NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women

Manufacturer/sponsor submission of evidence

Amgen UK Ltd.

Submitted 22 January 2010

Resubmitted 15 February 2010

(Template Issued: October 2009)

Foreword

On Friday, 22 January 2010 we made our full evidence submission to the Institute for their Single Technology Appraisal (STA) of Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women. Our evidence submission was comprehensive in addressing in full the decision problem as set out by the Institute in the final scope for the appraisal. The complexity of existing guidance in osteoporosis and the volume of potential comparators identified in the final scope necessitated our evidence submission being longer than the Institute recommends. This was compounded by the unusually high volume of denosumab randomised controlled trial (RCT) data available at time of launch. Subsequently, the Institute contacted us to inform us that the timelines set out within the STA process would not allow sufficient time for a complete review of our evidence submission by the evidence review group or appraisal committee members. Therefore, the Institute requested that we consider restructuring our evidence submission in order to enable the STA to proceed on the scheduled timelines. In response to this request from the Institute we have restructured the content of our full evidence submission in such a way as to reduce the length of the main submission document and, in doing so, increase the length of the appendices. As agreed with the Institute, we moved the detailed descriptions of our non-fracture endpoint RCTs to appendices and report only the primary efficacy endpoints for these studies in the main submission; moved the meta-analysis of BMD study endpoints to appendices and report a summary in the main submission; moved the forest plots for adjusted indirect comparisons and mixed treatment comparisons of fracture endpoints to appendices and report summary tables in the main submission; moved meta-analysis, adjusted indirect comparisons and mixed treatment comparisons with supplementary comparators to appendices; moved all economic sensitivity and sub-group analysis for secondary comparators to appendices and report the base case economic analyses for secondary comparators in the main submission. A full listing of changes has been provided to NICE and is available on request. Our restructured main evidence submission and associated appendices continue to address in full the decision problem as set out by Institute in the final scope for this appraisal.

Contents

List of tables

List of figures

Abbreviations

25(OH) vitamin D	25-hydroxyvitamin D
ANCOVA	analysis of covariance
ASBMR	American Society of Bone and Mineral Research
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BMQ	beliefs about medication
BNF	British National Formulary
BP	bisphosphonate
BSAP	bone-specific alkaline phosphatase
BTM	bone turnover marker
CHMP	Committee on Medicinal Products for Human Use
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRF	case report form
CrI	credible interval
CSR	clinical study report
CTX-1	serum type 1 C-telopeptide
DAPS	Denosumab Adherence Preference Satisfaction
DECIDE	Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate
DEFEND	DEnosumab FortifiEs BoNe Density
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5D
EU	European Union
FOB	fraction of benefit
FREEDOM	Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months
FSH	follicle-stimulating hormone
GIAE	gastrointestinal adverse event
GP	general practitioner
GPRD	General Practice Research Database
HALT	hormone ablation therapy
HR	hazard ratio
HR-pQCT	high resolution-peripheral quantitative computed tomography
HRQL	health-related quality of life
HRT	hormone replacement therapy
HTA	Health Technology Assessment
IC	indirect comparison
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IFU	information for use
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat

iv	intravenous
IVRS	interactive voice response system
LOCF	last observation carried forward
LS	least squares
LSM	least squares mean
MPR	medication possession ratio
MTC	mixed treatment comparison
NCCNSC	National Collaborating Centre for Nursing & Supportive Care
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	not reported
NS	not significant
OPAQ-SV	Osteoporosis Assessment Questionnaire–Short Version
OPCS	Office of Population Censuses and Surveys
OPG	osteoprotegerin
P1NP	procollagen type 1 N-telopeptide
PCT	Primary Care Trust
PMO	postmenopausal osteoporosis
PRO	patient-reported outcomes
PSQ	Preference and Satisfaction Questionnaire
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
PTH	parathyroid hormone
Q3M	every 3 months
Q6M	every 6 months
QALY	quality-adjusted life year
QCT	quantitative computerised tomography
QD	once daily
QW	once weekly
RANK	receptor activator of nuclear factor kappaB
RANKL	receptor activator of nuclear factor kappaB ligand
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
sc	subcutaneous
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SERM	selective estrogen receptor modulator
SMART	Selective estrogen Menopause And Response to Therapy
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
STAND	Study of Transitioning from Alendronate to Denosumab
STRATOS	STRontium Administration for Treatment of Osteoporosis
TIA	transient ischaemic attack
TRAP 5b	tartrate-resistant acid phosphatase 5b

