our analysis has not tried to position interventions within a care pathway as this has been the focus of a recent NICE appraisal,[125] which has drawn on our earlier work[5] and considered the costs of identifying women who should receive BMD scans. However, alendronate (and vitamin K_1 when efficacy is assumed to be equal at all sites) has a cost per QALY of below £20,000 for all women aged 50 years and over who are osteoporotic, which implies that these treatments would normally be considered cost-effective.[106]

No formal evaluation of vitamin K_2 has been undertaken for a number of reasons. This intervention is currently not permitted as a food supplement in the EU because there is no evidence for its independent role in health[26] and the price of the intervention is unknown. Additionally, the fracture efficacy data have wide confidence intervals, all of which spanned unity, and the only large ($n > 1500$ patients per arm) RCT reported a RR of 1.01 for vitamin K_2 compared with calcium or no active intervention.

No evaluation of treating with a combination of alendronate alongside vitamin K_1 has been undertaken. If vitamin K_1 is shown to be efficacious in future RCTs then the cost-effectiveness of combination treatment is a subject for future research.

Chapter 7
Conclusions

It would not be prudent to recommend the position of vitamin K_1 within a treatment algorithm without further information. EVSI analyses have been undertaken and it is recommended that an RCT comparing alendronate and vitamin K_1 and recruiting 2000 women per arm would represent a cost-effective use of resources. The cost implications to the NHS of undertaking such a trial have been estimated to be in the region of £4 million.

Vitamin K_2 has not been evaluated as it is not licensed as a food supplement in the EU and there is no statistically significant evidence that this intervention is effective at reducing fractures.

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Contribution of authors

Dr Matt Stevenson (Senior Research Fellow) led the project and was responsible for constructing, running and interpreting the output from the mathematical model. Myfanwy Lloyd Jones (Senior Research Fellow) carried out the review of the clinical effectiveness of each intervention. Diana Papaioannou (Systematic Reviews Information Officer) undertook the electronic literature searches.

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Appendix 1

MEDLINE clinical effectiveness search strategy

1. exp osteoporosis/
2. Osteoporo$.tw.
3. Bone diseases, metabolic/
4. 1 or 2 or 3
5. (Bone adj6 densit$).tw.
6. Bone density/
7. (Bone or bones).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8. exp Densitometry/
9. Tomography, x-ray computed/
10. Densit$.tw.
11. 9 and 10
12. 8 or 11
13. 7 and 12
14. 4 or 5 or 6 or 13
15. exp Vitamin K/
16. vitamin k1.tw.
17. vitamin k 1.tw.
18. menaquinone$.tw.
19. phylloquinone$.tw.
20. phytomenadione$.tw.
21. phytonadione$.tw.
22. aquamephyton$.tw.
23. konakion$.tw.
24. phyllohydroquinone$.tw.
25. vitamin k2.tw.
26. vitamin k 2.tw.
27. menaquinone$.tw.
28. vitamin k quinone$.tw.
29. vitamin k3.tw.
30. vitamin k 3.tw.
31. vitamin k sodium bisulfite.tw.
32. menadione$.tw.
33. 2-methyl-1, 4-napthalenedione.tw.
34. 2-methyl-1, 4-napthoquinone$.tw.
35. menadione bisulfite$.tw.
36. menadione sodium bisulfite$.tw.
37. vicasol.tw.
38. vikasol.tw.
39. phytonadione.tw.
40. or/15–39
41. 14 and 40

Appendix 2

Randomised controlled trial data extraction form

Study and design	Data extraction	
Trial	**Review details**	
	Author, year	
Study design	Objective	
	Publication type (i.e. full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	Interventions	
	Focus of interventions (comparisons)	
	Description:	
	T1: Intervention group, dose, timings	
	T2: Control group, dose, timings	
	Intervention site (health-care setting, country)	
	Duration of intervention	
	Length of follow-up	
	Study characteristics	
	Method of randomisation:	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	
	Blinding level	
	Numbers included in the study	
	Numbers randomised	T1:
		T2:
	Population characteristics	
	Target population (describe)	
	Inclusion/exclusion criteria (*n*)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline:	
	Age (mean, years)	
	Years since menopause	
	Ethnicity	
	BMD at lumbar spine:	
	Mean (g/cm^2)	
	T-score	

continued

Study and design	Data extraction
	BMD at femoral neck:
	Mean (g/cm^2)
	T-score
	BMD of total hip:
	Mean (g/cm^2)
	T-score
	Prevalent vertebral fracture:
	No. of women
	Mean no. of fractures
	Previous osteoporosis-related non-vertebral fracture:
	No. of women
	Mean no. of fractures
	Other information
	Were intervention and control groups comparable?
	Outcomes
	Definition of primary outcomes
	Definition of secondary outcomes
	Definition of tertiary outcomes
	Definition of other outcomes
	Analysis
	Statistical techniques used
	Intention to treat analysis
	Does technique adjust for confounding?
	Power calculation (priori sample calculation)
	Attrition rates (overall rates), i.e. loss to follow-up
	Was attrition adequately dealt with?
	Number (%) followed-up from each condition
	Compliance with study treatment
	Adherence to study treatment
	Results
	Adverse events
	Other information
	Summary
	Authors' overall conclusions
	Reviewers' comments

Based on NHS CRD Report No. 4.[66]

Appendix 3

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

The major publication for each study is indicated with an asterisk.

ECKO study

1. Anon. Vitamin K supplementation in post-menopausal osteoporosis. URL: http://clinicaltrials.gov/ct/show/NCT00150969?order=1. Accessed 31 July 2007.

2. Cheung AM, Tile L, Lee Y, Hawker G, Thompson L, Vieth R, *et al.* Evaluation of the clinical use of vitamin K supplementation in postmenopausal women with osteopenia (the ECKO trial): study design and baseline data. *J Bone Miner Res* 2004;**19**(Suppl.):S450.

3. Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, Scher J, *et al.* Vitamin K supplementation in post-menopausal osteoporosis: the ECKO trial. Presented at ASBMR 29th Annual Meeting, 16–19 September 2007, Honolulu, HI. Abstract M399.

4. Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, Scher J, *et al.* Vitamin K supplementation in postmenopausal women with osteopenia: the ECKO trial. Poster presented to the American Society for Bone and Mineral Research, 2007. Abstract available at: www.abstractsonline.com/.

5. *Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, Scher J, *et al.* Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med* 2008;**5**:e196.

Iwamoto 2001

1. Iwamoto J, Takeda T, Ichimura S. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. *J Orthop Sci* 2001;**6**:487–92.

Osteoporosis Fracture (OF) study

1. *Eisai. *Eisai announces the intermediate analysis of anti-osteoporosis treatment post-marketing research to investigate the benefits of menatetrenone as part of the Ministry of Health, Labour and Welfare's Pharmacoepidemiological Drug Review Program*. 2005. URL: www.eisai.co.jp/enews/enews200506.html. Accessed 26 July 2007.

2. Anon. Randomized, open, parallel, active controlled study on fracture prevention in antiosteoporosis treatment (OF Study). 2005. URL: http://clinicaltrials.gov/ct/show/NCT00165607?order=3. Accessed 30 July 2007.

Shiraki

1. *Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res* 2000;**15**:515–21.

2. Shiraki M. Vitamin K2 effects on the risk of fractures and on lumbar bone mineral density in osteoporosis – a randomized prospective open-label 3-year study. *Osteoporos Int* 2002;**13**(Suppl.1):S160.

Yamaguchi Osteoporosis Prevention Study (YOPS)

1. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, vitamin D and vitamin K in postmenopausal osteoporosis. *Bone* 2003;**33**(5 Suppl.1):S220.

2. Ishida Y, Kawai S. A two-year randomized controlled trial of hormone replacement therapy, etidronate, calcitonin, vitamin D, or vitamin K, in women with postmenopausal osteoporosis. *J Bone Miner Res* 2000;**17**(Suppl.1):S478.

3. *Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: the Yamaguchi Osteoporosis Prevention Study. *Am J Med* 2004;**117**:549–55.

4. Ishida Y, Soh H, Ogawa S, Kawahara S, Murata H. A one-year randomized controlled trial of hormone replacement therapy, bisphosphonate, calcitonin, vitamin D, and vitamin K, in women with postmenopausal osteoporosis. *J Bone Miner Res* 2000;**15**:SA409.

5. Ishida Y, Soh H, Tsuchida M, Kawahara S, Murata H. Comparison of the effectiveness of hormone replacement therapy, bisphosphonate, calcitonin, vitamin D, and vitamin K in postmenopausal osteoporosis: a one-year prospective, randomized, controlled trial. *Bone* 2001;**28**:S224.

6. Ishida Y, Soh H, Tsuchida S, Kawahara S, Murata H. Randomized trial of the effectiveness of hormone replacement therapy, etidronate, calcitonin, vitamin D, and vitamin K in women with postmenopausal osteoporosis. *J Bone Miner Res* 2001;**16**(Suppl.1):S536.

7. Ishida Y, Soh H, Tsuchida S, Kawahara S, Murata H, Kawai S. Effectiveness of hormone replacement therapy, etidronate, calcitonin, vitamin D, and vitamin K in postmenopausal women with osteoporosis. *Bone* 2002;**30**(Suppl. 3):50S.

Appendix 4

References excluded from the review of clinical effectiveness after a full reading

Reference/study name	Reason for exclusion
Alper 2007[126]	Not primary research
Clouatre and Shastri 2004[127]	Not primary research
Ishida and Kawai 2003[128]	Although this abstract states that it reports the findings of one RCT, the first author has clarified that it in fact combines the data from three trials (one of which was YOPS)
Iwamoto *et al.* 1999[129]	Population of women not selected for low BMD
Iwamoto *et al.* 2000[130]	Does not report fracture outcomes
Kenney 2006[131]	Not primary research
Meunier 1999[132]	Review
NCT00165698[133]	Wrong comparator (alfacalcidol). Results not published although the study is said to have been completed in January 2007
Purwosunu *et al.* 2006[134]	Does not report fracture outcomes
Radecki 2005[135]	Not primary research
Rejnmark *et al.* 2005[136]	Cross-sectional study
Rejnmark *et al.* 2006[137]	Cross-sectional study
Shiraki 2006[138]	Population not said to be postmenopausal women; participants not said to be randomised to treatment groups

Appendix 5
Evidence tables

TABLE 30 *Summary of study characteristics: general information*

Study	Study site	Length of study	Primary outcome measure/s	Population	Mean age, years (range)	Intervention/dose	Comparison/s
Phylloquinone							
ECKO study[71]	Canada	2 years, with 2-year extension	Changes in BMD from baseline to 2 years	Postmenopausal women with osteopenia	59 (40–82)	Phylloquinone 5 mg/day	Identical-looking and -tasting placebo
Menatetrenone							
Iwamoto 2001[72]	Japan	2 years	Changes in BMD Incidence of vertebral fracture	Postmenopausal women with osteoporosis	65 (53–78)	Menatetrenone 45 mg/day	Etidronate 200 mg/day for the first 2 weeks of a 12-week cycle Calcium lactate 2 g/day
OF study 2005[75]	Japan	3 years	Incidence of vertebral fracture	Women aged ≥ 50 with primary osteoporosis	No data	Menatetrenone 45 mg/day[77] (Glakay capsules 15 mg) plus calcium (unspecified dose)	Calcium (unspecified dose)
Shiraki 2000,[73] 2002[74]	Japan	Initially 2 years. Extension study 3 years (mean follow-up in extension study 1.8 years)	Changes in BMD Incidence of vertebral fracture	Ambulatory women with primary osteoporosis	67 in the original study; 69 in the extension study	Menatetrenone 45 mg/day + elemental calcium (150 mg/day in the original study; 200 mg/day in the extension study)	Elemental calcium (150 mg/day in the original study; 200 mg/day in the extension study)
YOPS 2004[76]	Japan	2 years	Changes in BMD	Ambulatory postmenopausal women with osteoporosis	69 (50–75)[a]	Menatetrenone 45 mg/day	Etidronate 200 mg/day for the first 2 weeks of a 12-week cycle No treatment

a Interim publications variously report the age range as 45–75[139] and 46–96[140]

DOI: 10.3310/hta13450

TABLE 31 *Summary of study characteristics: inclusion and exclusion criteria, etc.*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Definition of incident vertebral fracture	Comments
Phylloquinone					
ECKO study[71]	Female; postmenopausal (at least 1 year after last menses); lowest *T*-score in lumbar spine, total hip or femoral neck between –1.0 and –2.0	Osteoporosis; fragility fracture after the age of 40 years; known metabolic bone disease; any bone medication use in last 3 months; any bisphosphonate use for more than 6 months; decompensated diseases of the liver, kidney, pancreas, lung or heart; history of active cancer in past 5 years; chronic oral steroid or warfarin use; taking high doses of vitamins A (> 10,000 IU/day) or E (> 400 IU/day)	The groups were comparable at baseline	Not applicable. Only clinical fractures were studied	All women had a dietary assessment for calcium and vitamin D intake and were given supplements to approximate to a total intake of 1500 mg of calcium and 800 IU of vitamin D per day
Menatetrenone					
Iwamoto 2001[72]	Female; at least 5 years after menopause; diagnosis of osteoporosis based on the Japanese criteria [i.e. either BMD at distal one-third radius 30% below mean for young adults (a *T*-score of –3.7) or BMD 20% below young adult mean (a *T*-score of –2.5) plus one or more vertebral fractures[141]]	History of HRT or medication that affects bone metabolism	The groups were comparable at baseline	A decrease of at least 20% in any vertical height ratio; or central/anterior or central/posterior height less than 0.8; or anterior/posterior height less than 0.75	All women had a dietary assessment for calcium and vitamin D intake and were strictly encouraged to consume 800 mg of calcium and 400 IU of vitamin D per day in their meals
OF study 2005[75]	Female; postmenopausal; age ≥ 50 years; primary osteoporosis according to the Japanese diagnostic criteria[81]	On warfarin therapy; hypercalcaemia or renal calculus; known history of hypersensitivity to calcium or menatetrenone preparations; severe complication in the hepatic, renal, gastrointestinal, cardiovascular or cerebrovascular system; bilateral ovariectomy; radiotherapy in the pelvis or para-aortic area; radiographic evidence of osteophytes connecting with adjacent vertebral osteophytes; hyperostosis of ligament around the vertebral body; interbody fusion; surgical intervention(s) in the spine, or scoliosis, that would hinder diagnosis of vertebral fracture; treatment with antiosteoporotic agents, other than calcium, within 8 months of study treatment (unless discontinued, non-treated or shifted to calcium monotherapy for ≥ 8 weeks before starting study treatment); previous bisphosphonate use; likely to show insufficient absorption of liposoluble agents, e.g. biliary atresia, impaired bile secretion, etc; other patients judged to be ineligible by the investigator/s[81]	No data	'Morphological transformation'[81]	

continued

TABLE 31 *Summary of study characteristics: inclusion and exclusion criteria, etc. (continued)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Definition of incident vertebral fracture	Comments
Shiraki 2000,[73] 2002[74]	Female; ambulatory; diagnosis of primary osteoporosis by Japanese criteria[141] (i.e. lumbar BMD < 70% of young adult mean, or one or more non-traumatic vertebral fractures and lumbar BMD < 80% of young adult mean); apparently postmenopausal although this is not specifically stated	Treatment for osteoporosis within 3 months of study entry; fractures in the L2–L4 region	In the original study the groups were broadly comparable at baseline. In the extension study they were said to be comparable but insufficient data were presented to enable this to be assessed	≥ 20% decline in any of the three vertebral heights compared with baseline	Participants were given no specific instructions regarding daily calcium, vitamin D and vitamin K intake, or exercise
YOPS 2004[76]	Female; age 50–75 years; at least 5 years since natural or surgical menopause; osteoporosis, defined as either BMD at distal one-third radius 30% below mean for young adults (a *T*-score of –3.7) or BMD 20% below young adult mean (a *T*-score of –2.5) plus one or more vertebral fractures	Recent history of cancer; metabolic bone disease other than osteoporosis; important abnormalities in routine laboratory tests; recent use of drugs known to affect bone; history of bilateral hip fractures; any physical or mental condition that would preclude participation	The groups were broadly comparable at baseline	Quantitative and semiquantitative. The quantitative assessment defined incident fracture as a decrease of at least 20% in any vertical height ratio in vertebrae intact at baseline, or at least 4 mm in vertebrae fractured at baseline. Radiographs were evaluated independently by two physicians; if the diagnosis of fracture was not unanimous, an independent radiologist adjudicated	Participants were allocated to one of six groups; only data from the three relevant groups are summarised here 26% of women in the no treatment group suffered at least one incident vertebral fracture over a 2-year period; this rate is high but is said by the authors to be consistent with other Japanese findings

TABLE 32 *Summary of study characteristics: key aspects of methodological quality*

Study	Appropriate method of random-isation?	Appropriate concealment of study allocation?	Groups comparable at study entry?	Appropriate diagnosis of non-vertebral fracture?	Appropriate diagnosis of vertebral fracture?	Fracture outcome assessors blinded to treatment allocation?	No. of subjects randomised to study	% Completing study protocol	Reasons for withdrawal stated?	Source of funding
Phylloquinone										
ECKO study[71]	Yes; study pills labelled and dispensed by research pharmacy in blocks of 10 according to a computer-generated random number table	Yes, by research pharmacy; placebo pills looked and tasted identical to active treatment	Yes	Yes; reported clinical fractures were confirmed by radiography or radiological reports by two independent investigators; a third investigator resolved any differences	Not applicable	Yes	440	91% (400/440) to 2 years. 74% (325/440) were eligible to enter the 2-year extension and 59% (261/440) did so. Only 17% (73/440) completed the full 4 years; this was because the study terminated before 39% (172/440) had the opportunity to do so	Yes	Various, mainly government or charities (including the Wyeth Foundation). Vitamin K_1 provided by Roche Vitamins
Menatetrenone										
Iwamoto 2001[72]	Not clear	Not clear	Yes	Not applicable	Yes	Not clear	72	Not stated	No withdrawals reported	Not specified
OF study 2005[75]	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	4378	Not stated; 3257 (74%) included in analysis of incident vertebral fracture	No	Not specified

continued

TABLE 32 *Summary of study characteristics: key aspects of methodological quality (continued)*

Study	Appropriate method of random-isation?	Appropriate concealment of study allocation?	Groups comparable at study entry?	Appropriate diagnosis of non-vertebral fracture?	Appropriate diagnosis of vertebral fracture?	Fracture outcome assessors blinded to treatment allocation?	No. of subjects randomised to study	% Completing study protocol	Reasons for withdrawal stated?	Source of funding
Shiraki 2000,[73] 2002[74]	Not clear	Not clear	Broadly in the original study. Said to be comparable in the extension study but details not presented	Not clear	Yes	Yes	241 in the original study; 362 in the extension study	89% (215/241) in the original study in relation to the BMD analysis, and 79% (190/241) in relation to the fracture analysis. Not stated in the extension study	No	Not specified
YOPS 2004[76]	Not clear. Modified minimisation method used with two balancing factors: age and baseline prevalence of vertebral fracture	Not clear	Yes	Not clear	Yes	Yes	396 of whom 198 received treatments relevant to this review	94% (372/396) overall 93% (185/198) of those receiving treatments relevant to this review	Yes	Not specified

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TABLE 33 *Vitamin K: toxicity*

Study	Number of participants reporting adverse events	Withdrawal/discontinuation of study medication because of adverse events
Phylloquinone		
ECKO study[71]	During the first 2 years of the study, 384/440 women (87.3%) reported one or more adverse events; there were said to be no significant differences between groups. 11/217 (5.1%) women on phylloquinone and 10/223 (4.5%) on placebo reported nausea and vomiting ($p = 0.77$) During the extension study, 91/126 (72.2%) women on phylloquinone and 97/144 (67.4%) on placebo reported one or more adverse event ($p = 0.46$)	Withdrawn during first 2 years or ineligible for 2-year extension: phylloquinone: 3/217 (1 breast cancer, 2 thyroid cancer); placebo: 7/223 (3 breast cancer, 1 endometrial cancer, 1 thyroid cancer, 1 vaginal cancer, 1 oesophageal cancer) 2-year extension: phylloquinone: 1/121 (heart failure); placebo: 3/140 (2 breast cancer, 1 uterine cancer)
Menatetrenone		
Iwamoto 2001[72]	None	None
OF study 2005[75]	Not stated. The overall incidence of adverse events was 10.1 per 100 person-years, and the incidence of adverse drug reactions was 3.6 per 100 person-years Incidence of skin and skin appendage lesions per 100 patient-years: menatetrenone: 0.5; control: 0.1 ($p < 0.001$)	Not stated
Shiraki 2000,[73] 2002[74]	Not reported	Not reported
YOPS 2004[76]	None	None

Appendix 6

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

The initial individual patient model runs 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 to correct for this error.

To adjust for this factor, an estimation of the QALYs that could be gained by the prevention of mortality at each age was made. Calculations were only needed from the end of the 10-year modelling horizon as 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. It was assumed that any increase in mortality rate due to low bone mass would continue until death or an age of 110 years.

As the final utility value 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 utility equal to that of the general population as reported by Kind *et al.*[113] QALYs were discounted at 1.5% per annum, starting from the time of intervention, so that the results were consistent with those produced by the individual patient model.

Using these assumptions it was estimated that an average patient alive at the end of the model would accrue QALYs as given in *Table 34*.

TABLE 34 *The expected lifetime QALYs for women alive at the end of the model*

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

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

For example, the expected hip fracture rate at age 60 years for healthy women at the threshold of osteoporosis is estimated to be 0.1%. For women with severe osteoporosis it is assumed that this risk can be doubled in accordance with data reported by Klotzbuecher *et al.*[93] This would equate to an estimate of the hip fracture rate of 0.2% per annum, or 1.0% over a 5-year treatment period, assuming no additional mortality, which is one hip fracture for a cohort of 100 women.

The mortality rate following hip fracture is estimated to be 6% at age 60 years (*Table 21*), resulting in an estimated maximum of 0.06 hip fractures that were preventable over the intervention period. The number that were preventable is assumed to be equal to the sampled RR for each treatment; thus, if a RR of hip fracture of 0.5 was estimated then it was assumed that 0.03 deaths associated with hip fractures would be saved. When the RR was greater than 1, the model assumed that an additional number of deaths would occur and subtracted the expected QALYs from that estimated for the intervention.

The expected numbers of additional QALYs for women with severe osteoporosis suffering death from hip fracture are given in *Table 35*.

An alternative methodology had to be employed for deaths assumed to be associated with vertebral fractures because unlike mortalities associated with hip fracture these were not explicitly calculated within the 10-year time horizon.

It was assumed that all deaths from vertebral fracture would happen in year 3, the midpoint

TABLE 35 *The maximum number of QALYs gained per 100 women at the threshold of osteoporosis from preventing hip fracture and subsequent mortality*

Age (years)	Maximum QALYs gained per 100 women
50	0.174
60	0.398
70	0.832
80	0.807

of the treatment period. A 66% increase in the mortality rate in the year of a vertebral fracture was assumed, as reported by Center *et al.*[101] 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 36*.

TABLE 36 *The maximum number of QALYs gained per 100 women at the threshold of osteoporosis from preventing vertebral fracture and subsequent mortality*

Age (years)	Maximum QALYs gained per 100 women
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 proportional to the RR of the treatment. Hence, a treatment with a RR of 0.5 for vertebral fracture would be assumed to prevent 50% of the mortalities from vertebral fracture.