TSH	thyroid-stimulating hormone
UK	United Kingdom
uNTX	urinary N-telopeptide
US	United States
VAS	visual analogue scale
VTE	venous thromboembolism
WHO	World Health Organization

Definitions

Term	Definition
Adherence	Adherence was defined in the National Institute for Health and Clinical Excellence (NICE) Clinical Guideline for Medicines Adherence (CG76) as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber' (Nunes et al., 2009). Adherence was defined in the Denosumab Adherence Preference Satisfaction (DAPS) study based on subjects meeting the following three criteria:: 1. Received 2 denosumab injections (overall treatment compliance) 2. Took each injection 6 months (± 4 weeks) apart (treatment compliance over time) 3. Completed 12 months of treatment (treatment persistence) Subjects were considered adherent to alendronate treatment if the subject meets the following criteria: 1. Took at least 80% of once-weekly (QW) tablets (overall treatment compliance) 2. Took at least 2 tablets in the last month and completed 12 months of treatment (treatment persistence) This is based on at least one returned bottle containing 6 months of electronic monitored data, in the event one bottle is lost. An electronic event (opening and closing of the bottle) was regarded as equivalent to tablet ingestion. Subjects who did not meet all criteria for their respective therapy were deemed non-adherent to treatment. Because definitions for adherence vary, the more specific terms *compliance* and *persistence* (defined below) are used where possible in the submission to avoid confusion.
Compliance	Medication compliance refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking (International Society for Pharmacoeconomics and Outcomes Research [ISPOR] Medication Compliance and Persistence Special Interest Group [Cramer et al., 2008]).
Interaction	Quantitative interaction terms: smaller *P* values denote more evidence that the treatment effect is different between the subgroup levels. Qualitative interaction terms: smaller *P* values denote more evidence that the treatment effect is different between subgroup levels and that the difference is such that the treatment effect in at least one level of the subgroup is in the opposite direction as the other levels.

Postmenopausal osteoporosis (PMO)	PMO occurs in postmenopausal women at high risk of experiencing osteoporotic fractures based on the known independent risk factors, such as age, bone mineral density (BMD), previous low-trauma fracture, high bone turnover, maternal history of fracture and low body mass index (BMI), that result in an increased 10-year probability of fractures, regardless of the time elapsed since menopause (European Medicines Agency, 2005). Additional risk factors that have been identified include use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking and alcohol intake of 3 or more units daily (Kanis et al., 2008a).
Osteopenia	Osteopenia is defined as a BMD T-score between –1 standard deviation (SD) and –2.5 SD.
Osteoporotic fracture	A variety of definitions have been used for osteoporotic fracture. In the denosumab registration trial 20030216 (FREEDOM)/Cummings et al. (2009), a new radiographic vertebral fracture was defined as an increase of at least 1 Genant grade in a vertebral body between T4 and L4 that was normal at baseline. The definition for non-vertebral fracture excluded fractures of the skull, face, mandible, metacarpals, fingers or toes because they are not associated with decreased BMD; pathologic fractures and those that were associated with severe trauma (defined as a fall from a height higher than a stool, chair, or first rung of a ladder or severe trauma other than a fall) were also excluded. Clinical fractures included vertebral fractures that were associated with signs or symptoms (or both) and non-vertebral osteoporotic fractures. Clinical fractures were confirmed by diagnostic imaging or a radiologist's report.
Persistence	Persistence is the duration of time from initiation to discontinuation of therapy. Patients continuing to take any amount of the medication and satisfying the number of days allowed between refills (the 'permissible gap') are considered persistent. (ISPOR Medication Compliance and Persistence Special Interest Group [Cramer et al., 2008]).
T-score	T-score is the number of standard deviations (SD) from the mean BMD of young, healthy adults of the same gender at their peak bone mass.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.
- Tabulation of the base-case results as follows:
- When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance.
- Subgroup analyses considered and clinical- and cost-effectiveness results.
- When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance.
- Subgroup analyses considered and clinical- and cost-effectiveness results.