A similar methodology has been used for mortality associated with fractures of the proximal humerus. The maximum number of QALYs lost because of proximal humerus fracture and assumed to be preventable are shown in *Table 37*.

TABLE 37 *The maximum number of QALYs gained per 100 women at the threshold of osteoporosis from preventing proximal humerus fracture and subsequent mortality*

Age (years)	Maximum QALYs gained per 100 women
50	0.007
60	0.023
70	0.048
80	0.047

Appendix 7

Calculating the risk of fracture for women with a *Z*-score of 0 and no previous fracture

An estimate of the fracture risk for women with average BMD and no previous fracture has been calculated assuming that there are three sets of patient type at each age: women with a *T*-score of –2.5 SD or less with a previous fracture (group A), women with a *T*-score of –2.5 SD or less without a previous fracture (group B) and women with an average BMD and without previous fracture (group C).

The *T*-score values of the average female population and of those that are osteoporotic are provided in *Table 38*.

It is assumed that a previous fracture will increase the risk of subsequent fractures (at all sites) twofold compared with group C. The increased risk due to a woman being osteoporotic will be calculated from the data in *Table 38* and *Tables 17* and *18* of the main report. An example of how to calculate the RRs for hip fracture in groups A and B is provided for women aged 70–74 years.

At 70–74 years of age the average *T*-score is –1.69 SD and the decrease in *Z*-score to those who are osteoporotic is 1.31 (*Table 38*). This will equate to an increased risk of hip fracture in group B of $2.78^{1.31} = 3.82$ (see *Table 18*).

The RR of women in group A is assumed to be double that of group B, i.e. $2 \times 2.78^{1.31} = 7.63$.

The calculated RRs of groups A and B, by age and fracture site, are given in *Table 39*.

To estimate the risk of fracture within group C the percentages of patients suffering osteoporosis and severe osteoporosis must be estimated. Data on the percentage of women who are osteoporotic (including severe) at each age have been calculated from the average BMD, assuming that BMD is normally distributed and has a SD of 1. Estimates of the percentage of women with severe osteoporosis at each age have been calculated using data from Kanis *et al.*,[142] which indicate that the percentages of all fractures that are first fractures are approximately 90% below the age of 70 years and 80% above the age of 70 years. Assuming these figures to be applicable in the UK the percentage of the population with severe osteoporosis can be estimated from the incidence of fracture since age 50 years[142] and expected mortality rates,[35] assuming that all fractures at the hip, spine, wrist or proximal humerus were caused by osteoporosis. The estimated proportions of the female population with osteoporosis and severe osteoporosis are given in *Table 40* (calculations not shown).

At 70 years of age it is expected that 15.6% of women will have severe osteoporosis and 5.3% will have osteoporosis; 79.1% of women will not be osteoporotic (*Table 40*).

TABLE 38 *The T-score values of the average female population and of those that are osteoporotic*

Age (years)	Average UK *T*-score, Holt *et al.*[17a]	Average *T*-score for patients with a *T*-score of –2.5 SD or less, calculated from Holt *et al.*[17a]	The fall in *Z*-score between those women who are osteoporotic and those with average BMD
50–54	–0.66	–2.82	2.16
55–59	–0.92	–2.72	1.80
60–64	–1.17	–2.78	1.61
65–69	–1.43	–2.84	1.41
70–74	–1.69	–3.00	1.31
75–79	–1.94	–2.97	1.03

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

TABLE 39 *The relative risk of fracture for osteoporotic women with or without a previous fracture*

Age (years)	Hip		Vertebral		Wrist		Proximal humerus	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
50–54	33.36	16.68	7.12	3.56	4.14	2.07	5.52	2.76
55–59	17.62	8.81	5.76	2.88	3.66	1.83	4.66	2.33
60–64	12.17	6.09	5.15	2.58	3.44	1.72	4.26	2.13
65–69	8.93	4.47	4.58	2.29	3.21	1.61	3.88	1.94
70–74	7.63	3.82	4.32	2.16	3.11	1.55	3.70	1.85
75–79	5.31	2.65	3.66	1.83	2.83	1.41	3.25	1.62

TABLE 40 *The assumed proportion of women with osteoporosis by age*

Age (years)	Population of women with osteoporosis (including severe)	Population of women with severe osteoporosis
50–54	3.29%	0.49%
55–59	5.71%	2.40%
60–64	9.18%	5.28%
65–69	14.23%	9.46%
70–74	20.90%	15.60%
75–79	28.77%	22.40%

The average incidence of hip fracture (ignoring fractures at the pelvis and other femoral fractures) at age 70–74 years is estimated to be 0.38% per annum (*Table 2*).

This will comprise:

> Percentage in group A×RR group A×group C risk + percentage in Group B×RR group B×group C risk + percentage in group C×group C risk

which equates to:

> 15.6%×7.63×group C risk + 5.3%×3.82×group C risk + 79.1%×group C risk = 218%×group C risk

As 218%×group C risk equals the average incidence of 0.38% per annum, the risk in group C must equal 0.38%/2.18 = 0.18%. The risks in group A and group B will be 0.18%×7.63 and 0.18%×3.82, respectively, which correspond to 1.34% and 0.67%, respectively, per annum.

The risk for a woman aged 70–74 years can now be estimated at any *T*-score. Thus, at the threshold of osteoporosis, the *Z*-score decrease is 0.81 (see *Table 1*) and the risk of a hip fracture will be $0.18\% \times 2.78^{0.81} = 0.40\%$ per annum.

When fractures at the pelvis and other femoral fractures are considered the fracture risk is increased by 20% (see *Table 14*), which would increase the risk of fracture to 0.48% per annum.

This methodology was repeated for all fracture sites and all ages. Sensitivity analyses previously conducted[4] showed that the average risk for a healthy woman did not change markedly with small changes in the percentages of patients with severe osteoporosis.

Appendix 8

Systematic searching for evidence relating to Vitamin K and adverse effects in osteoporotic patients

An electronic search of MEDLINE was conducted in January 2008. This sought to identify studies of any type that dealt with the adverse effects associated with the administration of any type of supplementary vitamin K to adults with primary osteoporosis or osteopenia. The following search strategy was used:

1. (ae or po or to or co or de).fs.
2. adverse event$.tw.
3. adverse effect$.tw.
4. side effect$.tw.
5. safe$.tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Vitamin K/
8. vitamin k1.tw.
9. vitamin k 1.tw.
10. menaquinone$.tw.
11. phylloquinone$.tw.
12. phytomenadione$.tw.
13. phytonadione$.tw.
14. aquamephyton$.tw.
15. konakion$.tw.
16. phyllohydroquinone$.tw.
17. vitamin k2.tw.
18. vitamin k 2.tw.
19. vitamin k quinone$.tw.
20. vitamin k3.tw.
21. vitamin k 3.tw.
22. vitamin k sodium bisulfite.tw.
23. menadione$.tw.
24. 2-methyl-1, 4-napthalenedione.tw.
25. 2-methyl-1, 4-napthoquinone$.tw.
26. menadione bisulfite$.tw.
27. menadione sodium bisulfite$.tw.
28. vicasol.tw.
29. vikasol.tw.
30. phytonadione.tw.
31. or/7–30
32. 6 and 31
33. exp osteoporosis/
34. Osteoporo$.tw.
35. Bone diseases, metabolic/
36. 33 or 34 or 35
37. (Bone adj6 densit$).tw.
38. Bone density/
39. (Bone or bones).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40. exp Densitometry/
41. Tomography, x-ray computed/
42. Densit$.tw.
43. 41 and 42
44. 40 or 43
45. 39 and 44
46. 36 or 37 or 38 or 45
47. 32 and 46

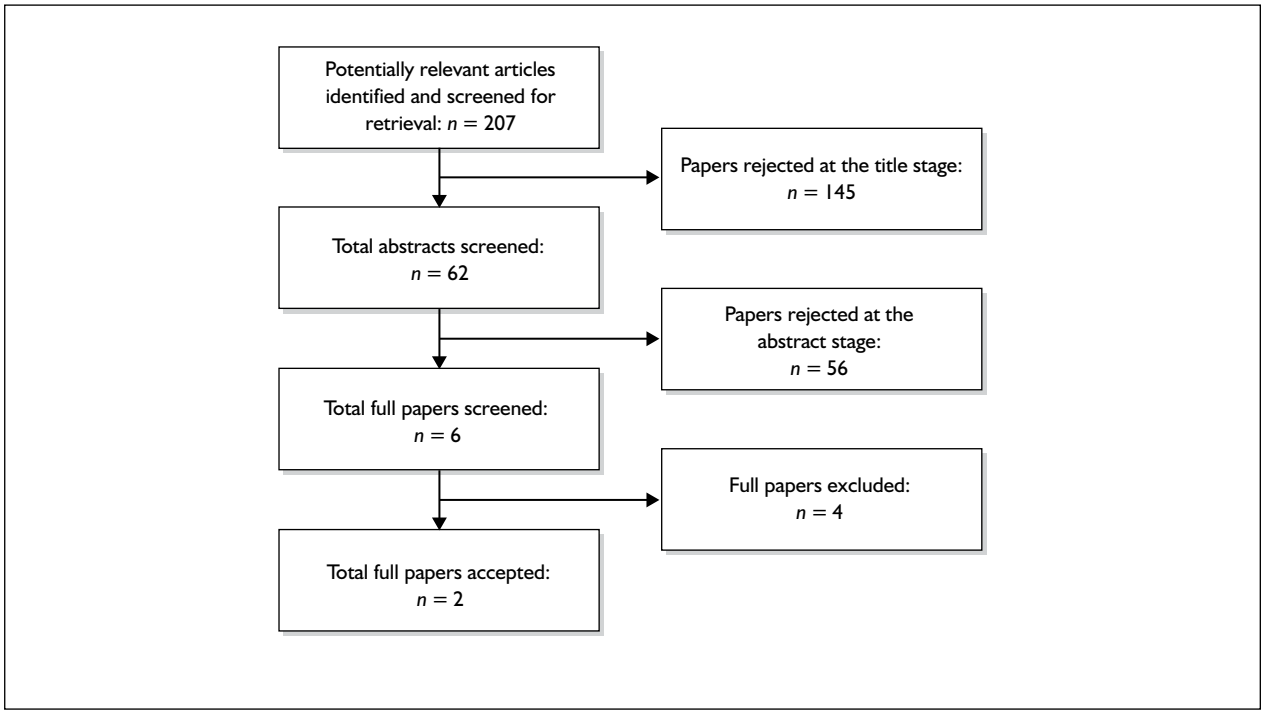

FIGURE 33 *Adverse effects: summary of study selection and exclusion – electronic literature searches.*

Appendix 9

Strontium ranelate for the prevention of osteoporotic fracture in postmenopausal women

A systematic review of the clinical effectiveness of strontium ranelate for the prevention of osteoporotic fracture in postmenopausal women was carried out on behalf of NICE in 2005.[4] Three studies that compared strontium ranelate with placebo met the review's inclusion criteria. These were:

- the STRATOS study,[143] a randomised, multicentre, double-blind, 2-year phase II dose-ranging study whose aim was to identify the smallest dose of strontium ranelate that was effective in treating postmenopausal vertebral osteoporosis, using BMD of the lumbar spine adjusted for bone strontium content as the primary end point
- the SOTI study,[144] a randomised, multicentre, double-blind, phase III study designed to evaluate the efficacy of strontium ranelate against vertebral fracture in postmenopausal women with osteoporosis and a history of vertebral fracture (although only 86.9% of the study population actually had prevalent vertebral fractures[145])
- the TROPOS study,[146] a randomised, multicentre, double-blind, phase III study designed to assess the efficacy of strontium ranelate in reducing the incidence of osteoporosis-related non-vertebral fractures in postmenopausal women with osteoporosis with or without fracture.

At that time, only 3-year data were available for the SOTI and TROPOS studies.

In August 2008, the search strategy used for the previous review was rerun in MEDLINE. No new trials were identified, but four publications were identified that presented new data from two of the three studies previously identified:

- 5-year results from the TROPOS study[147]
- quality of life data from the SOTI study[148]
- 4-year vertebral fracture data from the SOTI study (presented in a review article[149])
- fracture data from the TROPOS study (included in a Cochrane review[150]).

Marquis *et al.*,[148] in their article on quality of life data from the SOTI study, variously describe SOTI as a 5-year and a 3-year study, and Roux[149] included in his review 4-year data from the SOTI study. However, Roux did not reference the source of those data and we have been unable to identify any publication relating specifically to the SOTI study that presents data relating to efficacy at 4 or 5 years.

The additional data from the publications listed above have been incorporated into our earlier assessments of clinical effectiveness and the results relating to the licensed 2-g daily dose of strontium ranelate are summarised in the following sections.

Strontium ranelate: fracture data

Vertebral fracture

All three studies reported only those fractures that occurred in previously intact vertebrae. In the TROPOS study,[146] vertebral radiographs were not mandatory; although they were taken in as many patients as possible, baseline and follow-up radiographs were available for only 71% of the study population.

Meta-analysis of the 3-year fracture data from the SOTI and TROPOS studies found a RR of radiographic fracture over that period of 0.63 (95% CI 0.56 to 0.71) (*Figure 34*). It was not possible to include in the meta-analysis the results of the STRATOS study or the 5-year data from the TROPOS study because of the way that the data were published. However, the 5-year RR calculated by the authors for the TROPOS study (0.76, 95% CI 0.65 to 0.88) is not inconsistent with the 3-year results, although the point estimate is rather less favourable to strontium ranelate.

TABLE 41 *Strontium ranelate: vertebral fracture data*

Study	Fracture definition	Number in each group suffering vertebral fracture	Number needed to treat for a given period to avoid an event (95% CI)
STRATOS[143]	A decrease of at least 20% in one of the ratios of vertebral height	Radiographic fracture, 2 years: SR: 42.0%; placebo: 54.7% RR (calculated by study investigators): 0.77 (95% CI 0.54 to 1.09)	Not calculable
SOTI[144]	Semiquantitative (method of Genant *et al.*[53])	Radiographic fracture, 3 years: SR: 139/719 (19.3%); placebo: 222/723[a] (30.7%); RR 0.63 (95% CI 0.52 to 0.76), $p < 0.0001$ Clinical fracture, 3 years: SR: 75/719 (10.4%); placebo: 117/723[a] (16.2%); RR 0.64 (95% CI 0.49 to 0.85), $p < 0.001$ Unspecified fracture, 4 years (author's calculation):[149] RR 0.67 (95% CI 0.53 to 0.81), $p < 0.001$	Radiographic fracture, 3 years: 9 (6 to 14) Clinical fracture, 3 years: 18 (11 to 44) Unspecified fracture, 4 years: not calculable
TROPOS[146]	Semiquantitative (method of Genant *et al.*[53])	3 years:[150] SR: 202/1817 (11.1%); placebo: 321/1823 (17.6%); RR 0.63 (95% CI 0.54 to 0.74) 5 years:[147] SR: 307/? (20.8%); placebo: 384/? (24.9%); RR 0.76 (95% CI 0.65 to 0.88), $p < 0.001$	3 years: 16 (11 to 24) 5 years: not calculable

SR, strontium ranelate.
a PJ Meunier, Hôpital Edouard Herriot, Lyon, 11 March 2005, personal communication.

The pooled data from the SOTI and TROPOS studies suggest that it would be necessary to treat 13 women for 3 years to avoid a radiographic vertebral fracture (95% CI 10 to17). However, because the number needed to treat is related to the absolute rather than the relative risk of fracture, the number needed to treat for 3 years is noticeably lower in the SOTI study than in the TROPOS study (9 versus 16), even though the relative risk of fracture is very similar in both studies. This is because the absolute risk of a fracture is higher in the SOTI study, which set out to recruit only participants with osteoporosis with previous fracture; the 3-year radiographic fracture rate in the placebo group in the SOTI study is 30.7%, whereas in the TROPOS study, which recruited participants with osteoporosis with or without previous fracture, it is 17.6% (*Table 41*).

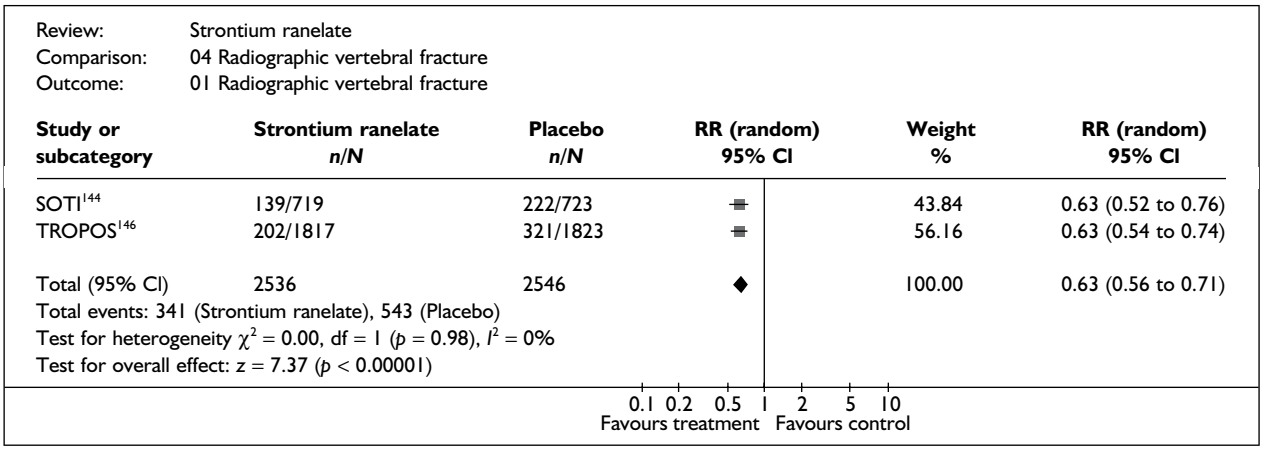

FIGURE 34 *Strontium ranelate: incident radiographic vertebral fracture.*

TABLE 42 *Strontium ranelate: all non-vertebral fractures*

Study	Number in each group suffering non-vertebral fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS[143]	SR 2 g: 9.2%; placebo: 7.7% As the number of women in each group was not stated, it was not possible to calculate the RR, nor was this reported by the study investigators	Not calculable
SOTI[144]	All non-vertebral fractures: SR: 112/826; placebo: 122/814; RR 0.90 (95% CI 0.71 to 1.15), $p = 0.41$	71[a]
TROPOS[146]	3 years:[146] SR: 233/2479; placebo: 276/2453; RR 0.84 (95% CI 0.71–0.99) 5 years:[147] SR: 312/2479; placebo: 359/2456; RR 0.86 (95% CI 0.75 to 0.99), $p = 0.04$	3 years: 54 (28–647) 5 years: 50 (25–839)

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

Non-vertebral fracture

All three studies reported non-vertebral fractures, although only the SOTI and TROPOS studies presented the data in such a way as to enable them to be included in a meta-analysis (*Table 42*). Meta-analysis of the 3-year data from these studies indicated that strontium ranelate was associated with a RR of any non-vertebral fracture of 0.86 (95% CI 0.75 to 0.98, $p = 0.03$) (*Figure 35*), with the number needed to treat for 3 years to avoid an event being 58 (95% CI 31 to 471).

Hip, wrist and other non-vertebral fractures

None of the studies was powered to identify a statistically significant difference in the incidence of fracture at any specific peripheral fracture site, and none reported a significant reduction in hip or wrist fracture in relation to its full intention to treat population (*Tables 43* and *44*).

Adverse effects

In the STRATOS, SOTI and TROPOS studies, a 2-g daily dose of strontium ranelate was not associated with a statistically significant increase in all-cause mortality (RR 0.99, 95% CI 0.64 to 1.53).[150] 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, and deaths that could be related to thrombosis/embolism (including pulmonary embolism, cerebrovascular accident and intestinal infarction) were also more common in patients receiving active treatment.[151] The 2-g dose of strontium ranelate was not associated with a statistically significant increase in serious adverse

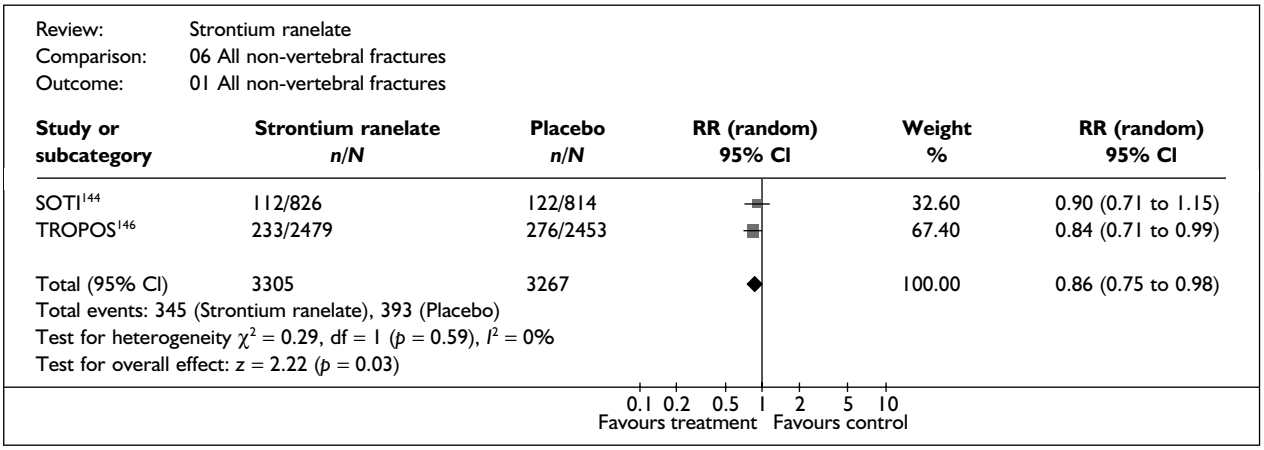

FIGURE 35 *Strontium ranelate: all incident non-vertebral fractures.*

TABLE 43 *Strontium ranelate in postmenopausal osteoporosis or osteopenia: hip fracture data*

Study	Number of women in each group suffering hip fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS[143]	Not reported	–
SOTI[144]	Not reported	–
TROPOS[147]	3-year data (actual numbers not reported):[150] RR 0.85 (95% CI 0.61 to 1.19) 5-year data:[147] SR: 88/2479; placebo: 98/2456; RR 0.89 (95% CI 0.67 to 1.18)	3 years: not calculable 5 years: 228[a]

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

TABLE 44 *Strontium ranelate in postmenopausal osteoporosis or osteopenia: wrist fracture data*

Study	Number of women in each group suffering wrist fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS[143]	Not reported	–
SOTI[144]	Not reported	–
TROPOS[147]	5-year data:[147] SR: 86/2479; placebo: 87/2456; RR 0.98 (95% CI 0.73 to 1.31), $p = 0.89$	1367[a]

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

TABLE 45 *Strontium ranelate in postmenopausal osteoporosis or osteopenia: humerus fracture data*

Study	Number of women in each group suffering humerus fracture	Number needed to treat for 3 years to avoid an event (95% CI)
STRATOS[143]	Not reported	–
SOTI[144]	Not reported	–
TROPOS[147]	5-year data:[147] SR: 26/2479; placebo: 43/2456; RR 0.60 (95% CI 0.37–0.97), $p = 0.04$	143 (74–2157)

events (RR 1.01, 95% CI 0.92 to 1.09), although it was associated with an increased risk of diarrhoea (RR 1.38, 95% CI 1.02 to 1.87).[150] Patients in the SOTI and TROPOS studies who discontinued study therapy because of adverse events did so mainly because of nausea, but diarrhoea was also associated with a statistically significant increase in the likelihood of discontinuing therapy.[151]

Postmarketing surveillance has identified isolated cases of hypersensitivity syndrome. This syndrome is very rare (16 cases in 570,000 patient-years of treatment) and typically occurs within 2–6 weeks of initiating therapy, generally resolving upon discontinuation. However, it is potentially fatal.[149]

Quality of life

The SOTI and TROPOS studies both recorded health-related quality of life every 6 months using the Short-Form 36 (SF-36) health questionnaire; the SOTI study also used the QUALIOST questionnaire.[152] No quality of life results have been published for the TROPOS study. In the SOTI study strontium ranelate therapy was associated with a slight improvement and placebo with a slight deterioration in quality of life as assessed by the QUALIOST specific scale; the difference between the groups, although small, was statistically significant. No significant differences were seen between the strontium ranelate and placebo groups on the SF-36 before imputation of missing data,

TABLE 46 *Compliance with study treatment*

Study	Definition of compliance	How measured	Compliance
STRATOS[143]	Not given	Unused tablets returned at study visits Drug concentrations	Mean global compliance: 93 ± 13%; said to be no relevant differences between groups
SOTI[144]	Not given	Not reported	Number compliant in each group: strontium ranelate: 83%; placebo: 85%
TROPOS[147]	Percentage of sachets of study medication given to the patient that were actually taken	Unused sachets of study medication returned at each 6-monthly visit	Global compliance: 81.6%

TABLE 47 *Proportion of participants completing study*

Study	Proportion of participants completing study protocol
STRATOS[143]	Proportion of participants completing study protocol (2 years): SR 0.5 g: 77%; SR 1 g: 73%; SR 2 g: 77%; placebo: 81%
SOTI[144]	Proportion of participants completing follow-up at 3 years: SR 2 g: 76%; placebo: 77%
TROPOS[146]	Proportion of participants completing follow-up at 3 years: SR 2 g: 66%; placebo: 64% Proportion of participants completing follow-up at 5 years:[147] SR 2 g: 1384/2554 (54%); placebo: 1330/2537 (52%) Mean duration of exposure to randomised treatment:[147] 1126 ± 668 days

and after imputation of missing data only the general health perception score was significantly better in the strontium ranelate group than in the placebo group. Strontium ranelate was also associated with a 31% reduction relative to placebo in the number of patients reporting back pain ($p = 0.023$).[148]

Continuance and compliance

All three studies presented data relating to compliance (*Table 46*).