Introduction

Denosumab has a unique and physiological mode of action and a convenient mode of administration. Large and significant reductions in the risk of new radiographic vertebral, non-vertebral and hip fractures have been demonstrated for denosumab treatment versus placebo. In a meta-analysis of three phase 3 randomised controlled trials (RCTs) comparing denosumab directly with alendronate, significantly greater increases in mean percentage change in bone mineral density (BMD) from baseline were observed for denosumab at multiple skeletal sites. Adjusted indirect comparison (IC) and mixed treatment comparisons (MTC) indicate that denosumab is significantly more effective than strontium ranelate (strontium), raloxifene, [redacted] in preventing morphometric vertebral fracture[1]. Denosumab was significantly more effective than strontium in preventing clinical vertebral fracture in the IC. Cost-utility analysis demonstrates that denosumab is a cost-effective treatment option for patients for whom oral bisphosphonates (BPs) are unsuitable.

United Kingdom (UK) approved name: Denosumab

Brand name: Prolia®

Marketing status: Denosumab does not currently have UK marketing authorisation for the indication detailed in this submission. On December 17 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion for the marketing authorization of Prolia® (denosumab) for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Full European Union marketing authorisation is expected to follow in due course.

Principal pharmacological action: Denosumab is a human monoclonal antibody (IgG2) that has a unique and physiological mode of action. Denosumab binds with high affinity and specificity to receptor activator of nuclear factor kappaB ligand

[redacted]

(RANKL), preventing activation of its receptor (RANK) on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone (Draft Summary of Product Characteristics; see section 9.1.1).

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost: Denosumab is formulated as a solution for injection (1 mL containing 60 mg denosumab) in a pre-filled syringe. Each pack contains one pre-filled syringe. Denosumab is administered by a single subcutaneous injection (1 mL) into the thigh, abdomen or back of arm. The injection is repeated once every 6 months. The acquisition cost is £183 for one pre-filled syringe, which is equivalent to £366 for 1 year of treatment. Denosumab is suitable for use in primary care and secondary care settings and it is anticipated to be administered predominantly in a primary care setting.

Indication(s): The indication being sought in the UK is for 'The treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia® significantly reduces the risk of vertebral, non-vertebral and hip fractures.' An indication is also being sought for 'The treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.' This second indication is outside of the scope of this STA.

Restriction(s): It is not anticipated that the marketing authorisation will be subject to any special conditions or restrictions.

Recommended course of treatment: Continuous treatment; administered as one injection every 6 months.

The main comparator(s): Standard care (interventions used in more than 1% of treated patients) includes oral BPs, strontium and raloxifene. Teriparatide has been recommended by NICE (NICE, 2008a), but is used in only 0.1% of treated patients. All other interventions are used in less than 1.0% of patients and have not been assessed by NICE. Amgen is mindful of the need to make efficient use of National Health Service (NHS) resources. Given the wide availability of generic BPs, in the

UK, denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable; reasons for unsuitability include inability to comply with the special instructions for administration, a contraindication or intolerance. Some patients within this group may currently receive no treatment because they are not at sufficiently high risk of fracture to be eligible for other treatments under current NICE guidance.

The primary comparators for denosumab are therefore strontium, raloxifene and no treatment. Ibandronate iv, zoledronate iv and teriparatide are considered secondary comparators as these management strategies are not standard care and the mode of administration of iv BPs limits their use to a secondary care setting; supplementary comparisons with oral BPs are also presented in appendices (section 9.15) for completeness.

Key clinical evidence: The key clinical evidence for denosumab comes from the randomised placebo-controlled registration trial 20030216 (FREEDOM)/Cummings et al. (2009). Supporting evidence is available from four RCTs comparing the effect of denosumab on BMD directly with that of alendronate. The comparison of efficacy with all comparators comes from a systematic review and adjusted ICs and MTC of RCTs based on fracture endpoints. Safety data are available from approximately 14,000 subjects who participated in 30 denosumab clinical studies, and includes up to 5 years of denosumab exposure.