All three studies provided information on the proportion of participants who completed follow-up (see *Table 47*). Although 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 what proportion of participants who completed follow-up in the SOTI and TROPOS studies were still taking the study medication at the end of the study period. However, the publication of the 5-year TROPOS data[147] gives the mean overall length of exposure to study medication, slightly over 3 years (*Table 47*). In total, 19% of participants were said to have discontinued study medication or withdrawn from the study because of adverse events, 21% for non-medical reasons, 0.2% because of protocol deviations and 0.3% because of aggravated osteoporosis.[147]

Appendix 10

The second-generation bisphosphonates alendronate and risedronate for the prevention of osteoporotic fracture in postmenopausal women

A systematic review of the clinical effectiveness of the second-generation bisphosphonates alendronate and risedronate for the prevention of osteoporotic fragility fractures in postmenopausal women was undertaken in 2007 on behalf of the NCCHTA. This review updated that carried out for NICE in 2003.[2]

In total, 23 randomised controlled studies were identified that met the inclusion criteria of the 2007 review. These compared alendronate or risedronate (or, in the case of Hosking *et al.*,[153] either) with either placebo or no treatment in postmenopausal women with osteoporosis or osteopenia, and reported fracture outcomes. The studies were as follows:

- alendronate:
  - Adami *et al.*[154]
  - Bone *et al.*[155]
  - Bone *et al.*[156]
  - Carfora *et al.*[157]
  - Chesnut *et al.*[158]
  - Durson *et al.*[159]
  - the Fracture Intervention Trial (FIT) fracture arm[79]
  - the Fracture Intervention Trial (FIT) non-fracture arm[80]
  - the FLEX trial[160]
  - Greenspan *et al.*[161]
  - Hosking *et al.*[153]
  - Kaadan[162]
  - Liberman *et al.*[163]
  - Lindsay *et al.*[164]
  - Or *et al.*[165]
  - Pols *et al.*[166]
  - Rossini *et al.*[167]
- risedronate:
  - Clemmesen *et al.*[168]
  - Fogelman *et al.*[169]
  - Harris *et al.*[170]
  - Hosking *et al.*[153]
  - McClung *et al.*[171]
  - McClung *et al.*[172] (the Hip Intervention Program)
  - Reginster *et al.*[173]

All studies except the FLEX trial appear to have evaluated the efficacy of alendronate or risedronate in women who were essentially bisphosphonate naive. The FLEX trial evaluated the efficacy of a further 5 years of alendronate therapy in participants in the FIT study who had already received alendronate for at least 3, and for a mean of 5, years during and after that study.[160] It therefore did not seem appropriate to include the results of the FLEX trial in meta-analyses of studies that recruited bisphosphonate-naive women.

All studies of alendronate except that by Hosking *et al.*[153] used a daily dose. Hosking *et al.* compared weekly alendronate both with placebo and with daily risedronate.

A number of articles presented data relating to extensions of earlier studies. These were:

- a 4-year extension[174] followed by a 3-year extension[175,176] of the study by Liberman *et al.*;[163] only 247 of the original 994 participants (25%) took part in the final extension study
- a 2-year extension of the study by Harris *et al.*,[170] open only to women who had both successfully completed the original study and undergone iliac crest bone biopsies at baseline and 36 months;[177] only 86 of the 2458 original participants (3%) took part in the extension
- two extensions[178,179] of the study by Reginster *et al.*;[173] these included only 265 (33%) and 164 (20%), respectively, of the 814 women randomised in the original study to either placebo or a 5-mg dose of risedronate.

TABLE 48 *Alendronate and risedronate trials: study characteristics*

Study	Disease status*	Length of intervention	Bisphosphonate dose	Calcium/vitamin D supplementation
Alendronate				
Adami 1995[154]	Osteoporosis or osteopenia, with or without previous fracture	2 years	10 and 20 mg/day	Elemental calcium 500 mg/day
Bone 1997[155]	Osteoporosis or osteopenia, with or without previous fracture	2 years	1, 2.5 and 5 mg/day	Elemental calcium 500 mg/day
Bone 2000[156]	Osteoporosis or osteopenia, with or without previous fracture	2 years	10 mg/day	Elemental calcium 500 mg/day
Carfora 1998[157]	Osteoporosis, with or without previous fracture	30 months	5 and 10 mg/day; 20 mg/day for 15 months/placebo for 15 months	Elemental calcium 500 mg/day
Chesnut 1995[158]	Osteoporosis or osteopenia, without previous fracture	2 years	5, 10, 20 and 40 mg/day	Elemental calcium 500 mg/day
Durson 2001[159]	Osteoporosis or osteopenia, with or without previous fracture	1 year	10 mg/day	Elemental calcium 1000 mg/day
FIT fracture arm 1996[79]	Osteoporosis or osteopenia, with previous fracture	Mean of 2.9 years	5 mg/day increased after 2 years to 10 mg/day	Elemental calcium 500 mg/day plus vitamin D 250 IU/day if baseline dietary calcium intake at baseline < 1000 mg/day
FIT non-fracture arm 1998[80]	Osteoporosis or osteopenia, without previous fracture	Mean of 4.2 years	5 mg/day increased after 2 years to 10 mg/day	Elemental calcium 500 mg/day plus vitamin D 250 IU/day if baseline dietary calcium intake at baseline < 1000 mg/day
FLEX 2004,[160] 2006[180]	Osteoporosis or osteopenia, with or without previous fracture, prior to at least 3 years of alendronate therapy	5 years	5 or 10 mg/day	All participants strongly encouraged to take calcium 500 mg/day and vitamin D 250 IU/day
Greenspan 2002[161]	Osteoporosis or osteopenia, with or without previous fracture	2 years	10 mg/day	Vitamin D 400 IU/day; elemental calcium 500 mg/day if baseline dietary calcium intake at baseline < 1500 mg/day
Hosking 2003[153]	Osteoporosis or osteopenia, with or without previous fracture	1 year	70 mg/week	Vitamin D 400 IU/day if baseline 25-hydroxy-vitamin D below 15 ng/ml (without evidence of vitamin D deficiency); participants required to maintain calcium intake of 1000 mg/day
Kaadan 2002[162]	Osteoporosis, fracture status unspecified	2 years	10 mg/day	None reported

Study	Disease status*	Length of intervention	Bisphosphonate dose	Calcium/vitamin D supplementation
Liberman 1995[163]	Osteoporosis, with or without previous fracture	3 years	5, 10 and 20 mg/day decreased to 5 mg/day after 2 years	Elemental calcium 500 mg/day
Lindsay 1999[164]	Osteoporosis or osteopenia, with or without previous fracture	1 year	10 mg/day	Vitamin D 400 IU/day; if baseline dietary calcium intake at baseline < 1000 mg/day, supplements provided to achieve intake of at least 1000 mg/day
Or 2001[165]	Osteoporosis, with previous fracture	1 year	10 mg/day	Calcium 1200 mg/day
Pols 1999[166]	Osteoporosis or osteopenia, with or without previous fracture	1 year	10 mg/day	Elemental calcium 500 mg/day
Rossini 1994[167]	Osteoporosis or osteopenia	6 months	20 mg/day	All participants counselled to achieve calcium intake of 1200 mg/day, using supplements if necessary
Risedronate				
Clemmesen 1997[168]	Osteoporosis or osteopenia with previous fracture	2 years	2.5 mg daily or cyclically	Elemental calcium 1000 mg/day
Fogelman 2000[169]	Osteoporosis or osteopenia, with or without previous fracture	2 years	2.5 and 5 mg/day	Elemental calcium 1000 mg/day
Harris 1999[170]	Osteoporosis or osteopenia, with or without previous fracture	3 years	2.5 and 5 mg/day	Elemental calcium 1000 mg/day
Hosking 2003[153]	Osteoporosis or osteopenia, with or without previous fracture	1 year	5 mg/day	Vitamin D 400 IU/day if baseline 25-hydroxy-vitamin D below 15 ng/ml (without evidence of vitamin D deficiency); participants required to maintain daily calcium intake of 1000 mg/day
McClung 1998[171]	Osteoporosis or osteopenia, with or without previous fracture	18 months	2.5 and 5 mg/day	Elemental calcium 1000 mg/day
McClung 2001[172] (Hip Intervention Program)	Age 70–79 years, osteoporosis, with or without previous fracture; age ≥ 80 years, osteoporosis, with or without previous fracture *or* at least one non-skeletal risk factor for hip fracture	3 years (mean duration of therapy 2 years)	2.5 and 5 mg/day	Elemental calcium 1000 mg/day; vitamin D 500 IU/day given if baseline serum 25-hydroxyvitamin D concentration below 16 ng/ml
Reginster 2000[173]	Osteoporosis or osteopenia, with previous fracture	3 years	2.5 and 5 mg/day	Elemental calcium 1000 mg/day; vitamin D ≤ 500 IU/day given if baseline 25-hydroxyvitamin D below 40 nmol/l

These extension studies were not included in the 2007 review because the attrition rates were such that they could no longer be considered truly randomised.

Details of the included studies are summarised in *Table 48*.

Nine studies[154–156,159,161,164,167,168,173] stated that they recruited women with osteoporosis but used definitions that included women who, by the current World Health Organization (WHO) definition, had osteopenia rather than osteoporosis; they are therefore classified as such in *Table 48*. Harris *et al.*[170] sought to include women who had either two or more vertebral fractures, regardless of *T*-score, or one vertebral fracture and a *T*-score at the lumbar spine of –2 or below; however, at baseline, only 79% of the placebo group, 80% of the 5-mg risedronate group and 85% of the 2.5-mg group had prevalent vertebral fractures, and it is therefore possible that some of the participants had osteopenia without prevalent fracture. Kaadan[162] and Or *et al.*[165] did not specify the definition of osteoporosis used.

The 2001 study by McClung *et al.*[172] was designed specifically to study the effect of risedronate on the risk of hip fracture in elderly women with osteoporosis or other risk factors for hip fracture. Two distinct groups were recruited: women aged 70–79 years with osteoporosis, and women aged 80 years or older with *either* at least one non-skeletal risk factor for hip fracture *or* osteoporosis. Each group was randomised separately to treatment, and the proportion of younger and older women with various risk factors was said to be balanced among the treatment groups. Only 16% of the older stratum was recruited on the basis of low femoral neck BMD; 58% were recruited solely on the basis of clinical risk factors such as a recent fall-related injury. In total, 39% of the younger stratum had evidence of at least one vertebral fracture at baseline.[172]

Alendronate and risedronate: fracture data

Vertebral fracture

Eleven studies of alendronate and four studies of risedronate provided information on the incidence of radiographic vertebral fractures. However, only seven of the alendronate studies and three of the risedronate studies used throughout a dose currently licensed in the UK for the treatment of postmenopausal osteoporosis (i.e. 10 mg/day or 70 mg/week of alendronate or 5 mg/day of risedronate), and two of those (the FLEX study[160] and Liberman *et al.*[163]) used a range of doses that included a licensed dose but only presented pooled data relating to all doses (*Table 49*). In the Fracture Intervention Trial,[79,80] the alendronate dose was increased from 5 mg to 10 mg after 2 years.

Ideally, only data relating to the licensed doses of alendronate and risedronate would have been included in the meta-analysis of vertebral fracture data. However, only one study, the small 1-year study by Durson *et al.*,[159] provided usable data relating to alendronate taken at a licensed dose throughout the study, and it did not produce a statistically significant result. Despite using a dose of only 5 mg for the first 2 years, both arms of the longer, and much larger, high-quality Fracture Intervention Trial[79,80] demonstrated a greater treatment effect, as did the study by Liberman *et al.*[163] (the latter pooled data relating to alendronate given at doses of either 5 or 10 mg for 3 years or 20 mg for 2 years followed by 5 mg for 1 year). Data from these studies have therefore been included in the meta-analysis of vertebral fracture risk, together with data from the arms of the risedronate studies by Fogelman *et al.*,[169] Harris *et al.*[170] and Reginster *et al.*[173] that used the licensed 5-mg dose.

The meta-analysis indicates that the second-generation bisphosphonates alendronate and risedronate are associated with a risk of vertebral fracture relative to placebo of 0.58 (95% CI 0.50 to 0.67) in women with osteoporosis or osteopenia (*Figure 36*).

Those studies that could not be incorporated into the meta-analysis because they only presented rates and not actual numbers of women with fracture (Carfora *et al.*,[157] Kaadan[162] and Or *et al.*[165]) also found that a 10-mg dose of alendronate was associated with a reduction in vertebral fracture rate (*Table 49*).

Non-vertebral fracture

Thirteen studies of alendronate and seven studies of risedronate presented data relating to non-vertebral fracture (*Table 50*).

As in the case of vertebral fractures, ideally only data relating to the current licensed doses of alendronate and risedronate would have been included in the meta-analysis. However, as before, data from the FIT fracture and non-fracture arms and from the study by Liberman *et al.* have been included. In addition, data have been included

TABLE 49 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment – radiographic vertebral fracture data*

Study	Bisphosphonate dose	Definition of morphometric fracture	Number of women in each group suffering vertebral fracture
Alendronate			
Adami 1995[154]	10 and 20 mg/day	Not applicable	Clinical fracture data only presented; site not specified
Bone 1997[155]	1, 2.5 and 5 mg/day	20%	Alendronate 1 mg: 4 Alendronate 2.5 mg: 3 Alendronate 5 mg: 4 Placebo: 6 RRs not calculable as denominators not available; difference between groups said by investigators not to be statistically significant
Bone 2000[156]	10 mg/day	Not applicable	Clinical fracture data only presented
Carfora 1998[157]	5 and 10 mg/day; 20 mg/day for 15 months/placebo for 15 months	Not given	Alendronate 5 mg: 5.88% Alendronate 10 mg: 2.94% Alendronate 20 mg: 8.82% Placebo: 11.8% RRs not calculable as the actual numbers of women suffering fracture were not stated
Chesnut 1995[158]	5, 10, 20 and 40 mg/day	Not given	There were no vertebral fractures in any subject
Durson 2001[159]	10 mg/day	20%	Alendronate: 12/38 (31.6%) Control: 14/35 (40.0%) RR 0.79 (95% CI 0.42 to 1.47)
FIT fracture arm 1996[79]	5 mg/day, increased after 2 years to 10 mg/day	20%	Alendronate: 78/981 (8.0%) Placebo: 145/965 (15.0%) RR 0.53 (95% CI 0.41 to 0.69)
FIT non-fracture arm 1998[80]	5 mg/day, increased after 2 years to 10 mg/day	20%	Alendronate: 43/2057 (2.1%) Placebo: 78/2077 (3.8%) RR 0.56 (95% CI 0.39 to 0.80) [The reduction in RR was significant in those women whose initial T score was –2.5 or less (RR 0.50, 95% CI 0.31 to 0.82), but not in those with initial *T*-scores greater than –2.5]
FLEX 2006[160]	5 or 10 mg/day	> 20% with a semiquantitative confirmation	Denominator not specified Alendronate: 60 (9.8%) Placebo: 46 (11.3%) RR 0.86 (95% CI 0.60 to 1.22) (authors' calculation, adjusted for centre and risk stratum)
Greenspan 2002[161]	10 mg/day	Not applicable	Clinical fracture data only presented; site not specified
Hosking 2003[153]	70 mg/week	Not applicable	Clinical fracture data only presented; site not specified

continued

TABLE 49 *Alendronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment – radiographic vertebral fracture data (continued)*

Study	Bisphosphonate dose	Definition of morphometric fracture	Number of women in each group suffering vertebral fracture
Kaadan 2002[162]	10 mg/day	Not stated	Alendronate: 3.3% Placebo: 6.3% RR not calculable as the actual numbers of women suffering fracture were not stated
Liberman 1995[163]	5, 10 and 20 mg/day, decreased to 5 mg/day after 2 years	20%	Pooled alendronate groups: 17/526 (3.2%) Placebo: 22/355 (6.2%) RR 0.52 (95% CI 0.28 to 0.97)
Lindsay 1999[164]	10 mg/day	Not applicable	No symptomatic vertebral fractures were identified in either group
Or 2001[165]	10 mg/day	Not stated	Alendronate: 2.5% Placebo: 9.8% RR not calculable as the actual numbers of women suffering fracture were not stated
Pols 1999[166]	10 mg/day	Not applicable	Vertebral fractures not investigated
Rossini 1994[167]	20 mg/day	Not stated	No subjects suffered vertebral fracture during the study period
Risedronate			
Clemmesen 1997[168]	2.5 mg daily or cyclically	15% or 25% (different fracture definitions used by the Danish and Belgian centres)	Gives number of vertebral fractures identified at each centre but not number of women suffering those fractures. States that there was a tendency towards a lower incidence and rate of new vertebral fractures in the group taking daily continuous risedronate, but this was not statistically significant
Fogelman 2000[169]	2.5 and 5 mg/day	Any vertebral height ratio below 3 SD of the mean for the study population	Risedronate 2.5 mg: 8/60 Risedronate 5 mg: 8/112 Placebo: 17/125 RR, 5 mg vs placebo, 0.53 (95% CI 0.24 to 1.17)
Harris 1999[170]	2.5 and 5 mg/day	15% + semiquantitative method	Risedronate 5 mg: 61/696 Placebo: 93/678 RR 0.64 (95% CI 0.47 to 0.87)
Hosking 2003[153]	5 mg/day	Not applicable	Clinical fracture data only presented; site not specified
McClung 1998[171]	2.5 and 5 mg/day	Not reported	Not reported
McClung 2001[172]	2.5 and 5 mg/day	Not reported	Not reported
Reginster 2000[173]	2.5 and 5 mg/day	15% + semiquantitative method	Risedronate 5 mg: 53/344 Placebo: 89/346 RR 0.60 (95% CI 0.44 to 0.81)

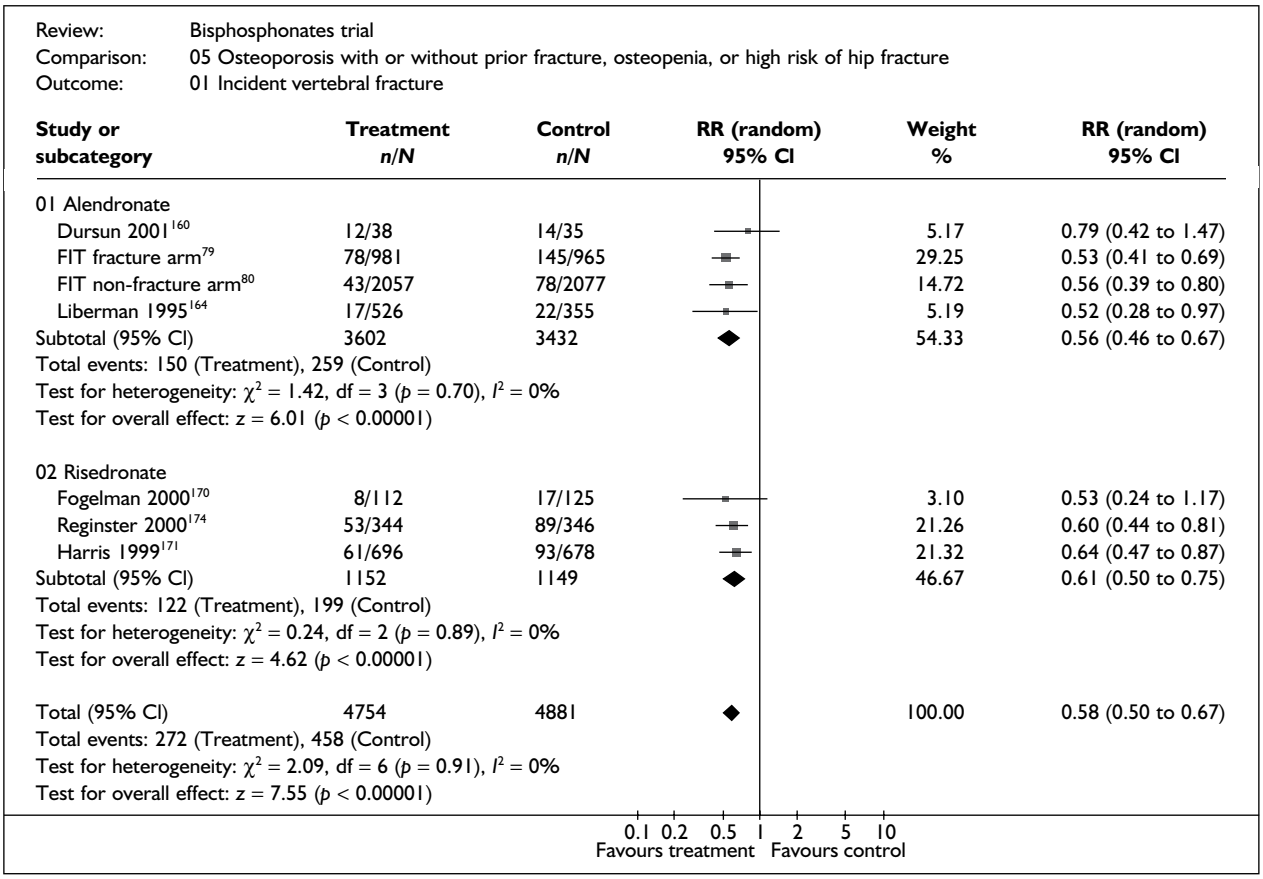

FIGURE 36 *Alendronate or risedronate: incident vertebral fracture in postmenopausal osteoporosis (with or without previous fracture) or osteopenia.*

from one large risedronate study (McClung *et al.*[172]), which only reported pooled data relating to participants receiving 2.5-mg and 5-mg doses of risedronate. Their reason for doing so was that the study by Reginster *et al.*[173] had shown that both doses were effective in reducing the risk of vertebral fractures. However, Reginster *et al.*[173] discontinued the 2.5-mg dose after 2 years on the basis that McClung *et al.*[171] had shown that the 5-mg dose had a more consistent effect on BMD and a similar safety profile, and both they and Harris *et al.*[170] published only 1-year data relating to the 2.5-mg dose and 3-year data relating only to the 5-mg dose. Consequently, the meta-analysis includes the 3-year data from the studies by Harris *et al.*[170] and Reginster *et al.*,[173] which relate to the licensed 5-mg dose, and does not include data relating to the 2.5-mg dose either from those studies or from the study by Clemmesen *et al.*[168]

The meta-analysis indicates that the second-generation bisphosphonates alendronate and risedronate are associated with a risk of non-vertebral fracture relative to placebo of 0.82 (95% CI 0.74 to 0.90) in women with osteoporosis or osteopenia or at high risk of hip fracture (*Figure 37*).