The main clinical results of the RCTs and any relevant non-RCT evidence: In trial 20030216 (FREEDOM), denosumab given subcutaneously twice yearly for 36 months resulted in large and significant reductions in the risk of new radiographic vertebral, non-vertebral and hip fractures in women with osteoporosis when compared with placebo. The relative risk (RR) for new radiographic vertebral fracture was 0.32 (95% confidence interval [CI], 0.26 to 0.41; $P < 0.001$). The cumulative incidence was 2.3% in the denosumab group, versus 7.2% in the placebo group (a relative decrease of 68%). The hazard ratios (HRs) for hip fracture and non-vertebral fracture (95% CI) were 0.60 (0.37 to 0.97; $P = 0.04$) and 0.80 (0.67 to 0.95; $P = 0.01$), respectively. The relative decreases in the cumulative incidence of hip fracture and non-vertebral fracture were 40% (0.7% compared with 1.2%) and 20% (6.5% compared with 8.0%), respectively.

There are no head to head trials measuring fracture outcomes for denosumab compared with any active comparator and there are few trials comparing fracture outcomes between any active treatments. Therefore, in order to address the decision problem for this appraisal, we undertook adjusted ICs and MTC. The results of such analyses should always be viewed with caution. The ICs showed that against strontium and raloxifene, denosumab had a statistically lower risk of morphometric vertebral fracture (RR ranging from 0.451 to 0.501). [redacted]. The IC showed that denosumab had a statistically significant lower risk of clinical vertebral fracture than strontium; [redacted]

Safety data for denosumab are available from approximately 14,000 subjects who participated in 30 denosumab clinical studies. The overall incidences of adverse events were generally similar between denosumab and placebo groups. In trial 20030216 (FREEDOM), there was an increase in eczema, flatulence and serious cellulitis in the denosumab group compared with the placebo group; however, there was no significant difference in the overall incidence of cellulitis between the two groups. There was no significant increase in the risk of cancer (*P* = 0.31), infection (*P* = 0.17), cardiovascular disease (adjusted *P* = 0.31), delayed fracture healing (*P* value not available) or hypocalcemia (*P* = 0.08), nor were there any cases of osteonecrosis of the jaw or adverse reactions to the injection of denosumab. Other

[2] [redacted]

adverse events associated with other osteoporosis interventions (e.g. atrial fibrillation, venous thromboembolism and heart disease) were not imbalanced between groups.

Type of economic evaluation and justification for the approach used: A cost-utility analysis was undertaken that complies with the NICE reference case. A lifetime analysis was performed using a Markov model (cycle length = 6 months; half-cycle correction used). Costs and outcomes were discounted at 3.5% per annum. The underlying risk of fracture (vertebral, hip, wrist and other) was estimated from epidemiological evidence; a sensitivity analysis was undertaken using the FRAX® algorithm. Treatment effects were estimated from an IC (for each treatment vs. placebo). Utility weights were taken from a systematic review and evidence synthesis. Drug therapy costs were taken from the British National Formulary. Administration, other treatment-related costs and hospital in- and out-patient costs associated with fractures were based on National Reference Costs.

Pivotal assumptions underlying the model/analysis: Evidence gaps for all comparators were filled as follows. Where RR for clinical vertebral fracture data were missing, estimates for morphometric vertebral fracture were applied. For interventions with missing wrist and hip fracture data, the RR was assumed to be 1.00. No efficacy evidence was identified for iv ibandronate versus placebo; efficacy was assumed to be equivalent to oral ibandronate. The RR for other fractures was assumed to be 1.00 for all therapies. The mean duration of treatment was 5 years for all interventions. The base-case analysis assumes 100% persistence and compliance over these periods (this is investigated in sensitivity analysis). After treatment discontinuation, treatment effects (RRs) for all treatments were assumed to return linearly to a value of 1.00 over a period of one year (this is investigated in sensitivity analysis). An increased risk of mortality was assumed following fracture. The impact of cellulitis and gastrointestinal adverse events on costs and health-related quality of life (HRQL) was modelled. The increased risk of venous thromboembolism (VTE), osteonecrosis of the jaw, infusion reactions or other adverse events associated with comparator treatment were not included.