As may be seen, the results are less consistent than those for vertebral fracture. There is no apparent reason why, in the study by Lindsay *et al.*,[164] the fracture rate should have been higher in women receiving HRT plus alendronate than in those receiving alendronate alone. In the study by McClung *et al.*,[172] risedronate appears less effective (RR 0.84, 95% CI 0.74 to 0.96) than is suggested by meta-analysis of data from the studies by Fogelman *et al.*,[169] Harris *et al.*[170] and Reginster *et al.*[173] relating to the 5-mg risedronate dose in women with osteoporosis or osteopenia, with or without previous fracture (RR 0.66, 95% CI 0.50 to 0.87). This finding may be spurious, as the confidence intervals around the two point estimates overlap. Alternatively, in the study by McClung *et al.*[172] the estimated efficacy of risedronate may have been reduced by the inclusion of data relating either

TABLE 50 *Alendronate or risedronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment –non-vertebral fracture data*

Study	Bisphosphonate dose	Fracture definition	Number of women in each group suffering non-vertebral fracture
Alendronate			
Adami 1995[154]	10 and 20 mg/day	Not given; may include clinical vertebral fractures	Alendronate 10 mg: 1/68 (1.5%) Alendronate 20 mg: 1/72 (1.4%) Placebo: 3/71 (4.2%) RR, 10 mg vs placebo, 0.35 (95% CI 0.04 to 3.26)
Bone 1997[155]	1, 2.5 and 5 mg/day	Not given	Alendronate 1 mg: 15/86 (17.4%) Alendronate 2.5 mg: 9/89 (10.1%) Alendronate 5 mg: 9/93 (9.7%) Placebo: 16/91 (17.6%) RR, 5 mg vs placebo, 0.55 (95% CI 0.26 to 1.18)
Bone 2000[156]	10 mg/day	Any clinical fracture (most were said to be non-vertebral, occurring at sites such as foot, ankle and rib; most occurred as a result of trauma)	Alendronate 10 mg: 4/92 (4.3%) Placebo: 4/50 (8.0%) RR 0.68 (95% CI 0.19 to 2.42)
Carfora1998[157]	5, 10 and 20 mg/day	Not given	RR, alendronate vs placebo, 0.55 (authors' calculation; confidence intervals and numbers of women suffering fractures not supplied)
Chesnut 1995[158]	5, 10, 20 and 40 mg/day	Not given	13 non-vertebral fractures occurred in 12 subjects. These were evenly distributed across treatment groups and were not considered related to therapy
FIT fracture arm 1996[79]	5 mg/day, increased after 2 years to 10 mg/day	Any clinical non-vertebral fracture that was not pathological (e.g. due to malignant disease), due to excessive trauma or involving the face or skull	Alendronate: 122/1022 (11.9%) Placebo: 148/1005 (14.7%) RR 0.81 (95% CI 0.65 to 1.01)
FIT non-fracture arm 1998[80]			Alendronate: 261/2214 (11.8%) Placebo: 294/2218 (13.3%) RR 0.89 (95% CI 0.76 to 1.04)
FLEX 2006[160]	5 or 10 mg/day	Any non-vertebral fracture other than pathological, skull and excessive trauma fractures	Alendronate: 132/662 (19.9%) Placebo: 93/437 (21.3%) RR 0.93 (95% CI 0.71 to 1.21) (authors' calculation, adjusted for centre and risk stratum)
Greenspan 2002[161]	10 mg/day	Not given	Alendronate: 13 (8%) Placebo: 18 (11%) RR not calculable as the number of women in each group was not stated
Hosking 2003[153]	70 mg/week	Not given; may include clinical vertebral fractures	Alendronate: 6/219 (2.7%) Placebo: 2/108 (1.9%)

TABLE 50 *Alendronate or risedronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment –non-vertebral fracture data (continued)*

Study	Bisphosphonate dose	Fracture definition	Number of women in each group suffering non-vertebral fracture
Liberman 1995[163]	5, 10 and 20 mg/day, decreased to 5 mg/day after 2 years	All symptomatic fractures, not excluding those due to trauma	Alendronate: 45/597 (7.5%) Placebo: 38/397[181] (9.6%) RR 0.79 (95% CI 0.52 to 1.19)
Lindsay 1999[164]	10 mg/day	Any clinically apparent fracture	Alendronate: 15/214 (7.0%) Control: 9/214 (4.2%) RR 1.67 (% CI 0.75 to 3.73)
Pols 1999[166]	10 mg/day	Any clinically confirmed fracture	Alendronate: 19/950 (2.0%) Control: 37/958 (3.9%) RR 0.52 (95% CI 0.30 to 0.89)
Risedronate			
Clemmesen 1997[168]	2.5 mg daily or cyclically	Not given, but all fractures occurred after falls	Continuous risedronate: 4/44 (9.1%) Cyclical risedronate: 9/44 (20.5%) Placebo: 4/44 (9.1%) RR, continuous risedronate vs placebo, 1.00 (95% CI 0.27 to 3.75)
Fogelman 2000[169]	2.5 and 5 mg/day	Not given	Risedronate 2.5 mg: 4/184 (2.2%) Risedronate 5 mg: 7/177 (4.0%) Placebo: 13/180 (7.2%) RR, 5 mg vs placebo, 0.55 (95% CI 0.22 to 1.34)
Harris 1999[170]	2.5 and 5 mg/day	All radiographically confirmed fractures of the clavicle, humerus, wrist, pelvis, hip or leg, whether or not associated with trauma	Risedronate 5 mg: 33/812 (4.1%) Placebo: 52/815 (6.4%) RR 0.64 (95% CI 0.42 to 0.97)
Hosking 2003[153]	5 mg/day	Not given; may include clinical vertebral fractures	Risedronate: 6/222 (2.7%) Placebo: 2/108 (1.9%) RR 1.46 (95% CI 0.30 to 7.11)
McClung 1998[171]	2.5 and 5 mg/day	Not given	Non-vertebral fractures were said to be few in number and comparable between groups. More specific data were not available
McClung 2001[172]	2.5 and 5 mg/day	All radiographically confirmed fractures of the clavicle, humerus, wrist, pelvis, hip or leg	Risedronate: 583/6197 (9.4%) Placebo: 351/3134[2] (11.2%) RR 0.84 (95% CI 0.74 to 0.95)
Reginster 2000[173]	2.5 and 5 mg/day	All radiographically confirmed fractures of the clavicle, humerus, wrist, pelvis, hip or leg, whether or not associated with trauma	Risedronate 5 mg: 36/406 (8.9%) Placebo: 51/406 (12.6%) RR 0.71 (95% CI 0.47 to 1.06)

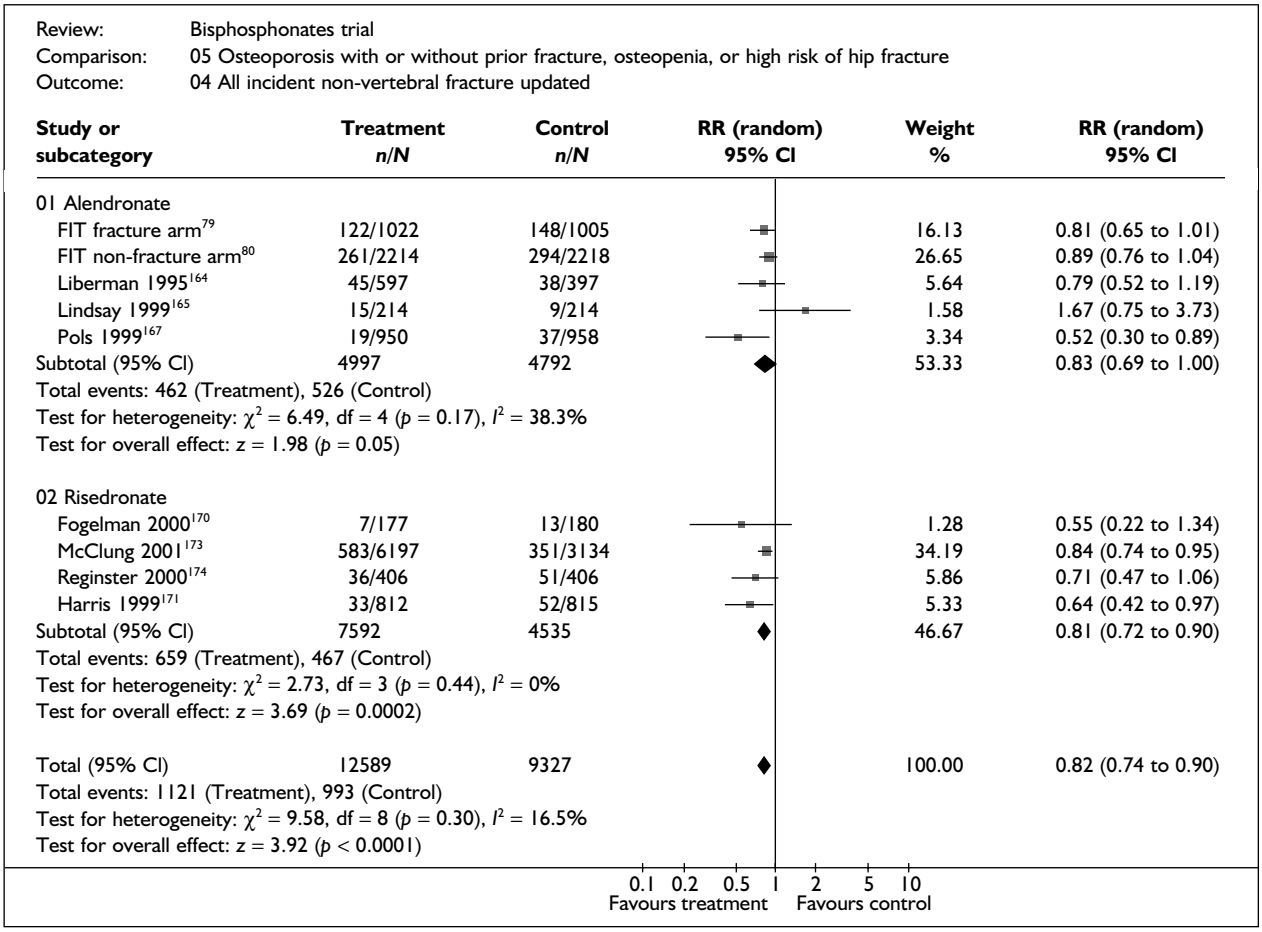

FIGURE 37 *Alendronate or risedronate: incident non-vertebral fracture in women with postmenopausal osteoporosis (with or without previous fracture) or osteopenia or at high risk of hip fracture.*

to women receiving a 2.5-mg dose of risedronate or to women selected for risk factors other than low BMD, or both. However, although McClung *et al.*[172] did not publish the data for all non-vertebral fractures in such a way as to enable the inclusion in the meta-analysis of only those women selected for low BMD (or indeed only those receiving a 5-mg dose), they did publish an analysis which indicated that the RR of non-vertebral fracture in women in the younger osteoporotic stratum who received risedronate was not very different, at 0.8 (95% CI 0.7 to 1.0), from that in the study as a whole.

Subgroup data from the FIT non-fracture arm[80] suggest that alendronate may have a significant effect on non-vertebral fractures in osteoporotic women (RR 0.64, 95% CI 0.58 to 0.82), but not in those who are only osteopenic (RR 1.08, 95% CI 0.87 to 1.35).

Hip fracture

Few studies reported specifically on hip fracture (*Table 51*).

Studies were included in the meta-analysis on the same basis as for the meta-analysis of all non-vertebral fractures. Pooled data for all participants for both the 2.5-mg and 5-mg doses of risedronate from the 2001 study by McClung *et al.*[172] were again included as usable data were not provided separately for the two doses. However, the authors calculated that, in the younger osteoporotic stratum, the risk of hip fracture relative to placebo was 0.5 (95% CI 0.3 to 0.9) in women receiving 2.5 mg of risedronate and 0.7 (95% CI 0.4 to 1.1) in those receiving 5 mg, suggesting that the higher dose did not confer increased protection.

The meta-analysis indicates that the second-generation bisphosphonates alendronate and risedronate are associated with a risk of hip fracture relative to placebo of 0.72 (95% CI 0.58 to 0.88) in women with osteoporosis (with or without previous fracture) or osteopenia or at high risk of hip fracture (*Figure 38*).

TABLE 51 *Alendronate or risedronate in postmenopausal osteoporosis or osteopenia: comparisons with placebo or no treatment – hip fracture data*

Study	Bisphosphonate dose	Number of women in each group suffering hip fracture
Alendronate		
FIT fracture arm 1996[79]	5 mg/day, increased after 2 years to 10 mg/day	Alendronate: 11/1022 (1.1%) Placebo: 22/1005 (2.2%) RR 0.49 (95% CI 0.24 to 1.01)
FIT non-fracture arm 1998[80]	5 mg/day, increased after 2 years to 10 mg/day	Alendronate: 19/2214 (0.9%) Placebo: 24/2218 (1.1%) RR 0.79 (95% CI 0.44 to 1.44)
FLEX 2006[160]	5 or 10 mg/day	Alendronate: 20/662 (3.0%) Placebo: 13/437 (3.0%) RR 1.02 (95% CI 0.51 to 2.10) (authors' calculation, adjusted for centre and risk stratum)
Greenspan 2002[161]	10 mg/day	Alendronate: 2 Placebo: 4 As the number of women in each group was not stated, it was not possible to calculate a RR
Liberman 1995[163]	5, 10 and 20 mg/day, decreased to 5 mg/day after 2 years	Alendronate: 1/597 (0.2%) Placebo: 3/397[182] (0.8%) RR 0.22 (95% CI 0.02 to 2.12)
Risedronate		
Harris 1999[170]	2.5 and 5 mg/day	Risedronate 5 mg: 12/812 (1.5%) Placebo: 15/815 (1.8%) RR 0.80 (95% CI 0.38 to 1.70)
McClung 2001[172]	2.5 and 5 mg/day	Risedronate: 137/6197 (2.2%) Placebo: 95/3134 (3.0%) RR 0.73 (95% CI 0.56 to 0.94) Younger osteoporotic group: Risedronate: 55/3624 (1.5%) Placebo: 46/1821 (2.5%) RR 0.60 (95% CI 0.41 to 0.89) Older high-risk group: Risedronate: 82/2573 (3.2%) Placebo: 49/1313 (3.7%) RR 0.85 (95% CI 0.60 to 1.21)
Reginster 2000[173]	2.5 and 5 mg/day	Risedronate 5 mg: 9/406 (2.2%) Placebo: 11/406 (2.7%) RR 0.82 (95% CI 0.34 to 1.95)

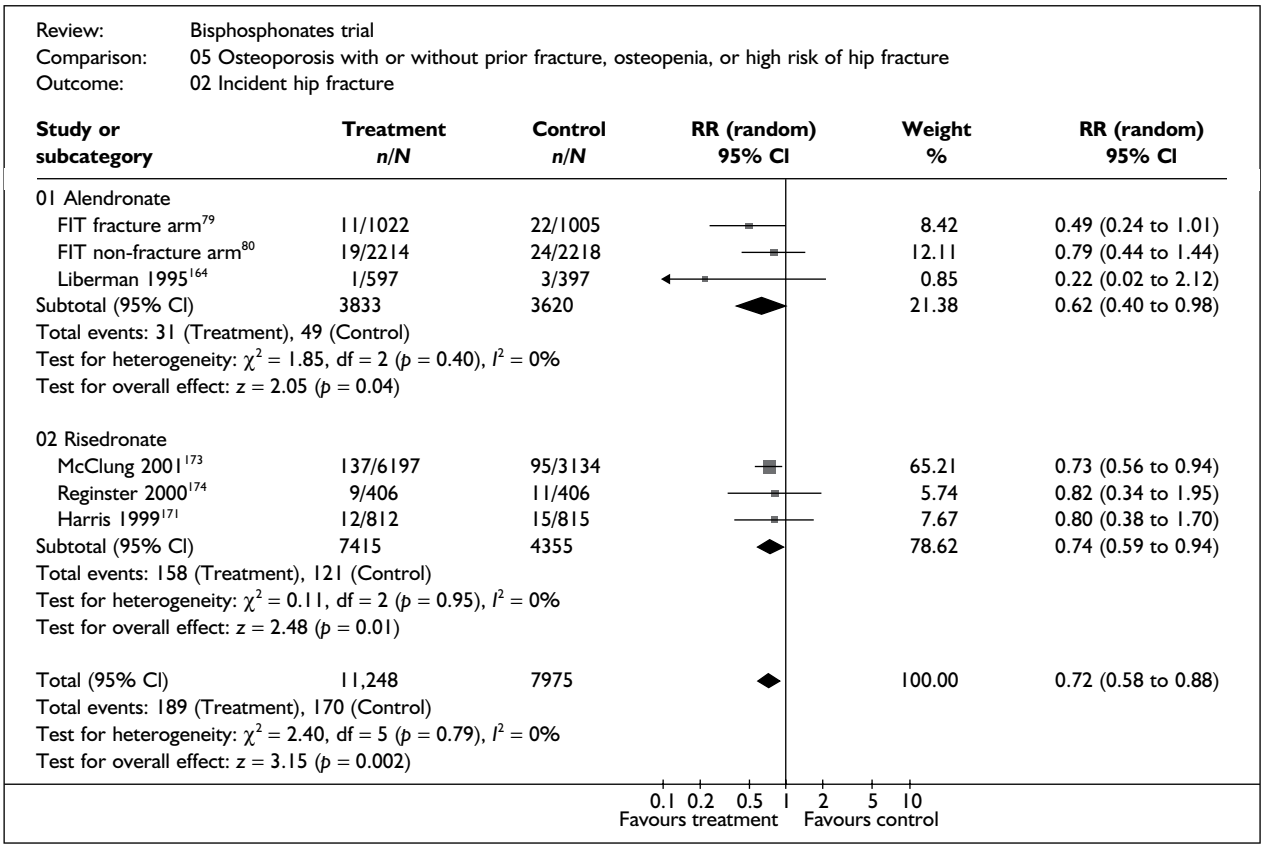

FIGURE 38 *Alendronate or risedronate: incident hip fracture in women with postmenopausal osteoporosis (with or without previous fracture) or osteopenia or at high risk of hip fracture.*

Adverse events

The studies included in our 2003 review[2] generally did not identify an increase in adverse events in women taking bisphosphonates. Moreover, Steinbuch *et al.*[181] undertook a retrospective cohort study in which they used routinely collected data to compare mortality rates in women enrolled in the risedronate and placebo groups of the North American risedronate trials (Harris *et al.*,[170] McClung *et al.*[171] and the Hip Intervention Program[172]) over the period from initiation of study medication to 31 December 1997. They found no association between risedronate and an increase in all-cause mortality, cancer mortality or stroke mortality; although risedronate was associated with a non-significant increase in mortality from coronary artery disease, it was associated with a significant decrease in stroke mortality.

The more recent studies summarised here do not suggest that second-generation bisphosphonates are associated with an increase in adverse events other than gastrointestinal disturbances. Hosking *et al.*[153] found that, although there was no significant increase in serious upper gastrointestinal adverse events in women randomised to weekly alendronate or daily risedronate compared with those randomised to placebo, women randomised to either bisphosphonate were more likely than those randomised to placebo to discontinue study medication because of upper gastrointestinal adverse events. Or *et al.*[165] also found that gastrointestinal disturbances were more common in the alendronate than in the placebo group.

A systematic review[183] has indicated that bisphosphonates are associated with an increased risk of osteonecrosis of the jaw. Although this risk appears to be linked primarily to intravenous bisphosphonates, some cases were reported in patients taking daily alendronate (10 mg) for osteoporosis. However, no cases of osteonecrosis of the jaw were identified in the long-term users of oral alendronate in the FLEX study.[160]

Quality of life

Only one study, that by Durson *et al.*,[159] set out to measure the effect of alendronate treatment on

health-related quality of life, as measured by the Nottingham Health Profile (NHP). At 12 months they found statistically significant improvements in the NHP scores for pain, social isolation, energy level and physical ability in the alendronate group, but not in the control group; pain, as measured on a visual analogue scale, decreased significantly from baseline in the alendronate group but not in the control group. Or *et al.*[165] noted no obvious improvement in quality of life in the alendronate group compared with the placebo group, but did not state how this was measured.

The FIT fracture arm collected data on the effects of alendronate on back pain and days of functional limitation or bed rest.[184] Women in the alendronate group had significantly fewer days in bed because of back pain than women in the placebo group (mean of 1.9 days over a 3-year period versus 5.1 days, $p = 0.001$), and fewer days of limited activity because of such pain (mean of 61.8 days versus 73.2, $p = 0.04$).

None of the studies of risedronate reported on its effect on quality of life.

Continuance and compliance

Continuance with medication decreases over time. In the studies reviewed here, the percentage of subjects receiving daily alendronate who completed the study protocol ranged from 100% at 1 year in the very small study by Rossini *et al.* to 81% at 4 years in the FIT non-fracture arm and 72% at 6 years in the FLEX trial; surprisingly, the figure for weekly alendronate was lower, at 78% at 3 months (*Table 52*). The figures for daily risedronate ranged from 82% at 1 year to 60% at 3 years (*Table 52*). The FIT trial found that discontinuation of study medication was greatest in the first month post randomisation: 4.8% of participants had withdrawn at 3 months, and 11.1% at 12 months. Although clinical adverse events formed the most common reason for withdrawal, causing 6.9% of women to withdraw, the proportion of women discontinuing

TABLE 52 *Continuance in randomised controlled trials: percentage of patients receiving a licensed bisphosphonate dose still taking bisphosphonate therapy by year*

Study	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Alendronate 10 mg/day						
Bone 2000[156]	NR	74				
FIT fracture arm 1996[79] (5 mg/day, increased to 10 mg/day after 2 years)	NR	NR	89			
FIT non-fracture arm 1998[80] (5 mg/day, increased to 10 mg/day after 2 years)	NR	NR	NR	81		
FLEX 2006[160]	NR	NR	86	NR	NR	72
Liberman 1995[163]	92	89	84			
Lindsay 1999[164]	95					
Pols 1999[166]	88					
Rossini 1994[167]	100[a]					
Alendronate 70 mg/week						
Hosking 2003[153]	78[b]					
Risedronate 5 mg/week						
Fogelman 2000[169]	NR	78				
Harris 1999[170]	NR	NR	60			
Hosking 2003[153]	80[b]					
Reginster 2000[173]	82	NR	62			

NR, not reported.
a 6 months of blinded treatment followed by 6 months of blinded follow-up.
b First 12 weeks only.

treatment was comparable in the alendronate and placebo groups (RR 2.10, 95% CI 1.47 to 2.99).[185]

Four studies defined compliance as taking at least 75% of the study medication since the last clinic visit. In both arms of the FIT trial,[79,80] 96% of participants who continued to take the study medication (alendronate or placebo) were found to be compliant with that medication at the final clinic visit, as were 96% of participants in the FLEX trial[160] who were still taking the study medication at 36 months. Hosking *et al.*[153] also found that, although in their study continuance at 12 weeks was perhaps disappointing, 95% of those taking either bisphosphonate were compliant with that medication over that period according to patient-completed medication diaries validated by tablet counts.

Summary

The aggregated results suggest that the second-generation bisphosphonates alendronate and risedronate have a protective effect in relation to vertebral fracture in women with osteoporosis or osteopenia, with or without previous fracture, and that they also have a protective effect in relation to non-vertebral fracture generally, and hip fracture specifically, in women with osteoporosis or osteopenia, with or without previous fracture, or who are at increased risk of hip fracture.

Appendix 11

The calculation of the costs of fracture using Healthcare Resource Groups (HRGs)

Healthcare Resource Groups (HRGs) detail the costs that are expected to be incurred by a trust when treating a patient with a certain condition. These costs can be modified if the patient has an exceptionally long duration of stay, which is defined as beyond the 'trim point', with additional costs per day after this period. These costs have been centrally calculated, across a large number of NHS trusts, and this is the approach recommended by NICE for calculating costs.

The HRGs used in the estimation of costs are shown in the following table.

H36	Closed pelvis or lower limb fractures > 69 or w cc
H37	Closed pelvis or lower limb fractures < 70 w/o cc
H39	Closed upper limb fractures or dislocations > 69 or w cc
H40	Closed upper limb fractures or dislocations < 70 w/o cc
H45	Minor fractures or dislocations
H82	Extracapsular neck of femur fracture with fixation w cc
H83	Extracapsular neck of femur fracture with fixation w/o cc
H84	Intracapsular neck of femur fracture with fixation w cc
H85	Intracapsular neck of femur fracture with fixation w/o cc
H86	Neck of femur fracture with hip replacement w cc
H87	Neck of femur fracture with hip replacement w/o cc
H88	Other neck of femur fracture w cc
H89	Other neck of femur fracture w/o cc
R15	Thoracic or lumbar spinal disorders > 69 or w cc
R16	Thoracic or lumbar spinal disorders < 70 w/o cc

cc, complications or comorbidities; w, with; w/o, without.

The costs estimated for a hip, clinical vertebral, wrist and proximal humerus fracture have been provided.

Based on the work previously undertaken it has been assumed that:

- the costs for a hip fracture will also incorporate pelvis and other femoral fractures
- the costs for a wrist fracture will also incorporate rib, scapula, sternum and clavicle fractures
- the costs for a proximal humerus fracture will also incorporate tibia, fibula and humeral shaft fractures.

Home help costs

The costs for home help following a fracture will be heavily dependent on the health resources within a region and on whether the patient chooses to pay for their own help. Questioning a small number of clinicians on the NICE Appraisal Committee and on the NICE Osteoporosis Guideline Development Group it appeared that home help for 2 hours a day for 8 weeks following a hip fracture would not be unreasonable. Similar resources are required for vertebral fractures and for wrist and proximal humerus fractures when the dominant arm has been fractured. Assuming costs of £14 per hour for home care[115] this would imply additional home help costs of £1568 for hip and vertebral fractures and £784 for wrist and proximal humerus fractures. An alternative source of data for the amount of home help required is the Swedish study by Borgstrom *et al.*[186] This estimates home help costs to be £1143, £1699 and £85 for hip, vertebral and wrist fractures respectively. We have used the Borgstrom data as these have been empirically collected and are likely to be conservative compared with our estimated UK values.

Hip fracture costs (not requiring nursing home admission)

The average cost from HRGs H82–H89, which represent hip fracture, is £5419, with a range from £4357 to £7136. The average cost for pelvis and lower limb fracture is dependent on age. For those patients aged over 70 years the cost is £4582 (H36). For patients under 69 years the cost is £4582 (H36) if there are complications and £2417 if there are no complications (H37).

In the absence of data on the frequency of fractures in relation to HRG code we have assumed that the cost of a hip fracture is that of the cost of an average hip fracture or £5419. We have also assumed that an additional 11% of this cost is incurred from outpatient appointments, as indicated by Swedish data,[186] resulting in an average cost of £6015. We have age weighted this figure in accordance with data reported by Borgstrom *et al.*[186]

Some additional costs will be borne for patients who stay longer than the trim point. We do not have data on this and have instead arbitrarily added £50 to the cost of a 'hip' fracture, which is approximately 1 additional day's stay beyond the trim point for every three patients. An additional £93 has been added to each case as a high-cost A&E attendance patient. We have assumed an additional £1568 for home help as previously described.

The costs at each age band are shown in the following table.

Age range (years)	HRG costs for hip fracture including home help (£)
50–54	5696
55–59	5696
60–64	5696
65–69	6426
70–74	6750
75–79	6750
80–84	6750

Note that these figures are markedly different from those reported in Lawrence *et al.*,[187] in which the average hip fracture cost at a Nottingham hospital was approximately £12,000 for direct medical costs only, and from that reported in Stevenson *et al.*[188] (£10,760 excluding home help costs).

Additional costs associated with admission to a nursing home following a hip fracture

The additional costs associated with admission to a nursing home and the ongoing treatment costs per year have been taken from Stevenson *et al.*[4] These are approximately £26,000 in the year of fracture and between £23,000 and £25,000 per annum thereafter.

Vertebral fracture costs

For patients aged over 69 years we have used the R15 HRG, at a cost of £2269. For patients aged below 70 years we have arbitrarily assumed that 20% have complications (and used HRG R15) and that 80% do not (and used HRG R16, at a cost of £1069). This gives a weighted cost of £1309.

Some additional costs will be borne for patients who stay longer than the trim point. We do not have data on this and have instead arbitrarily added £50 to the cost of a vertebral fracture, which is approximately 1 additional day's stay beyond the trim point per three patients. An additional £93 has been added to each case as a high-cost A&E attendance patient. This equates to costs of £1452 and £2412 for hospitalised vertebral fractures for patients aged below 70 years and above 70 years respectively. Assuming that 35% of clinical vertebral fractures are hospitalised,[189] this results in costs of £508 and £844, respectively, on average for all clinical vertebral fractures.

We have assumed additional outpatient costs of 9% of inpatient costs, which are assumed applicable to all patients with a clinical vertebral fracture.[186] This results in costs of £639 for patients below 70 years and £1061 for patients over 69 years.

We have assumed an additional £1568 for home help. As in our previous modelling work[2] it is assumed that all clinical vertebral fractures will receive medication, at a cost of £222 per annum.

The costs at each age band are shown in the following table.

Age range (years)	Costs for a clinical vertebral fracture including home help (£)
50–59	2338
60–69	2338
70–79	2760
80–89	2760

Note that these costs are lower than those in Puffer *et al.*,[190] which are over £2500 for clinical vertebral fracture, excluding home help costs. These costs may be seen as conservative as length of stay was assumed to be 6 days, whereas Hospital Episode Statistics (HES) data record 10.8 days. These are UK data and have been attempted to be case-matched to try and ensure that only the costs of the vertebral fractures are included.

It is possible that these costs may be overestimated if patients with a vertebral fracture also sustain a hip fracture in the 2-year collection period, as these costs would also be calculated in the model at the time of the hip fracture.

The costs of a 'wrist' fracture

For patients aged over 69 years we have used HRG H39, which has a cost of £2762. For patients aged below 70 years, we have arbitrarily assumed that 20% have complications (and used H39) and that 80% do not (and used H40, at a cost of £1447). This gives a weighted cost of £1692 for patients under 70 years.

Some additional costs will be borne for patients who stay longer than the trim point. We do not have data on this but have arbitrarily added £50 to the cost of a wrist fracture, which is approximately 1 additional day's stay beyond the trim point per three patients. An additional £61 has been added to each case as a standard A&E attendance patient. This equates to costs of £1803 and £2873 for hospitalised wrist fractures for patients aged below 70 years and above 70 years respectively. Assuming that 25% of wrist fractures are hospitalised, this results in costs of £451 and £718, respectively, on average for all wrist fractures.

We have assumed additional outpatient costs of 31% of inpatient costs,[186] which are assumed applicable to all patients with a wrist fracture. This results in costs of £1010 for patients below 70 years and £1609 for patients over 69 years. We have further assumed an additional £85 for home help.

Rib, clavicle, scapula and sternum fractures have been classified as HRG H45, at a cost of £1232. We have arbitrarily added £50 to the cost of a wrist fracture, which is approximately 1 additional day's stay beyond the trim point per three patients. An additional £61 has been added to each case as a standard A&E attendance patient. This equates to costs of £1343 per hospitalised fracture.

Using Swedish hospitalisation, incidence and census data, it is assumed that 7% of such fractures are hospitalised[112,186,191] and that 10% of inpatient costs are borne by all fractures as outpatient costs.[186] This equates to £340 per fracture including £85 for home help costs.

The costs at each age band have been weighted to take the proportion of each fracture type into account.

Age range (years)	Costs for 'wrist' fracture including home help costs (£)
50–54	762
55–59	887
60–64	964
65–69	903
70–74	1261
75–79	1109
80+	1004

The costs for 'proximal humerus' fractures

For patients aged over 69 years we have used HRG H39, which has a cost of £2762. For patients aged below 70 years we have arbitrarily assumed that 20% have complications (and used H39) and that 80% do not (and used H40, at a cost of £1447). This gives a weighted cost of £1692. Humerus shaft fractures are assumed to cost the same as proximal humerus fractures.

Some additional costs will be borne for patients who stay longer than the trim point. We do not have data on this but have arbitrarily added £50 to the cost of a proximal humerus fracture, which is approximately 1 additional day's stay beyond the trim point per three patients. An additional £61 has been added to each case as a standard A&E attendance patient. This equates to costs of £1803 and £2873 for hospitalised proximal humerus fractures for patients aged below 70 years and above 70 years respectively. Assuming that 32% of proximal humerus fractures are hospitalised,[112,186,191] this results in costs of £577 and £919, respectively, on average for proximal humerus fractures.

We have assumed additional outpatient costs of 10% of inpatient costs,[186] which are assumed applicable to all patients with a proximal humerus fracture. This results in costs of £757 for patients below 70 years and £1207 for patients over 69

years. We have further assumed an additional £85 for home help.

Tibia and fibula fractures have been assumed to cost the same as pelvis and other femoral fractures, which is £4582 for patients over 69 years or with complications (H36) and £2850 for patients under 70 years without complications (H37). At all ages an additional £50 has been added for patients staying beyond the trim point. An additional £61 per patient has been included as the cost of a standard A&E admission.

Assuming that 90% of tibia and fibula fractures are hospitalised,[112,186,191] this results in costs of £2665 for those below 70 years and £4224 for those above 69 years.

We have assumed additional outpatient costs of 10% of inpatient costs,[186] which are assumed applicable to all patients with a proximal humerus fracture. This results in costs of £2950 for patients below 70 years and £4682 for patients over 69 years. We have further assumed an additional £1143 for home help for tibia and fibula fractures, equal to that associated with a hip fracture.

The costs at each age band have been weighted to take the proportion of each fracture type into account.

Age range (years)	Costs for a 'proximal humerus' fracture including home help costs (£)
50–54	2357
55–9	2237
60–64	2100
65–69	1941
70–74	2565
75–79	2256
80+	1882

Appendix 12
Detailed results

This appendix will be subdivided into results for osteoporotic women without a previous fracture and results for osteoporotic women with a previous fracture. These results will be reported by combinations of age and *T*-score.

Results for women without a previous fracture

Women aged 50–54 years without previous fracture

The mean results for each intervention compared with no treatment for women aged 50–54 years with a *T*-score of –2.5 SD are given in *Table 53*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 39*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

The mean results for each intervention compared with no treatment for women aged 50–54 years with a *T*-score of –3.0 SD are given in *Table 54*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 40*. However, it is seen that if the efficacy associated with vitamin K_1 is only applicable to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 55–59 years without previous fracture

The mean results for each intervention compared with no treatment for women aged 55–59 years with a *T*-score of –2.5 SD are given in *Table 55*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 41*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

TABLE 53 *Cost-effectiveness of interventions in women aged 50–54 years with a* T*-score of –2.5 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	25,985	1.71	15,239	8804 to 40,684
Alendronate	23,947	1.36	17,653	12,091 to 28,137
Risedronate	125,793	1.36	92,727	73,093 to 126,186
Strontium ranelate	164,317	0.90	182,942	115,564 to 540,523
Vitamin K_1[b]	40,263	0.47	84,842	54,355 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.

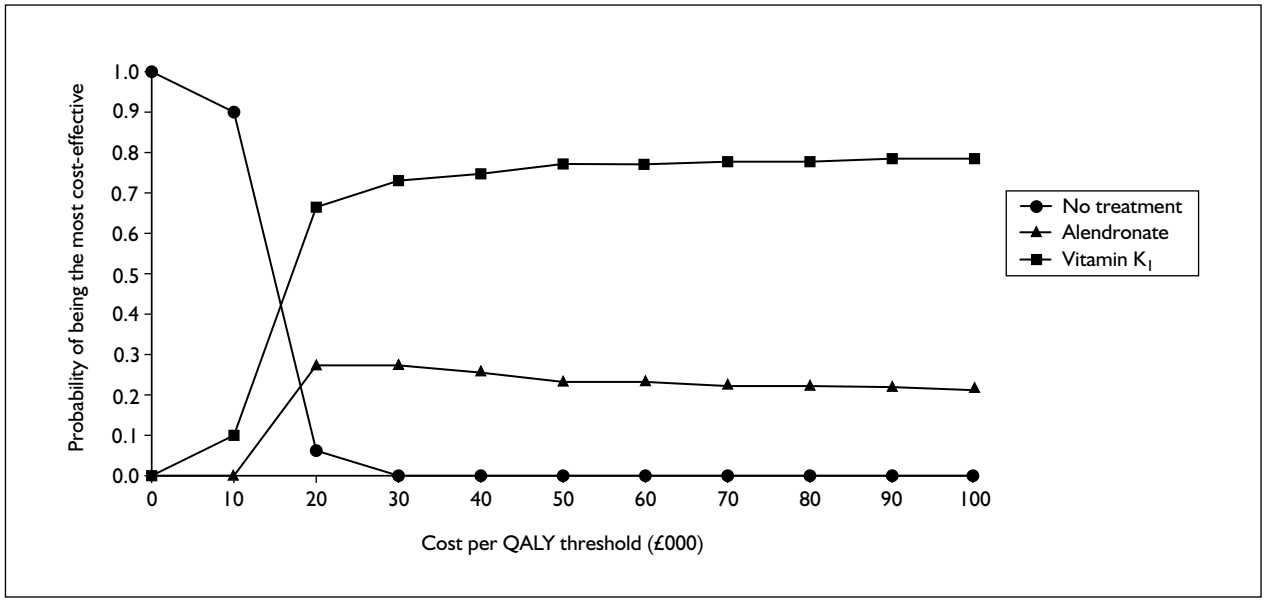

FIGURE 39 *Cost-effectiveness acceptability curves for interventions in women aged 50–54 years with a* T-score *of –2.5 SD and no previous fracture.*

TABLE 54 *Cost-effectiveness of interventions in women aged 50–54 years with a* T-score *of –3.0 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	14,825	2.60	5694	895 to 26,623
Alendronate	15,171	2.14	7097	2691 to 15,514
Risedronate	116,966	2.14	54,728	41,069 to 81,612
Strontium ranelate	160,368	1.35	118,627	68,244 to 648,233
Vitamin K_1[b]	40,430	0.60	67,481	43,340 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.

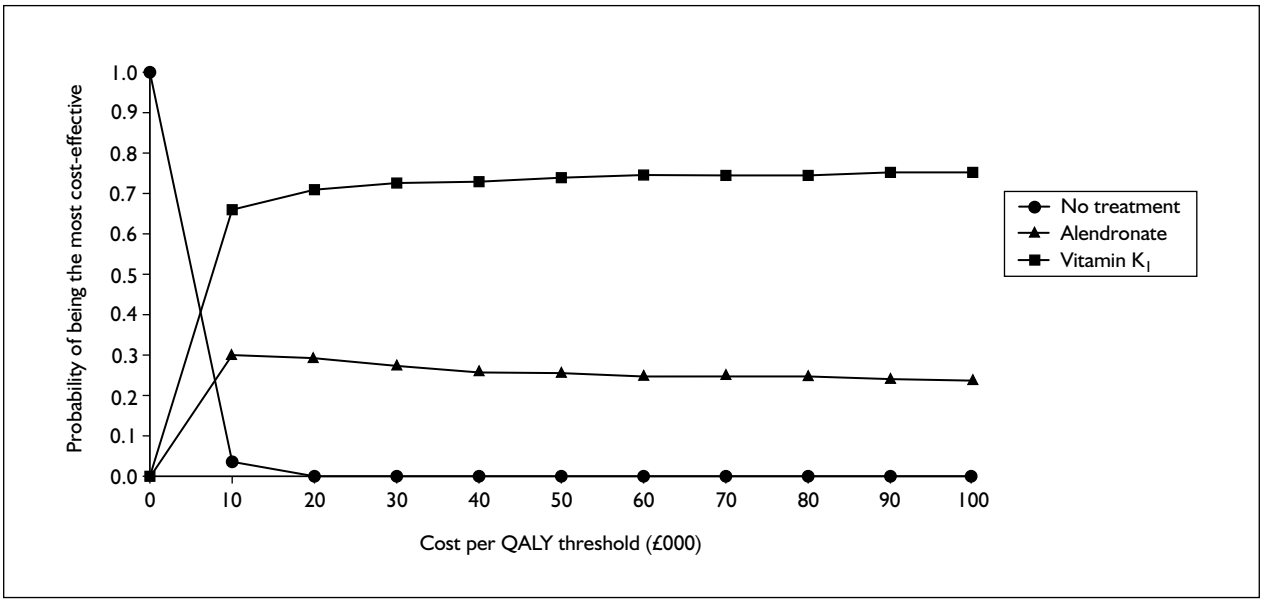

FIGURE 40 *Cost-effectiveness acceptability curves for interventions in women aged 50–54 years with a* T-score *of –3.0 SD and no previous fracture.*

TABLE 55 *Cost-effectiveness of interventions in women aged 55–59 years with a T-score of –2.5 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	23,594	1.90	12,407	6825 to 34,856
Alendronate	20,879	1.47	14,185	9412 to 23,095
Risedronate	122,721	1.47	83,375	65,777 to 112,756
Strontium ranelate	161,455	0.99	163,585	104,850 to 450,867
Vitamin K_1[b]	38,674	0.50	77,149	38,256 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost

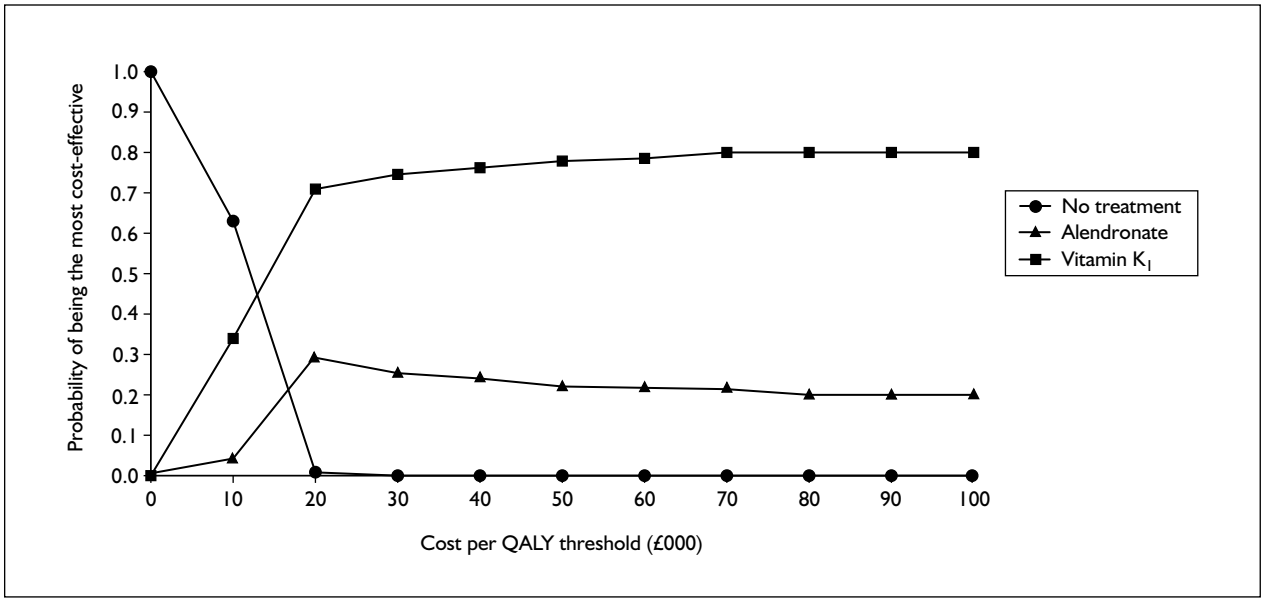

FIGURE 41 *Cost-effectiveness acceptability curves for interventions in women aged 55–59 years with a T-score of –2.5 SD and no previous fracture.*

The mean results for each intervention compared with no treatment for women aged 55–59 years with a *T*-score of –3.0 SD are given in *Table 56*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 42*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 60–64 years without previous fracture

The mean results for each intervention compared with no treatment for women aged 60–64 years with a *T*-score of –2.5 SD are given in *Table 57*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 43*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

TABLE 56 *Cost-effectiveness of interventions in women aged 55–59 years with a* T*-score of –3.0 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	11,583	2.84	4075	Dominating to 21,912
Alendronate	10,622	2.26	4700	909 to 11,670
Risedronate	112,442	2.26	49,750	37,506 to 73,282
Strontium ranelate	155,739	1.46	106,789	62,990 to 467,595
Vitamin K_1[b]	37,512	0.63	59,266	38,256 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

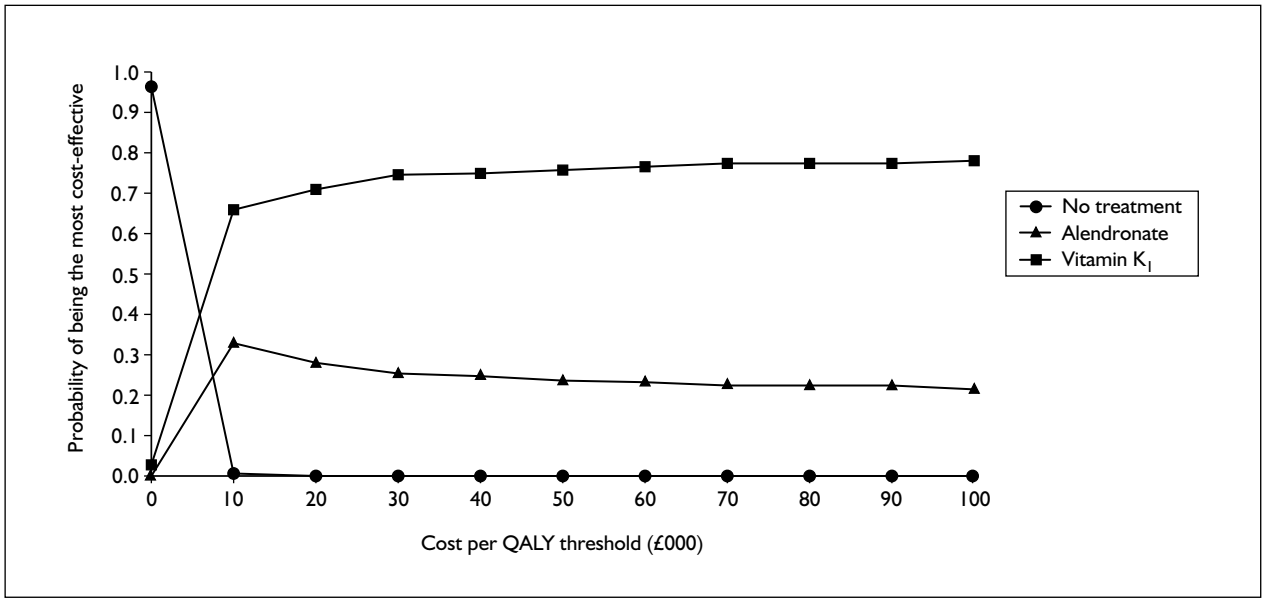

FIGURE 42 *Cost-effectiveness acceptability curves for interventions in women aged 55–59 years with a* T*-score of –3.0 SD and no previous fracture.*

TABLE 57 *Cost-effectiveness of interventions in women aged 60–64 years with a* T*-score of –2.5 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	22,238	2.17	10,235	4973 to 31,641
Alendronate	20,846	1.70	12,270	7731 to 20,594
Risedronate	122,683	1.70	72,209	56,644 to 98,655
Strontium ranelate	162,628	1.14	142,055	90,743 to 386,976
Vitamin K_1[b]	40,572	0.56	72,608	46,719 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.