Cost-effectiveness results

For a base-case population of women aged 70 years with a femoral neck T-score of –2.5 SD across all sites, denosumab is a cost-effective treatment option for patients for whom oral BPs are unsuitable. Compared with the primary comparators, regardless of prior fracture status, denosumab dominates strontium and is within the cost-effective threshold range against both raloxifene and no treatment (Table 1). Against secondary comparators, denosumab dominates ibandronate iv; while denosumab is estimated to be marginally less effective and less costly than both zoledronate iv and teriparatide. Zoledronate iv and teriparatide have positive incremental cost-effectiveness ratios compared with denosumab that are either at or above the cost-effective threshold range (between £29,029 and £772,424 per QALY gained compared with denosumab) (Table 2).

Subgroup analyses varying prior fracture status, age (55-75 years) and T-score (–2.5 to –4 SD) demonstrate that denosumab is always a cost-effective option (within the cost-effective threshold range) compared with the primary comparators. For the majority of subgroups denosumab dominates strontium and also dominates raloxifene in many subgroups. Compared with no treatment in patients with a prior fracture, denosumab is always a cost-effective option regardless of T-score or age. In patients without a prior fracture denosumab is always cost-effective in patients over 70 years of age regardless of T-score and is cost-effective in the majority of subgroups with T-score at or below –3.5 SD.

The budget impact for patients expected to receive denosumab treatment in England and Wales is estimated to be between £1.42 million to £2.77 million in 2010, rising to between £6.31 million to £11.71 million in 2015. Cost-offsets arising from a reduced incidence of fractures in patients treated with denosumab rather than existing treatments are estimated to be between approximately £1.36 million to £2.77 million over the lifetimes of the cohort of patients beginning treatment in each year.

Base-case results

Table 1 Primary comparisons: base-case cost-effectiveness for denosumab, strontium, raloxifene and no treatment

				vs. lowest cost comparator			ICER vs. low-cost comparator		ICER for comparison with Denosumab[a]	
	LYs	QALYs	Costs	Δ LY	Δ QALY	Δ Cost	LYs	QALYs	LYs	QALYs
No prior fracture										
No Treatment	11.606	7.991	9,455	0.000	0.000	0	—	—	47,220	29,223
Raloxifene[b]	11.628	8.009	10,764	0.022	0.018	1,310	60,786	74,239	26,383	9,289
Denosumab	11.642	8.048	11,135	0.036	0.057	1,680	47,220	29,223	—	—
Strontium	11.622	8.007	11,138	0.016	0.016	1,684	104,069	102,592	Denosumab dominant	Denosumab dominant
Prior fracture										
No Treatment	11.492	7.797	12,060	0.000	0.000	0	—	—	17,719	12,381
Raloxifene	11.548	7.852	13,410	0.056	0.055	1,351	24,021	24,524	4,820	2,046
Denosumab	11.576	7.917	13,543	0.084	0.120	1,483	17,719	12,381	—	—
Strontium	11.531	7.841	13,698	0.039	0.044	1,638	41,767	37,123	Denosumab dominant	Denosumab dominant

ICER, incremental cost-effectiveness; LY, life years; QALY, quality-adjusted life years.

[a] Pairwise ICERs for denosumab versus each strategy are presented to demonstrate the cost-effectiveness of denosumab relative to the existing guidance recommendations in TA160 and TA161 (NICE, 2008a; 2008b).

[b] Raloxifene is not recommended by NICE in patients with no prior fracture.

Table 2 Secondary comparisons: base-case cost-effectiveness for denosumab, ibandronate iv, zoledronate iv and teriparatide

				vs. lowest cost comparator			ICER vs. low-cost comparator	
	LYs	**QALYs**	**Costs**	**Δ LY**	**Δ QALY**	**Δ Cost**	**LYs**	**QALYs**
No prior fracture								
Denosumab	11.642	8.048	11,135	0.000	0.000	0	—	—
Zoledronate (iv)[a]	11.646	8.053	11,490	0.004	0.005	355	88,386	70,900
Ibandronate (iv)[a]	11.624	8.011	13,890	–0.017	–0.037	2,756	Denosumab dominant	Denosumab dominant
Teriparatide[b]	11.648	8.066	24,710	0.007	0.018	13,576	2,073,082	772,424
Prior fracture								
Denosumab	11.576	7.917	13,543	0.000	0.000	0	—	—
Zoledronate (iv)[a]	11.586	7.930	13,903	0.010	0.012	360	34,292	29,029
Ibandronate (iv)[a]	11.540	7.849	16,526	–0.036	–0.068	2,984	Denosumab dominant	Denosumab dominant
Teriparatide	11.584	7.947	26,867	0.008	0.030	13,324	1,580,601	451,269

ICER, incremental cost-effectiveness; LY, life years; QALY, quality-adjusted life years

ICERs compared with denosumab are not presented separately, as denosumab is the lowest cost treatment in this scenario

[a] NICE has not appraised ibandronate iv or zoledronate iv.