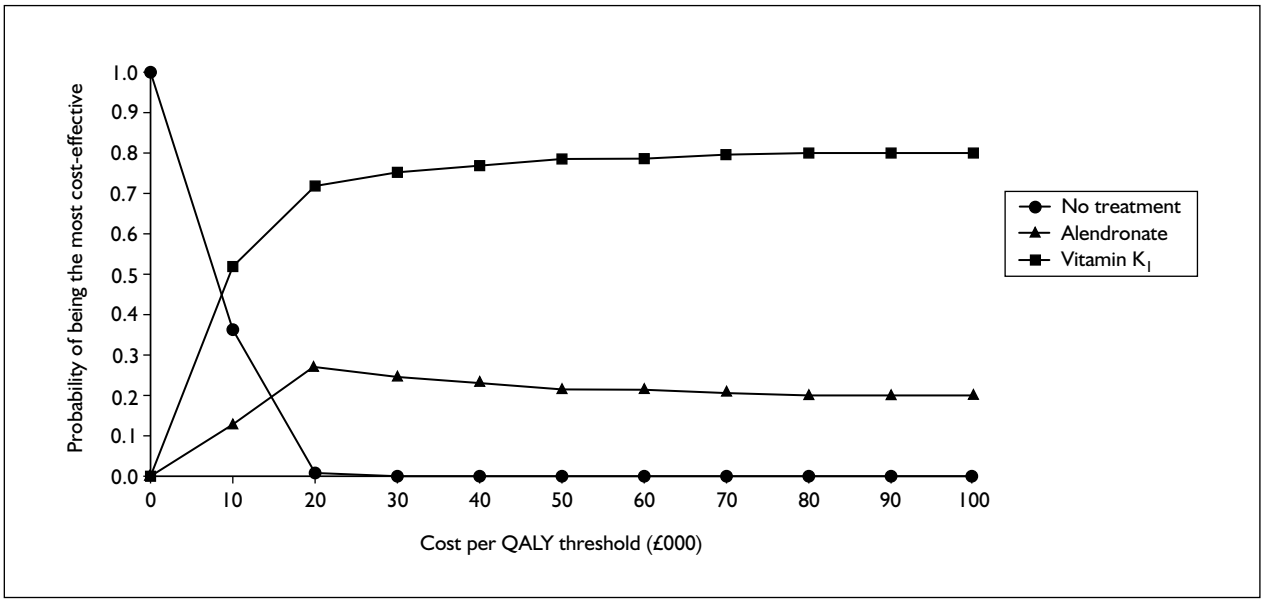

FIGURE 43 *Cost-effectiveness acceptability curves for interventions in women aged 60–64 years with a* T-*score of –2.5 SD and no previous fracture.*

TABLE 58 *Cost-effectiveness of interventions in women aged 60–64 years with a* T-*score of –3.0 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	10,354	3.19	3244	Dominating to 20,762
Alendronate	11,522	2.55	4517	691 to 11,443
Risedronate	113,337	2.55	44,435	33,317 to 65,618
Strontium ranelate	158,284	1.66	95,172	55,947 to 383,786
Vitamin K_1[b]	40,771	0.71	57,815	37,307 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

The mean results for each intervention compared with no treatment for women aged 60–64 years with a *T*-score of –3.0 SD are given in *Table 58*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 44*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 65–69 years without previous fracture

The mean results for each intervention compared with no treatment for women aged 65–69 years with a *T*-score of –2.5 SD are given in *Table 59*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 45*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

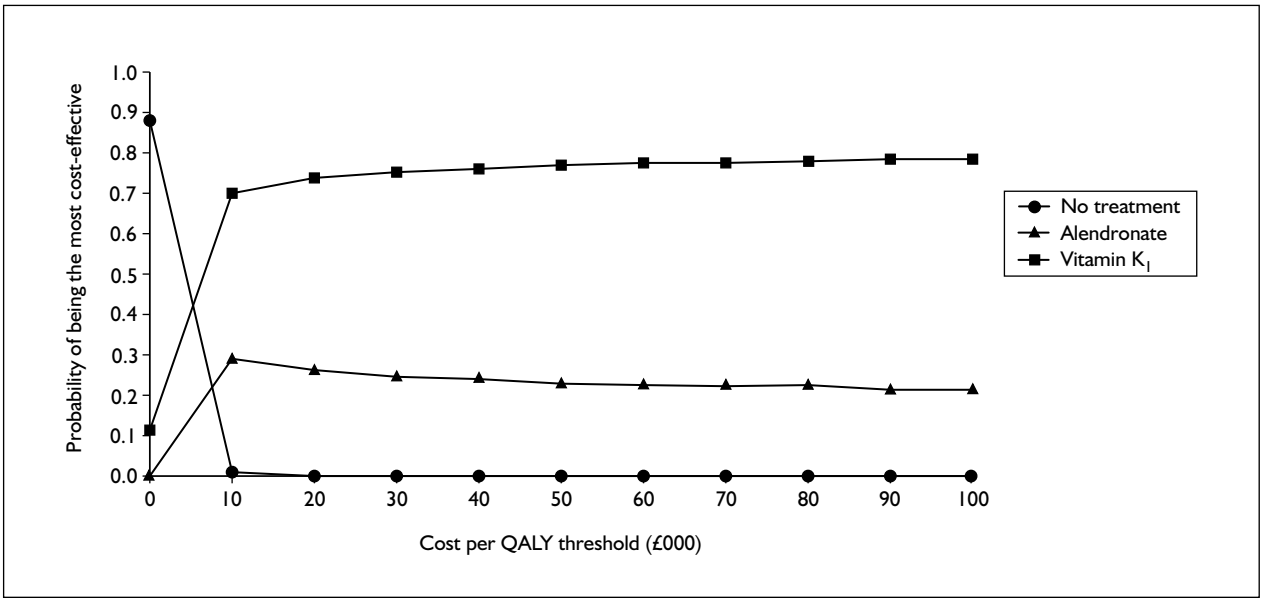

FIGURE 44 *Cost-effectiveness acceptability curves for interventions in women aged 60–64 years with a* T-score *of –3.0 SD and no previous fracture.*

TABLE 59 *Cost-effectiveness of interventions in women aged 65–69 years with a* T-score *of –2.5 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	16,300	2.43	6719	1689 to 28,573
Alendronate	16,306	1.95	8349	3816 to 16,248
Risedronate	118,135	1.95	60,492	46,580 to 85,872
Strontium ranelate	160,538	1.31	122,893	75,829 to 370,798
Vitamin K_1[b]	40,351	0.52	77,817	49,921 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.

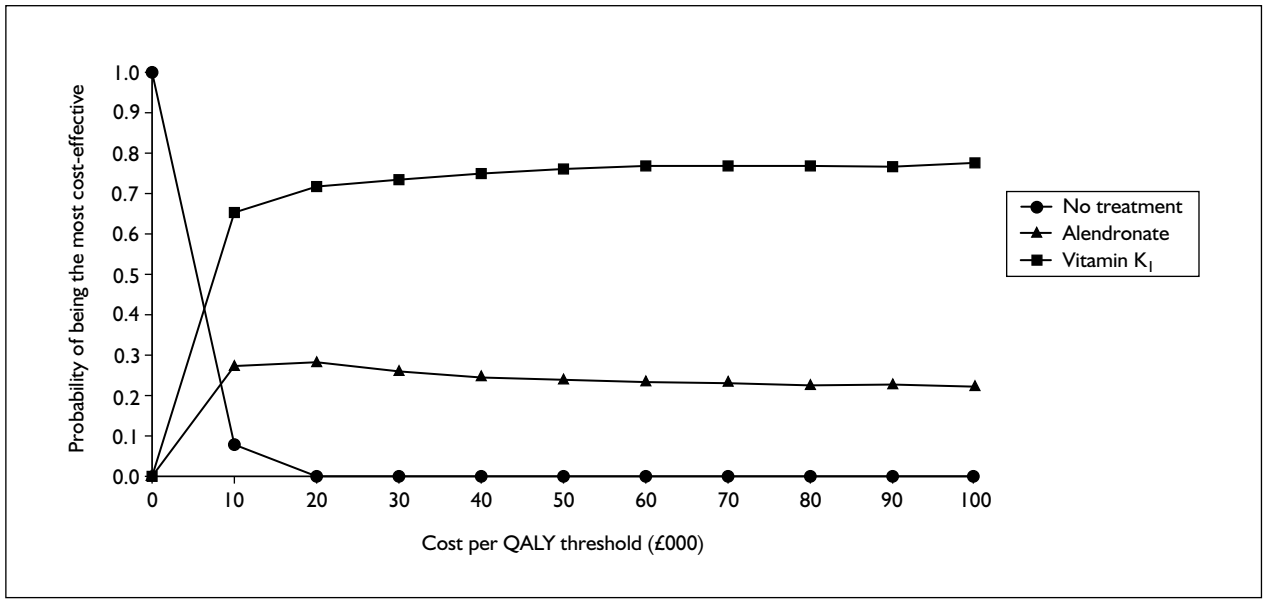

FIGURE 45 *Cost-effectiveness acceptability curves for interventions in women aged 65–69 years with a* T-score *of –2.5 SD and no previous fracture.*

TABLE 60 *Cost-effectiveness of interventions in women aged 65–69 years with a T-score of –3.0 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	1309	3.55	368	Dominating to 21,912
Alendronate	4641	2.91	1596	Dominating to 14,305
Risedronate	106,444	2.91	36,613	26,528 to 55,835
Strontium ranelate	155,174	1.89	82,245	45,579 to 380,423
Vitamin K_1[b]	40,488	0.65	61,838	39,753 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

The mean results for each intervention compared with no treatment for women aged 65–69 years with a *T*-score of –3.0 SD are given in *Table 60*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 46*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 70–74 years without previous fracture

The mean results for each intervention compared with no treatment for women aged 70–74 years with a *T*-score of –2.5 SD are given in *Table 61*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 47*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

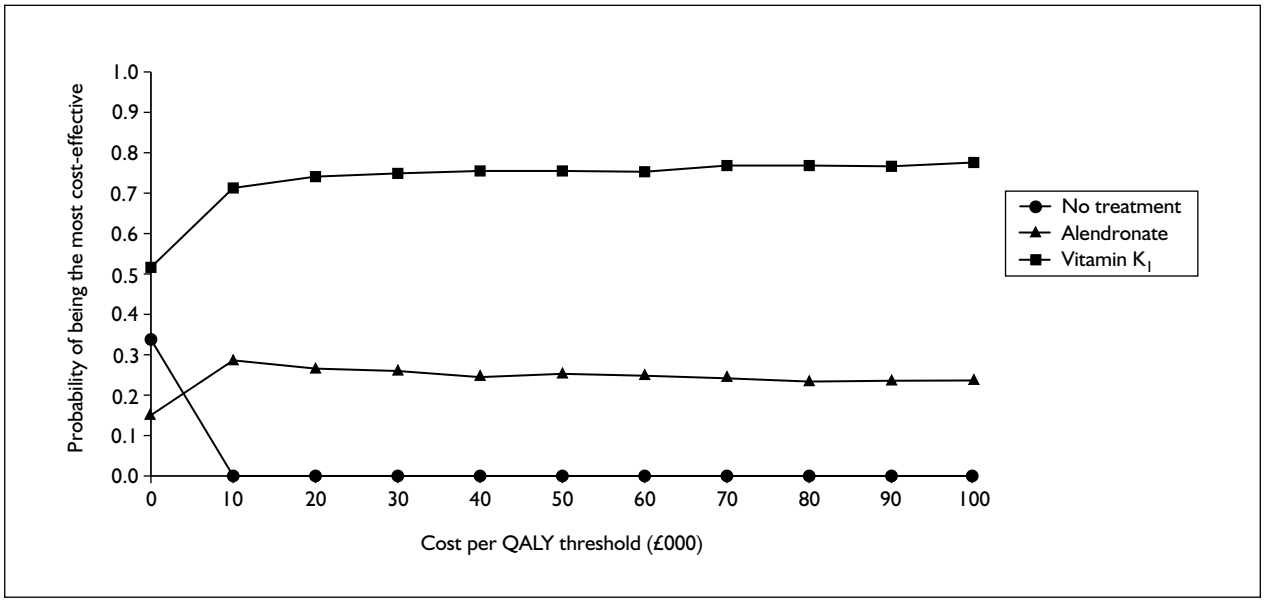

FIGURE 46 *Cost-effectiveness acceptability curves for interventions in women aged 65–69 years with a T-score of –3.0 SD and no previous fracture.*

TABLE 61 *Cost-effectiveness of interventions in women aged 70–74 years with a T-score of –2.5 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	11,426	2.78	4113	Dominating to 25,268
Alendronate	12,560	2.23	5635	1335 to 13,269
Risedronate	114,683	2.23	51,319	38,900 to 74,558
Strontium ranelate	158,787	1.48	107,188	63,930 to 354,275
Vitamin K_1[b]	41,571	0.57	73,312	47,802 to dominating

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.
Dominating denotes more health provided at a lower or equal acquisition cost.

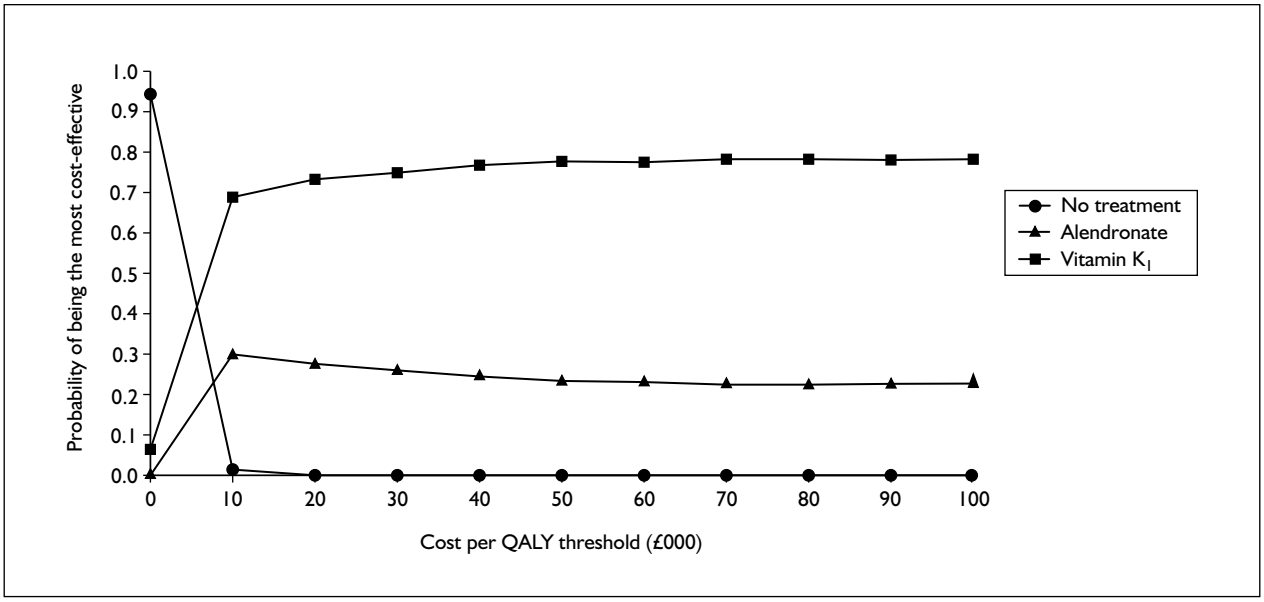

FIGURE 47 *Cost-effectiveness acceptability curves for interventions in women aged 70–74 years with a T-score of –2.5 SD and no previous fracture.*

The mean results for each intervention compared with no treatment for women aged 70–74 years with a *T*-score of –3.0 SD are given in *Table 62*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 48*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 75–79 years without previous fracture

The mean results for each intervention compared with no treatment for women aged 75–79 years with a *T*-score of –2.5 SD are given in *Table 63*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 49*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

TABLE 62 *Cost-effectiveness of interventions in women aged 70–74 years with a* T-score *of –3.0 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–6325	4.05	Dominating	Dominating to 14,915
Alendronate	–933	3.28	Dominating	Dominating to 6350
Risedronate	100,860	3.28	30,714	21,512 to 48,318
Strontium ranelate	152,594	2.12	71,955	38,418 to 367,355
Vitamin K_1[b]	42,007	0.72	58,702	38,495 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

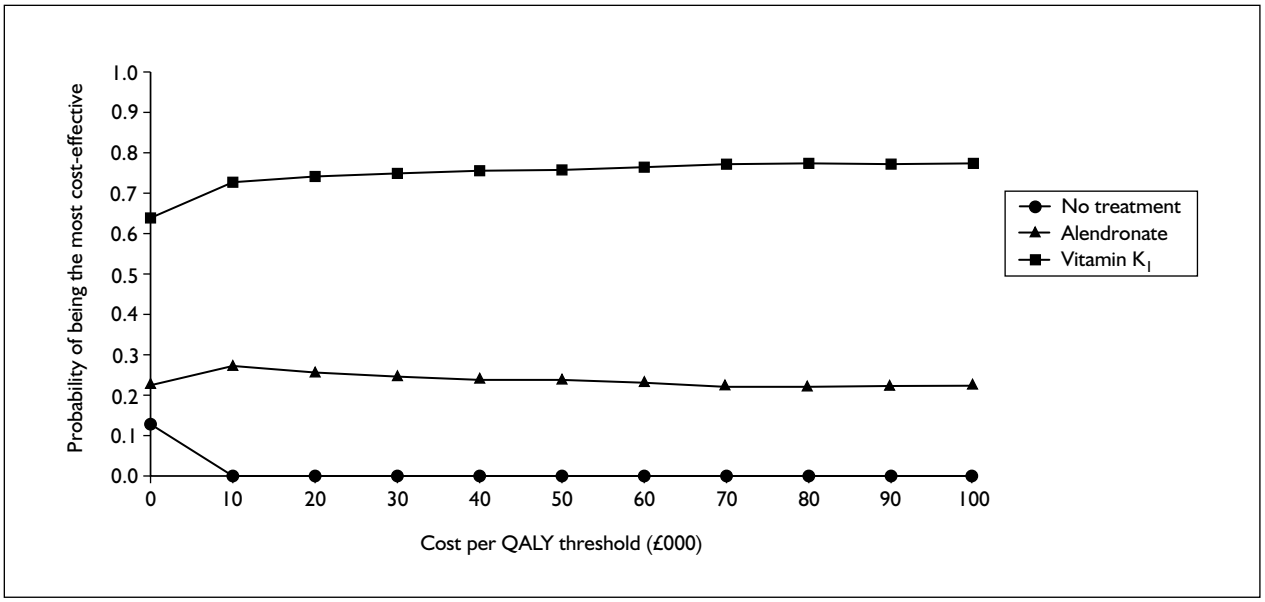

FIGURE 48 *Cost-effectiveness acceptability curves for interventions in women aged 70–74 years with a* T-score *of –3.0 SD and no previous fracture.*

TABLE 63 *Cost-effectiveness of interventions in women aged 75–79 years with a* T-score *of -2.5 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–2020	3.48	Dominating	Dominating to 17,433
Alendronate	3383	2.76	1226	Dominating to 8757
Risedronate	105,184	2.76	30,714	27,362 to 58,785
Strontium ranelate	154,586	1.78	71,955	47,443 to 438,311
Vitamin K_1[b]	40,795	0.53	77,424	49,981 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

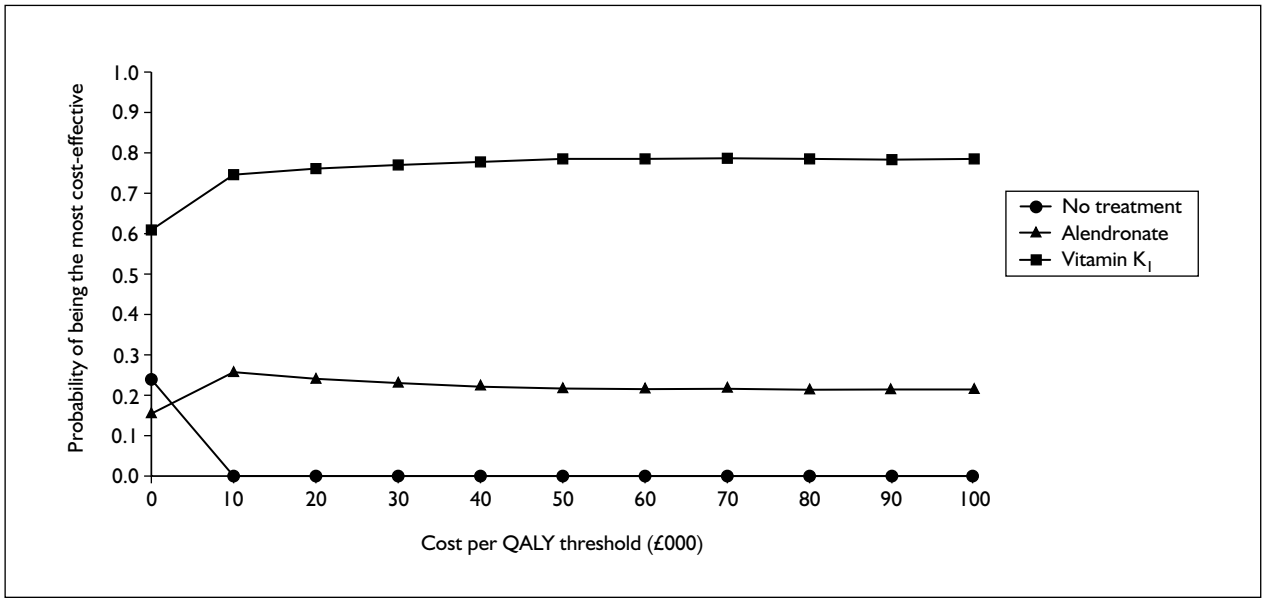

FIGURE 49 *Cost-effectiveness acceptability curves for interventions in women aged 75–79 years with a* T-score *of –2.5 SD and no previous fracture.*