[b] Teriparatide is not recommended by NICE in patients with no prior fracture.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Prolia®

Approved name: Denosumab

Therapeutic class: Fully human monoclonal antibody (Anatomical Therapeutic Chemical [ATC] classification: M05BX04: Other drugs affecting bone structure and mineralisation)

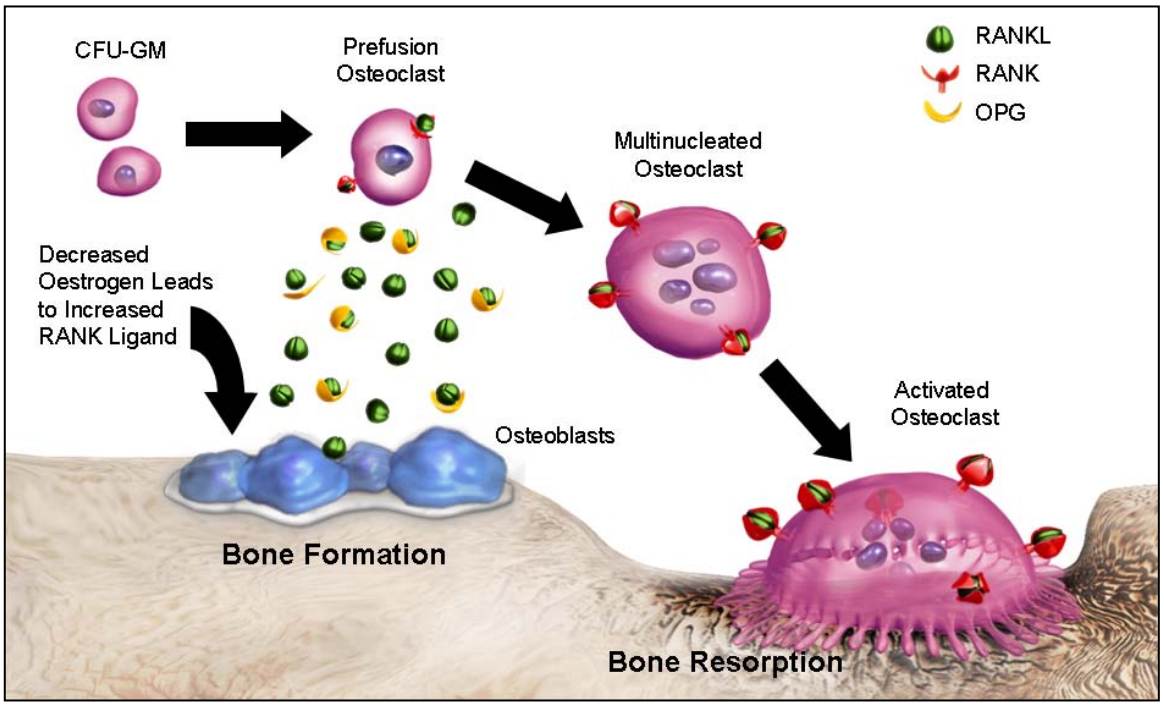
1.2 What is the principal mechanism of action of the technology?

Denosumab is a fully human monoclonal antibody (IgG2) that binds with high affinity to human receptor activator of nuclear factor kappaB ligand (RANKL) and inhibits its activity (Bekker et al., 2004). RANKL has been identified as the primary mediator of osteoclast formation, function and survival in both cortical and trabecular bone (Yasuda et al., 1998; Fuller et al., 1998; Lacey et al., 1998; Lacey et al., 2000). Postmenopausal women with lower oestrogen levels express higher levels of RANKL, which leads to excessive bone resorption (Hofbauer and Schoppet, 2004).