The mean results for each intervention compared with no treatment for women aged 75–79 years with a *T*-score of –3.0 SD are given in *Table 64*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 50*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Results for women with a previous fracture

Women aged 50–54 years with a previous fracture

The mean results for each intervention compared with no treatment for women aged 50–54 years with a *T*-score of –2.5 SD are given in *Table 65*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 51*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and

TABLE 64 *Cost-effectiveness of interventions in women aged 75–79 years with a* T-score *of –3.0 SD and no previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–25,815	5.06	Dominating	Dominating to 14,915
Alendronate	–14,001	4.02	Dominating	Dominating to 6350
Risedronate	87,759	4.02	21,807	13,434 to 38,567
Strontium ranelate	146,678	2.53	58,090	27,634 to 470,415
Vitamin K_1[b]	41,316	0.89	46,674	38,495 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

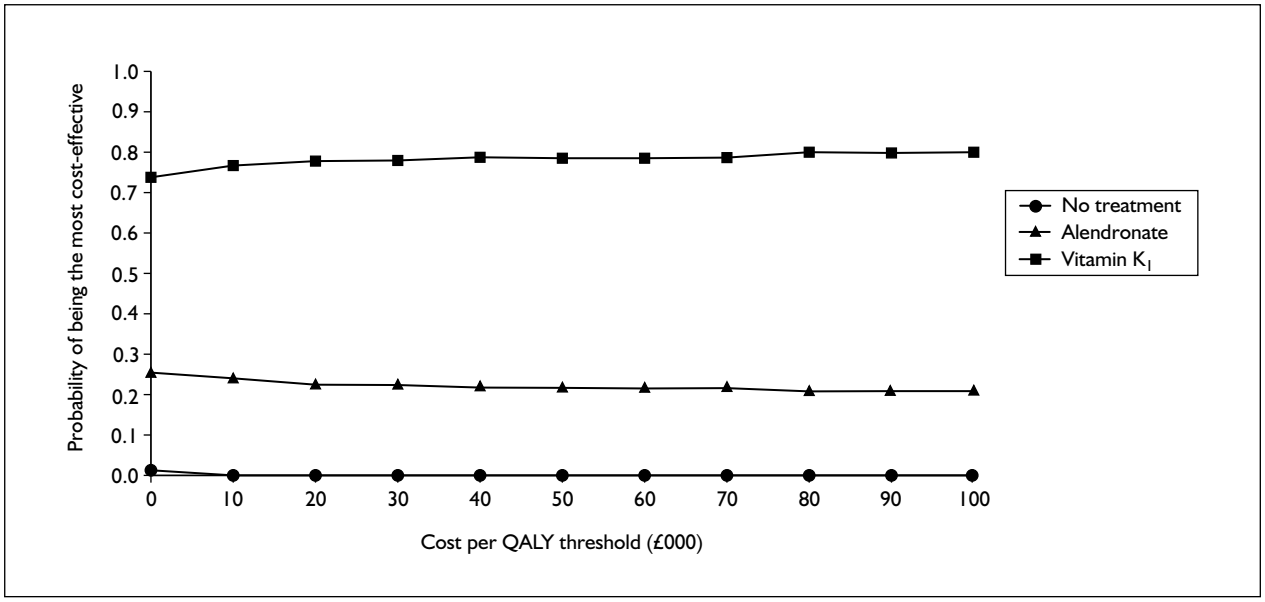

FIGURE 50 *Cost-effectiveness acceptability curves for interventions in women aged 75–79 years with a* T*-score of –3.0 SD and no previous fracture.*

TABLE 65 *Cost-effectiveness of interventions in women aged 50–54 years with a* T*-score of –2.5 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	18,911	2.52	7500	2761 to 26,132
Alendronate	18,062	2.09	8625	4720 to 15,615
Risedronate	119,902	2.09	57,255	44,474 to 79,065
Strontium ranelate	161,219	1.41	114,241	72,240 to 320,586
Vitamin K_1[b]	40,327	0.68	59,678	38,270 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.

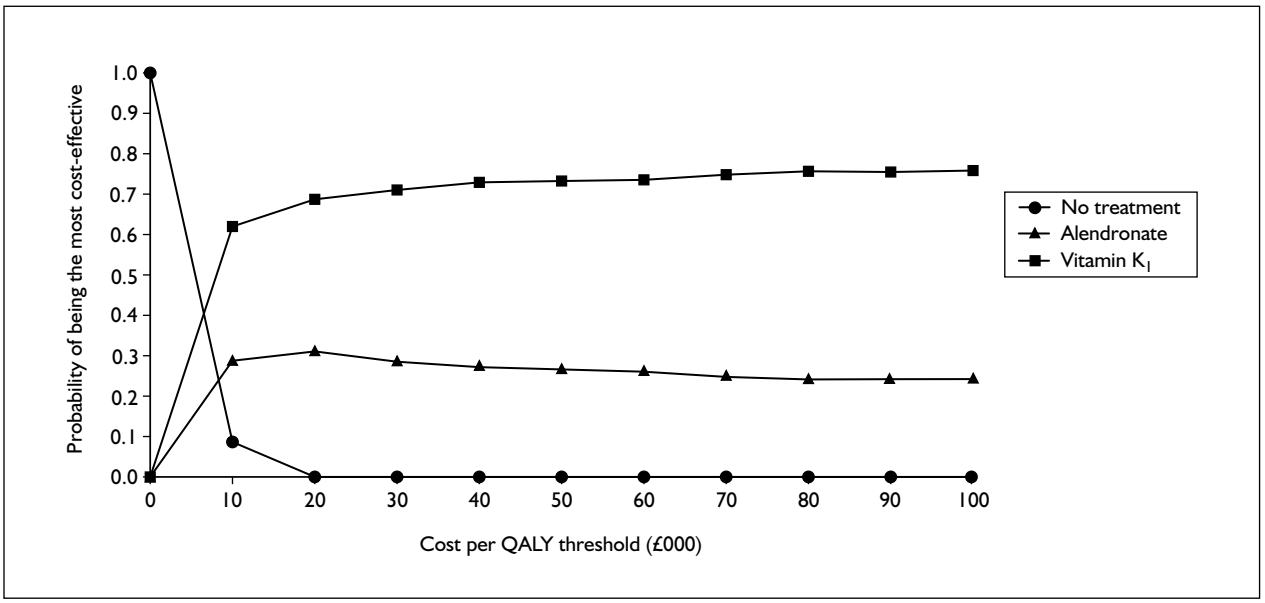

FIGURE 51 *Cost-effectiveness acceptability curves for interventions in women aged 50–54 years with a* T*-score of –2.5 SD and with a previous fracture.*

TABLE 66 *Cost-effectiveness of interventions in women aged 50–54 years with a T-score of –3.0 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	2170	3.86	562	Dominating to 16,895
Alendronate	4898	3.26	1502	Dominating to 7812
Risedronate	106,706	3.26	32,721	23,719 to 50,372
Strontium ranelate	155,294	2.09	74,373	41,314 to 384,617
Vitamin K_1[b]	40,579	0.85	47,537	30,596 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

The mean results for each intervention compared with no treatment for women aged 50–54 years with a *T*-score of –3.0 SD are given in *Table 66*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 52*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 55–59 years with a previous fracture

The mean results for each intervention compared with no treatment for women aged 55–59 years with a *T*-score of –2.5 SD are given in *Table 67*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 53*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

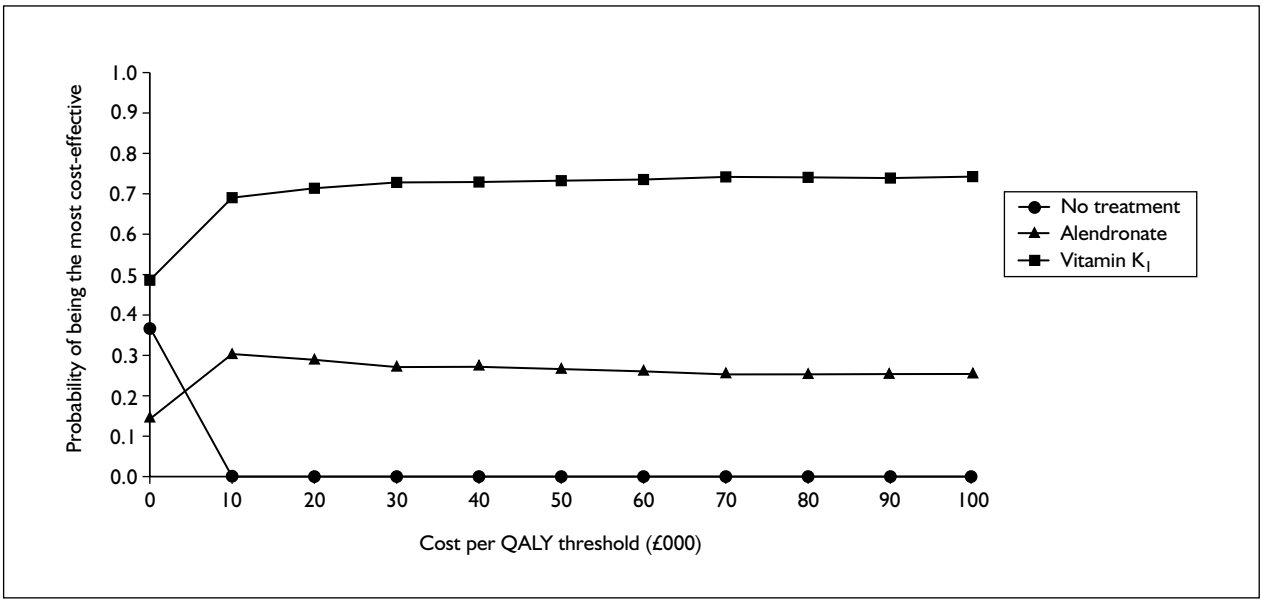

FIGURE 52 *Cost-effectiveness acceptability curves for interventions in women aged 50–54 years with a T-score of –3.0 SD and with a previous fracture.*

TABLE 67 *Cost-effectiveness of interventions in women aged 55–59 years with a T-score of –2.5 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	15,324	2.82	5441	1388 to 21,588
Alendronate	13,460	2.27	5935	2459 to 11,751
Risedronate	115,294	2.27	50,833	39,453 to 70,322
Strontium ranelate	156,925	1.55	101,563	65,044 to 267,052
Vitamin K_1[b]	37,945	0.72	53,007	34,025 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominated means that less health is provided at a higher or equal acquisition cost.

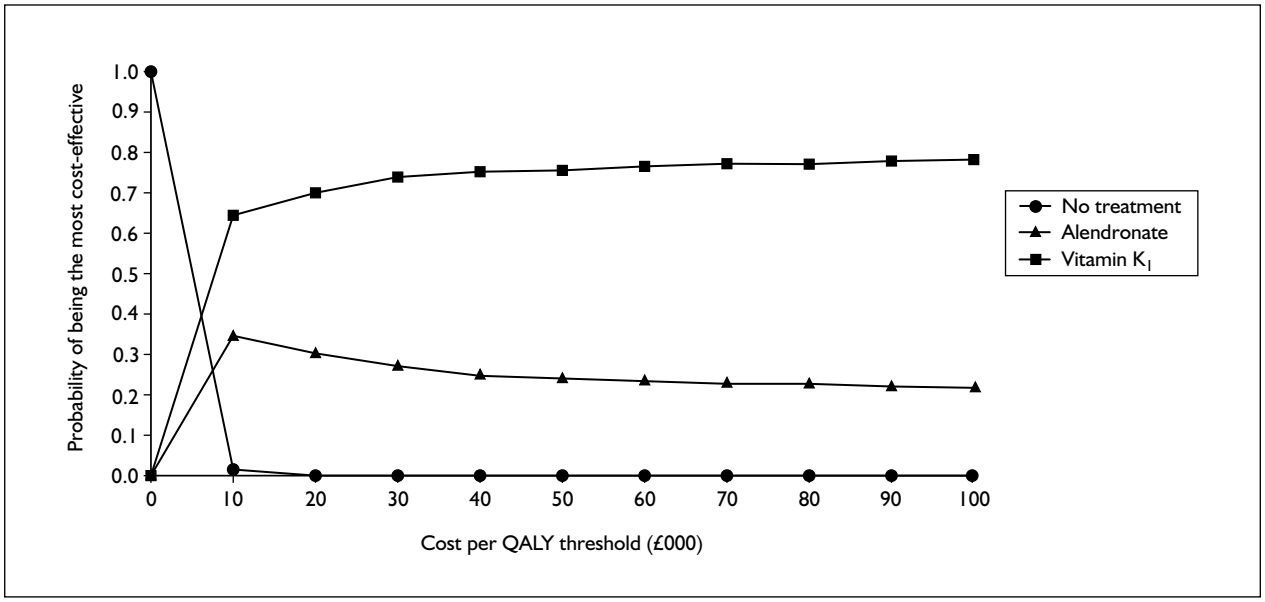

FIGURE 53 *Cost-effectiveness acceptability curves for interventions in women aged 55–59 years with a T-score of –2.5 SD and with a previous fracture.*

The mean results for each intervention compared with no treatment for women aged 55–59 years with a *T*-score of –3.0 SD are given in *Table 68*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 54*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 60–64 years with a previous fracture

The mean results for each intervention compared with no treatment for women aged 60–64 years with a *T*-score of –2.5 SD are given in *Table 69*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 55*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

TABLE 68 *Cost-effectiveness of interventions in women aged 55–59 years with a* T-score *of –3.0 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–2692	4.22	Dominating	Dominating to 11,688
Alendronate	–1926	3.45	Dominating	Dominating to 4547
Risedronate	99,876	3.45	28,985	20,968 to 44,285
Strontium ranelate	148,351	2.25	65,972	37,095 to 282,316
Vitamin K_1[b]	34,807	1.27	27,329	38,495 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

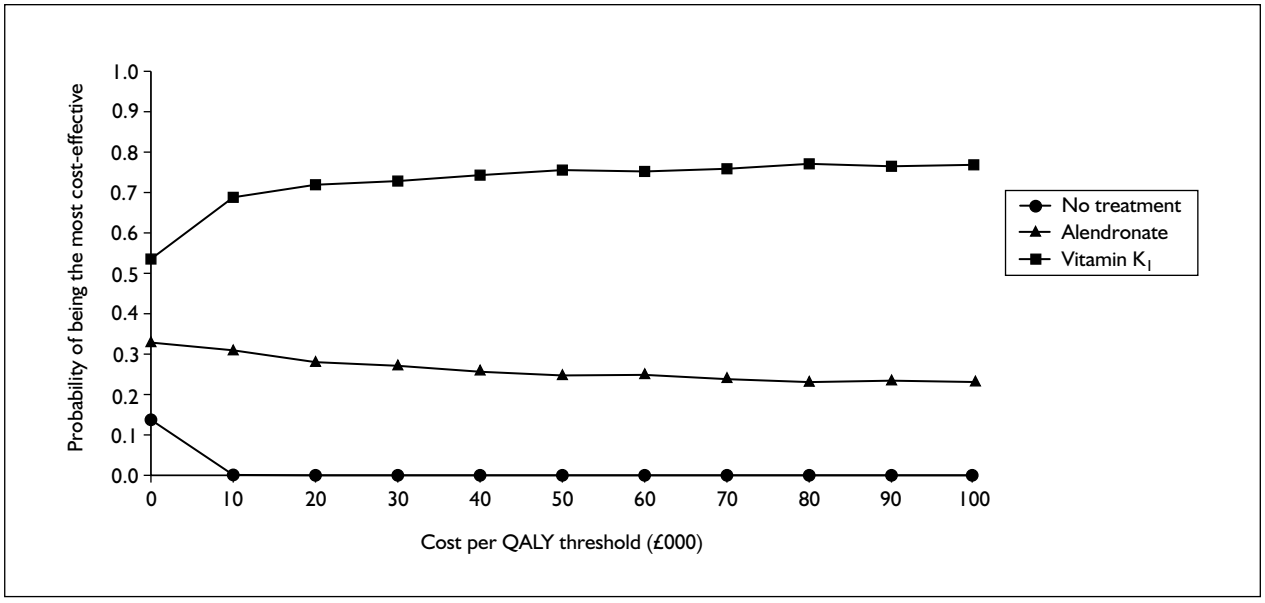

FIGURE 54 *Cost-effectiveness acceptability curves for interventions in women aged 55–59 years with a* T-score *of –3.0 SD and with a previous fracture.*

TABLE 69 *Cost-effectiveness of interventions in women aged 60–64 years with a* T-score *of –2.5 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	13,290	3.20	4149	Dominating to 20,229
Alendronate	13,411	2.60	5161	1833 to 11,565
Risedronate	115,237	2.60	44,347	34,351 to 62,489
Strontium ranelate	158,684	1.77	89,445	57,137 to 246,718
Vitamin K_1[b]	40,791	0.78	52,159	33,663 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
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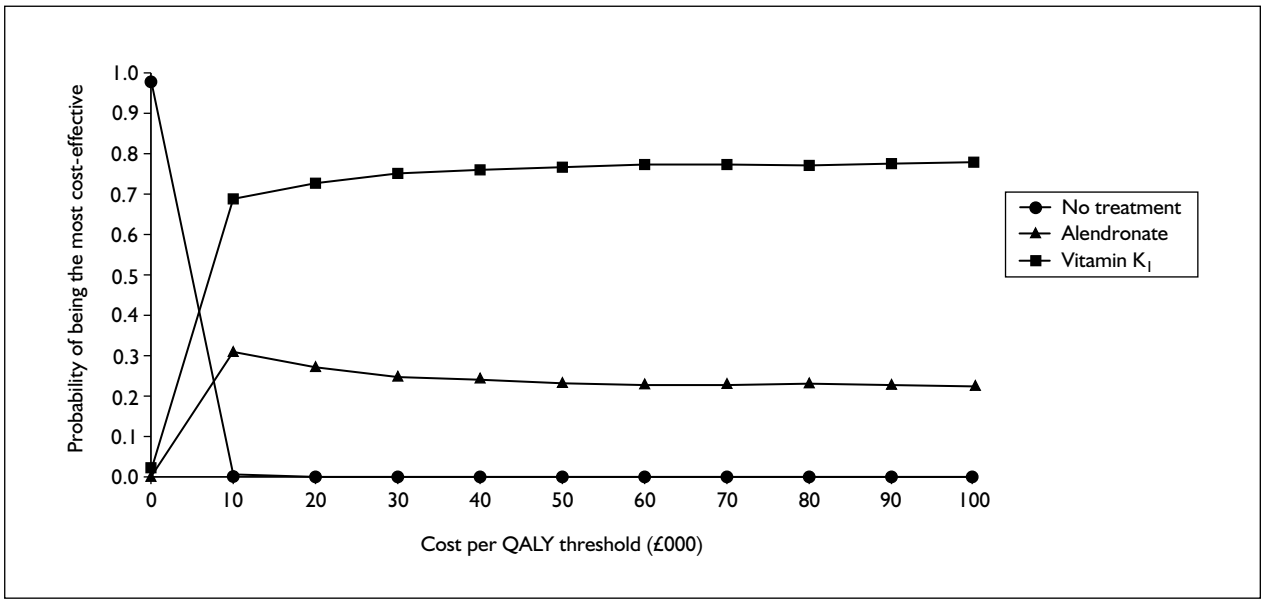

FIGURE 55 *Cost-effectiveness acceptability curves for interventions in women aged 60–64 years with a* T*-score of –2.5 SD and with a previous fracture.*

The mean results for each intervention compared with no treatment for women aged 60–64 years with a *T*-score of –3.0 SD are given in *Table 70*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 56*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 65–69 years with a previous fracture

The mean results for each intervention compared with no treatment for women aged 65–69 years with a *T*-score of –2.5 SD are given in *Table 71*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 57*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

The mean results for each intervention compared with no treatment for women aged 65–69 years with a *T*-score of –3.0 SD are given in *Table 72*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 58*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 70–74 years with a previous fracture

The mean results for each intervention compared with no treatment for women aged 70–74 years with a *T*-score of –2.5 SD are given in *Table 73*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 59*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

The mean results for each intervention compared with no treatment for women aged 70–74 years with a *T*-score of –3.0 SD are given in *Table 74*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the

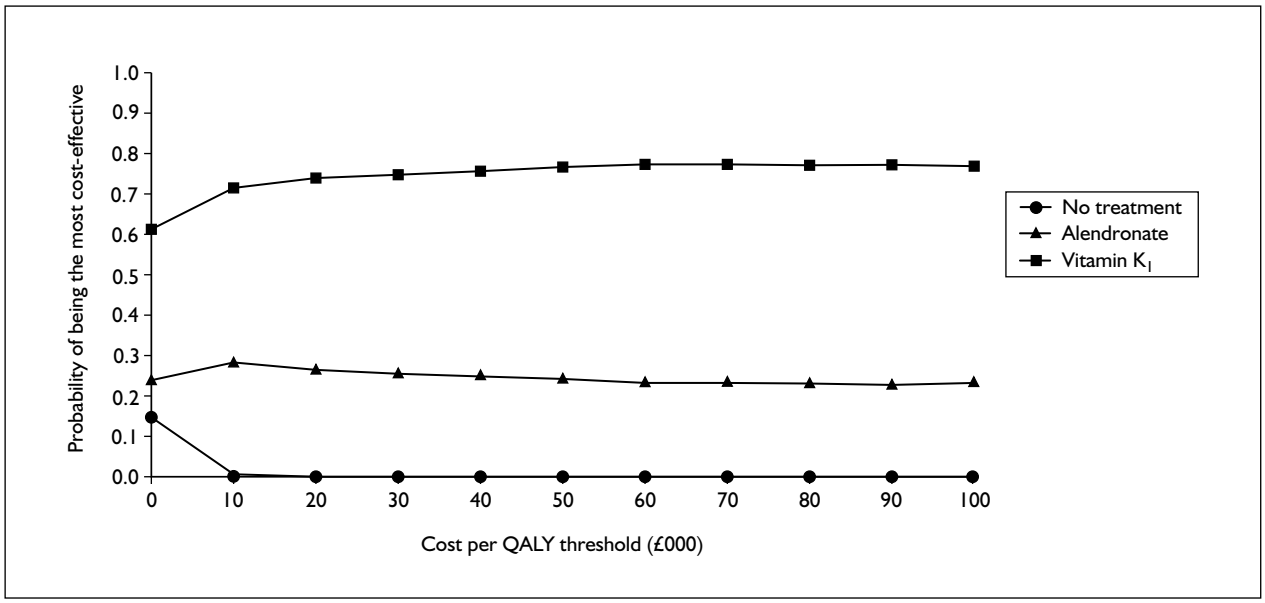

FIGURE 56 *Cost-effectiveness acceptability curves for interventions in women aged 60–64 years with a* T-score *of –3.0 SD and with a previous fracture.*

TABLE 71 *Cost-effectiveness of interventions in women aged 65–69 years with a* T-score *of –2.5 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in Cost per QALY (£)
Vitamin K_1	4383	3.60	1217	Dominating to 16,987
Alendronate	6600	2.99	2208	Dominating to 8117
Risedronate	108,415	2.99	36,263	27,068 to 53,153
Strontium ranelate	155,549	2.02	76,845	45,675 to 230,525
Vitamin K_1[b]	40,458	0.74	54,549	35,050 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

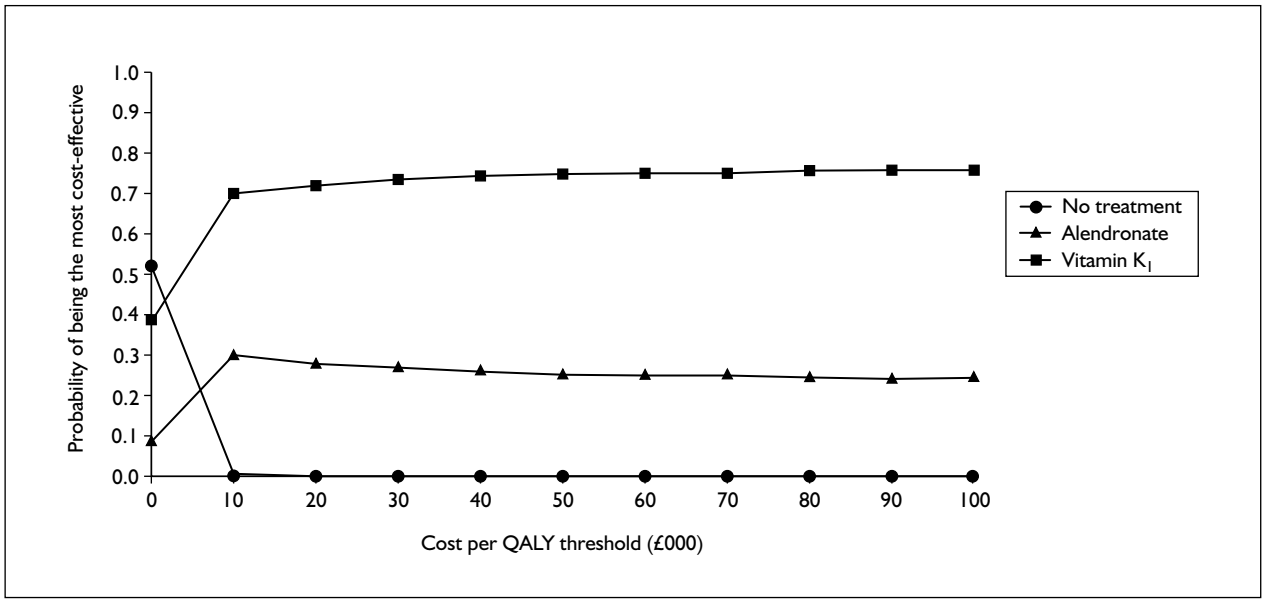

FIGURE 57 *Cost-effectiveness acceptability curves for interventions in women aged 65–69 years with a* T-score *of –2.5 SD and with a previous fracture.*

TABLE 72 *Cost-effectiveness of interventions in women aged 65–69 years with a* T-score *of –3.0 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–18,103	5.29	Dominating	Dominating to 9277
Alendronate	–10,9877	4.42	Dominating	Dominating to 2851
Risedronate	90,879	4.42	20,576	18,617 to 33,783
Strontium ranelate	147,504	2.89	51,015	33,130 to 238,938
Vitamin K_1[b]	40,665	0.94	43,398	27,971 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

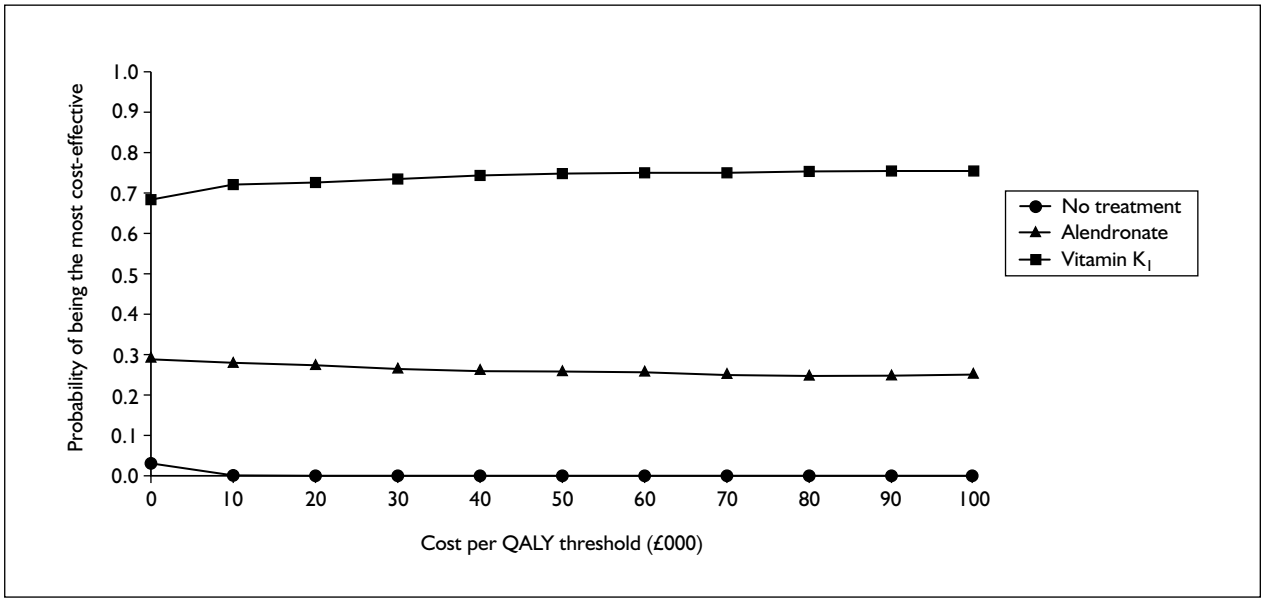

FIGURE 58 *Cost-effectiveness acceptability curves for interventions in women aged 65–69 years with a* T-score *of –3.0 SD and with a previous fracture.*

TABLE 73 *Cost-effectiveness of interventions in women aged 70–74 years with a* T-score *of –2.5 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–2927	4.11	Dominating	Dominating to 14,924
Alendronate	981	3.39	289	Dominating to 6122
Risedronate	102,787	3.39	30,307	21,865 to 45,710
Strontium ranelate	152,923	2.28	67,144	38,251 to 224,900
Vitamin K_1[b]	42,291	0.79	53,522	35,219 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
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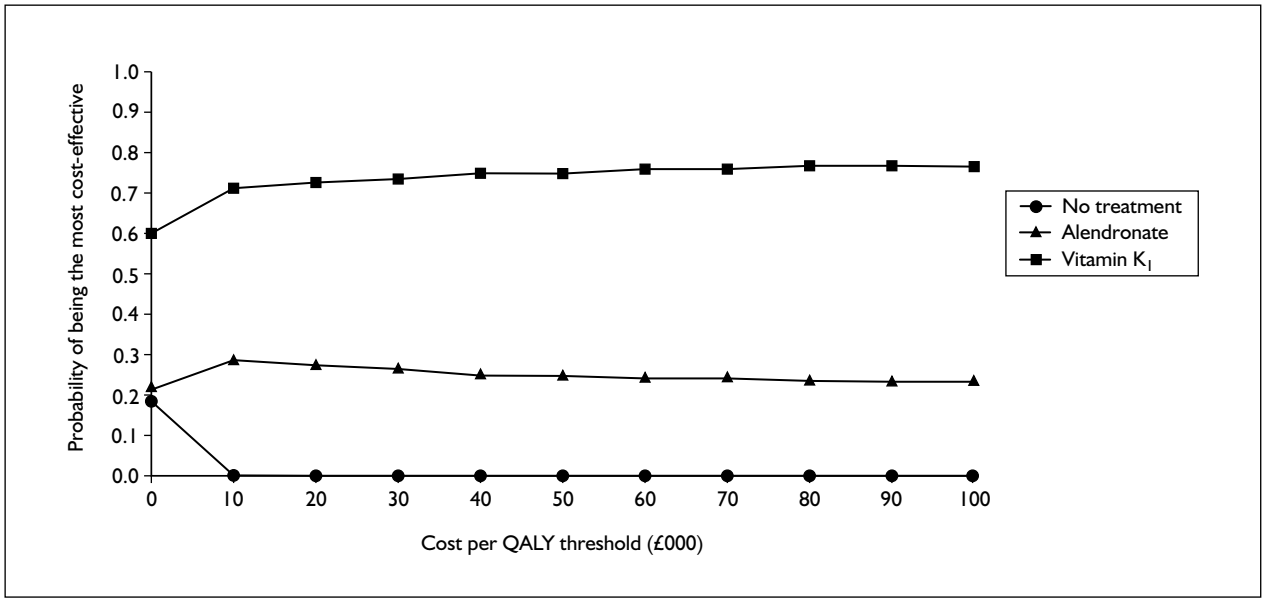

FIGURE 59 *Cost-effectiveness acceptability curves for interventions in women aged 70–74 years with a T-score of –2.5 SD and with a previous fracture.*

TABLE 74 *Cost-effectiveness of interventions in women aged 70–74 years with a T-score of –3.0 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–29,554	6.00	Dominating	Dominating to 8391
Alendronate	–19,258	4.97	Dominating	Dominating to 1426
Risedronate	82,503	4.97	16,612	9843 to 29,107
Strontium ranelate	143,633	3.23	44,457	21,477 to 227,060
Vitamin K_1[b]	42,944	1.00	43,039	28,552 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 60*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

Women aged 75–79 years with a previous fracture

The mean results for each intervention compared with no treatment for women aged 75–79 years with a *T*-score of –2.5 SD are given in *Table 75*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 61*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

The mean results for each intervention compared with no treatment for women aged 75–79 years with a *T*-score of –3.0 SD are given in *Table 76*.

It is seen that both alendronate and vitamin K_1 have relatively low cost per QALY ratios. Incremental analyses suggest that vitamin K_1 is the

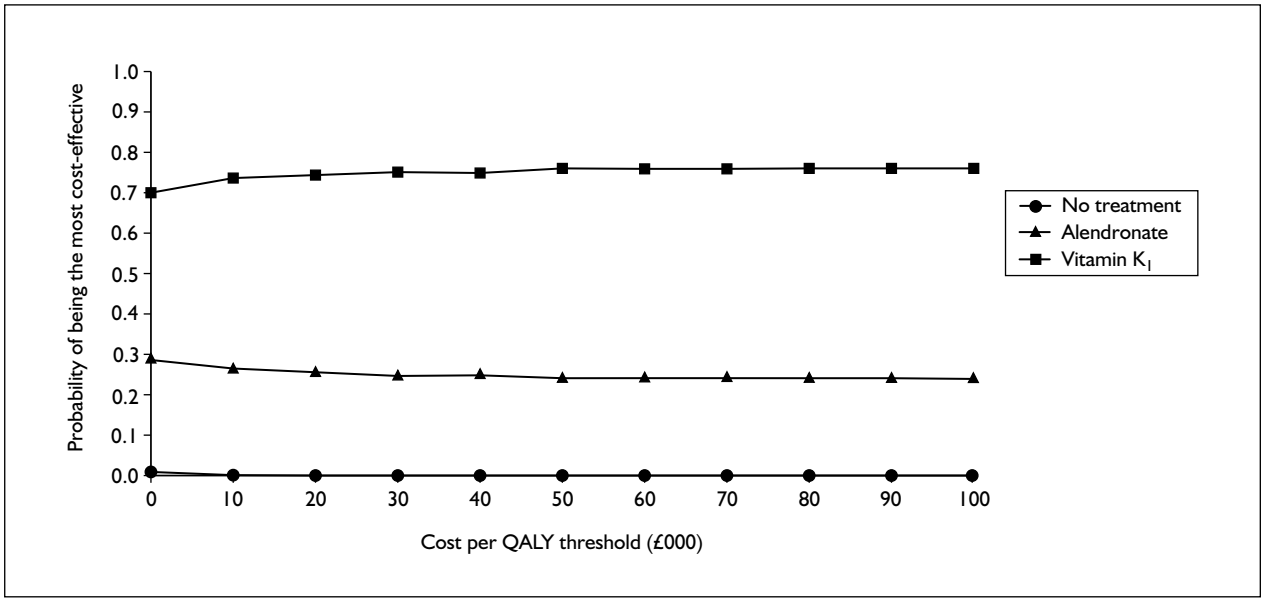

FIGURE 60 *Cost-effectiveness acceptability curves for interventions in women aged 70–74 years with a* T-score *of –3.0 SD and with a previous fracture.*

TABLE 75 *Cost-effectiveness of interventions in women aged 75–79 years with a* T-score *of –2.5 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–23,097	5.18	Dominating	Dominating to 9598
Alendronate	–12,784	4.20	Dominating	Dominating to 2716
Risedronate	88,988	4.20	21,187	13,497 to 35,546
Strontium ranelate	143,633	3.23	53,727	27,028 to 265,902
Vitamin K_1[b]	41,125	0.75	54,524	35,361 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

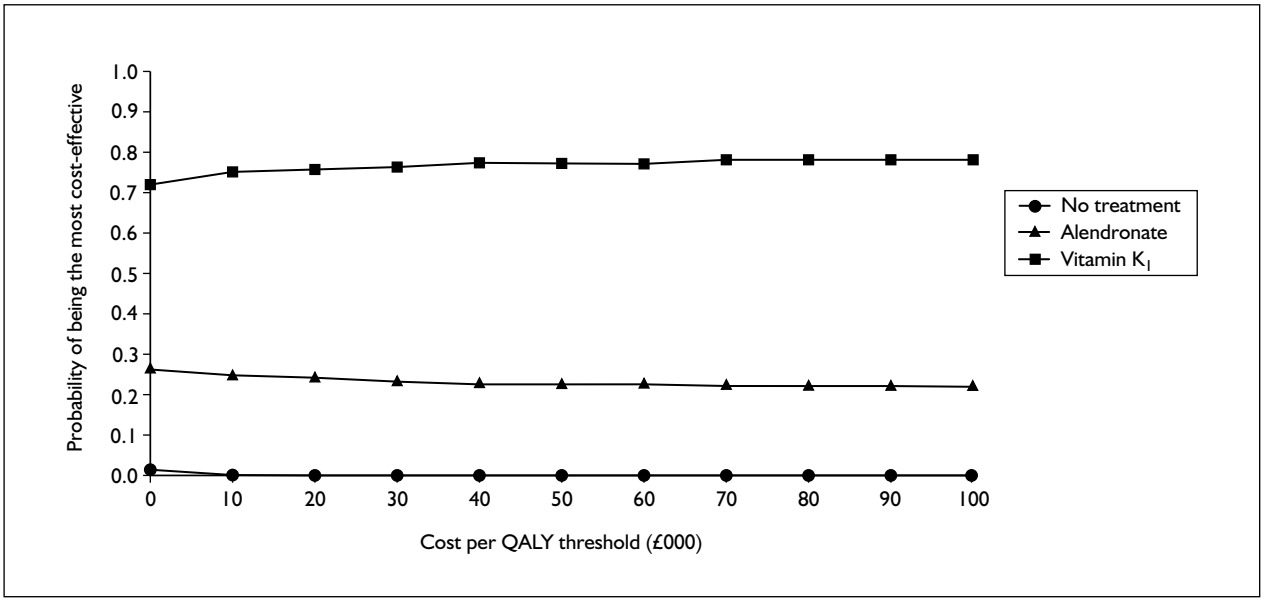

FIGURE 61 *Cost-effectiveness acceptability curves for interventions in women aged 75–79 years with a* T-score *of –2.5 SD and with a previous fracture.*

TABLE 76 *Cost-effectiveness of interventions in women aged 75–79 years with a T-score of –3.0 SD and with a previous fracture*

	Incremental cost compared with no treatment (£)[a]	Incremental QALYs compared with no treatment[a]	Cost per QALY compared with no treatment (£)	95% CI for range in cost per QALY (£)
Vitamin K_1	–58,789	7.54	Dominating	Dominating to 6220
Alendronate	–38,860	6.09	Dominating	Dominating to dominating
Risedronate	62,851	6.09	10,314	4232 to 22,238
Strontium ranelate	134,759	3.85	35,006	13,506 to 295,993
Vitamin K_1[b]	41,503	0.95	43,554	28,397 to dominated

a Per 100 women.
b Assuming no effect on hip or vertebral fractures.
Dominating denotes more health provided at a lower or equal acquisition cost.
Dominated means that less health is provided at a higher or equal acquisition cost.

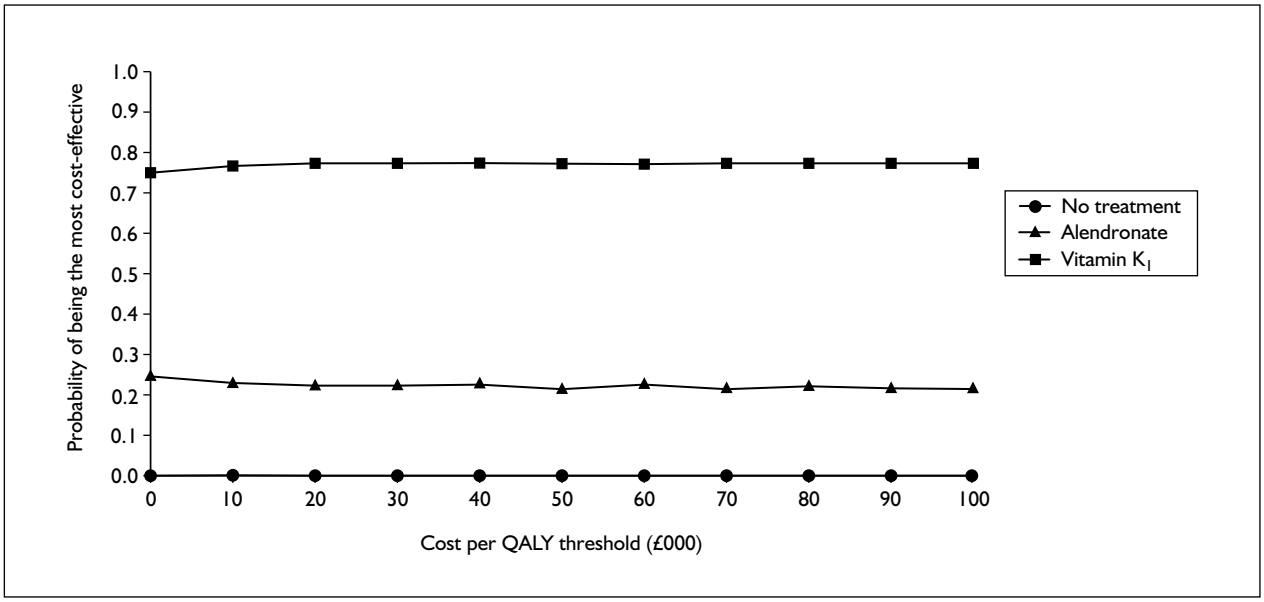

FIGURE 62 *Cost-effectiveness acceptability curves for interventions in women aged 75–79 years with a T-score of –3.0 SD and with a previous fracture.*

most cost-effective intervention. The dominance of alendronate and vitamin K_1 is shown in *Figure 62*. However, it is seen that if the efficacy associated with vitamin K_1 is applicable only to wrist and proximal humerus fractures and not to hip or vertebral fractures then the QALYs gained are dramatically reduced.

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Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al.*

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al.*

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Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al.*

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al.*

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

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Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

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Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al.*

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Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al.*

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The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
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Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al.*

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al.*

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

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Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.*

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al.*

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al.*

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al.*

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.
By Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, *et al.*

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.
By Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, *et al.*

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.
By McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, *et al.*

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, *et al.*

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

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Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.
By Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al.*

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A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).
By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al.*

No. 29
Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.
By Andronis L, Barton P, Bryan S.

Suppl. 1
Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.
By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.
By Chilcott J, Lloyd Jones M, Wilkinson A.

The use of paclitaxel in the management of early stage breast cancer.
By Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, *et al.*

Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma.
By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.
By Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, *et al.*

Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.
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Erlotinib for the treatment of relapsed non-small cell lung cancer.
By McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, *et al.*

Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.
By Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, *et al.*

Infliximab for the treatment of adults with psoriasis.
By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.

No. 30
Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.
By Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, *et al.*

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The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.
By Rogowski R, Burch J, Palmer S, Craigs C, Golder S, Woolacott N.

No. 32
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.
By Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, *et al.*

No. 33
A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.
By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al.*, on behalf of the 3CPO study investigators.

No. 34
Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.
By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

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Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.
By Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al.*

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Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.
By Hewitt CE, Gilbody SM, Brealey S, Paulden M, Palmer S, Mann R, *et al.*

No. 37
A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.
By Williamson I, Benge S, Barton S, Petrou S, Letley L, Fasey N, *et al.*

No. 38
The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.
By Bond M, Pitt M, Akoh J, Moxham T, Hoyle M, Anderson R.

No. 39
Rehabilitation of older patients: day hospital compared with rehabilitation at home. A randomised controlled trial.
By Parker SG, Oliver P, Pennington M, Bond J, Jagger C, Enderby PM, *et al.*

No. 40
Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis
By Renfrew MJ, Craig D, Dyson L, McCormick F, Rice S, King SE, *et al.*

No. 41
The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation.
By Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, *et al.*

No. 42
Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness.
By Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, *et al.*

No. 43
Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Honest H, Forbes CA, Durée KH, Norman G, Duffy SB, Tsourapas A, *et al.*

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The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.
By Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS, *et al.*

Suppl. 2
Gemcitabine for the treatment of metastatic breast cancer.
By Jones J, Takeda A, Tan SC, Cooper K, Loveman E, Clegg A.

Varenicline in the management of smoking cessation: a single technology appraisal.
By Hind D, Tappenden P, Peters J, Kenjegalieva K.

Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal.
By Lloyd Jones M, Holmes M.

Rituximab for the treatment of rheumatoid arthritis.
By Bagust A, Boland A, Hockenhull J, Fleeman N, Greenhalgh J, Dundar Y, *et al.*

Omalizumab for the treatment of severe persistent allergic asthma.
By Jones J, Shepherd J, Hartwell D, Harris P, Cooper K, Takeda A, *et al.*

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.
By Boland A, Bagust A, Hockenhull J, Davis H, Chu P, Dickson R.

Adalimumab for the treatment of psoriasis.
By Turner D, Picot J, Cooper K, Loveman E.

Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal.
By Holmes M, C Carroll C, Papaioannou D.

Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal.
By Mowatt G, Boachie C, Crowther M, Fraser C, Hernández R, Jia X, *et al.*

Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.
By Bond M, Hoyle M, Moxham T, Napier M, Anderson R.

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