RANKL binds to the receptor activator of nuclear factor kappaB (RANK) receptor on immature and mature osteoclasts (Boyle et al., 2003) resulting in maturation of prefusion osteoclasts to multinucleated osteoclasts and finally to activated

osteoclasts (Figure A1). Excessive RANKL activity has been shown to cause bone destruction across a broad range of conditions, and in osteoporosis, RANKL has direct catabolic effects on cortical and trabecular bone, including reductions in bone density, volume and strength (Ross et al., 2001; Mochizuki et al., 2002; Capparelli et al., 2003; Smith et al., 2003; Ichinose et al., 2004; Kostenuik et al., 2005).

Figure A1 Excess RANKL can increase bone resorption, leading to osteoporosis



CFU-GM, granulocyte-macrophage colony forming unit; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor kappaB; RANKL, receptor activator of nuclear factor kappaB ligand.

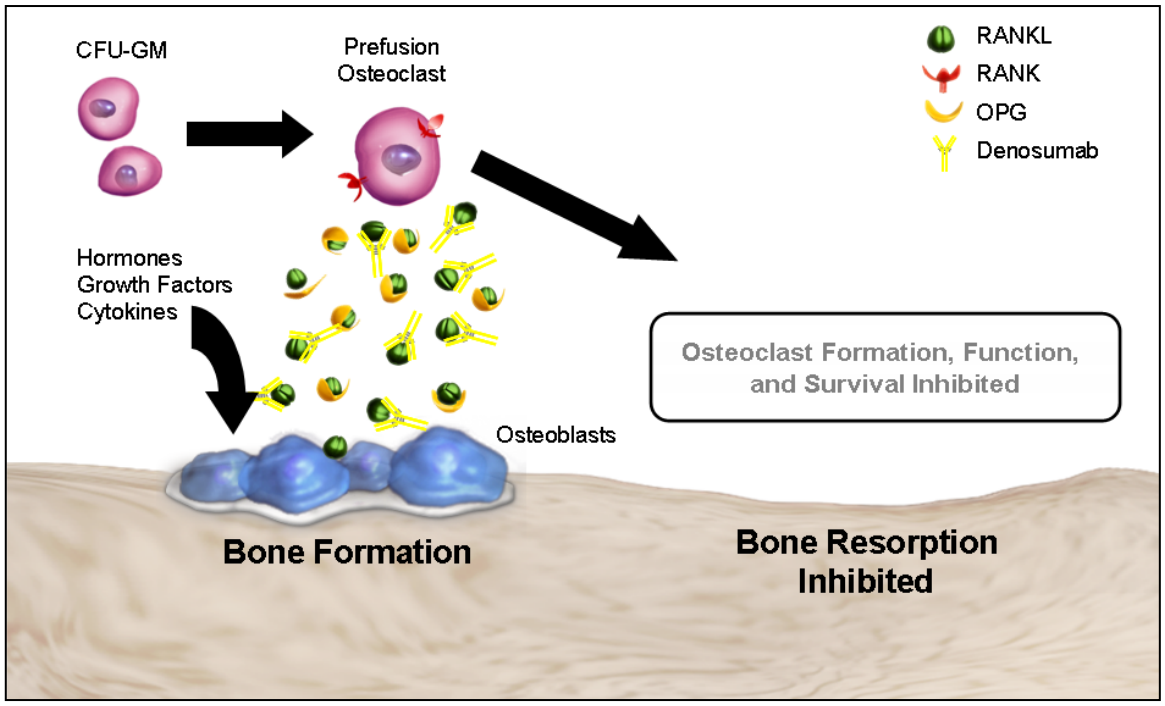
Adapted from: Boyle et al., 2003.

Denosumab inhibits the action of RANKL through the same pathway as osteoprotegerin (OPG), the physiologic inhibitor of RANKL (Figure A2).

Denosumab is the first and only osteoporosis therapy with this mechanism of action, which is physiologic and mimics the body's natural bone-protection mechanism. Unlike BPs, denosumab does not cause osteoclast death or dysfunction, and inhibits all stages of osteoclast activity without incorporation into the bone matrix. Denosumab inhibits osteoclast activity through a physiologic and reversible mechanism that may avoid possible long-term adverse effects on new bone formation and bone quality that are of concern for BPs (National Institute for Health and Clinical Excellence [NICE], 2008a). Unlike teriparatide, denosumab does not promote new bone formation, and there is no indication of an increased risk of

osteosarcoma (Eli Lilly, 2009). The targeted nature of denosumab allows inhibition of RANKL-medicated osteoclast formation, function and survival in both cortical and trabecular bone throughout the skeleton.

Figure A2 Denosumab binds RANKL and inhibits osteoclast formation, function and survival



CFU-GM, granulocyte-macrophage colony forming unit; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor kappaB; RANKL, receptor activator of nuclear factor kappaB ligand.

Adapted from: Boyle et al., 2003.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Denosumab does not currently have a United Kingdom (UK) marketing authorisation for the treatment of osteoporosis in postmenopausal women at increased risk of fractures; however, authorisation is pending. On 17 December 2009, the CHMP of the European Medicines Agency adopted a positive opinion for the marketing authorization of denosumab for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Full

European Union marketing authorisation is expected to follow in due course. The EPAR is not available at this time.

The Centralised Marketing Authorisation Application included an additional indication for the treatment of bone loss associated with hormone ablation therapy (HALT) in men with prostate cancer at increased risk of fractures. This indication is outside the scope of this STA.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The European Centralised assessment for denosumab began on 28 January 2009 (Day 1) and is currently under review. All procedural steps have occurred in accordance with the standard European Centralised procedural timelines, and it is not anticipated that the marketing authorisation will be subject to any special conditions. [redacted]

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The following indications have been sought:

- Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia® significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia® significantly reduces the risk of vertebral fractures. This indication is outside the scope of this STA.

Despite the European Medicines Agency's consideration that [redacted]

Amgen does not consider this patient group to be included within the scope of this appraisal as subjects in our HALT trial (20040135) were not osteoporotic as defined by the World Health Organization (WHO). Further, denosumab for the treatment of bone loss associated with HALT in women with breast cancer is the subject of a separate NICE appraisal.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Randomised controlled trials and extension studies investigating denosumab in postmenopausal women at increased risk of fracture that have been reported are summarised in Table A1; those that are expected to report before 30 January 2011 are summarised in Table A2. Note that trial 20040135 (HALT) is included in Table A1 for completeness, but will not form part of the evidence base for this appraisal.

Table A1 List of reported RCTs and extension studies

Trial no. (Acronym) Phase	Interventions	Population	Primary outcome measure	Primary reference
20030216 (FREEDOM) Phase 3 registration trial for the PMO indication	• Denosumab (60 mg) Q6M • Placebo Q6M For 3 years	7,808 postmenopausal women aged between 60 and 90 years with osteoporosis (BMD T-score < −2.5 SD at either the lumbar spine or total hip, or at both locations, but ≥ –4.0 at both locations)	New radiographic vertebral fracture at 3 years (non-vertebral fracture and hip fracture were also measured)	Cummings et al., 2009
20050141 (DECIDE) Phase 3	• Denosumab (60 mg) Q6M • Alendronate (70 mg) QW For 12 months	1,189 postmenopausal women with a BMD T-score ≤ −2.0 SD at the lumbar spine or total hip	BMD at total hip at 12 months	Brown et al., 2009
20050234 (STAND) Phase 3	• Denosumab (60 mg) Q6M for 12 months • Alendronate (70 mg) QW for 12 months (after 1 month of open-label alendronate [70 mg] QW for both groups)	504 postmenopausal women ≥ 55 years of age with a BMD T-score of ≤ –2.0 SD and ≥ –4.0 SD at the lumbar spine or total hip that have received ≥ 6 months of alendronate prior to screening	BMD at total hip at 12 months	Kendler et al., 2009
20060232 (DAPS) Phase 3b	• Denosumab (60 mg) Q6M for 1 year followed by alendronate (70 mg) QW for 1 year • Alendronate (70 mg) QW for 1 year followed by denosumab (60 mg) Q6M for 1 year	250 postmenopausal women, naïve to BPs, with BMD T-score ≤ −2.0 SD and ≥ −4.0 SD at the lumbar spine, total hip or femoral neck	Adherence to treatment at 12 months	Amgen data on file (20060232 [DAPS] 12-month interim analysis)
20040132 (DEFEND) Phase 3	• Denosumab (60 mg) Q6M • Placebo Q6M For 24 months, then discontinued for a further 24-month follow-up	332 postmenopausal women with osteopenia (BMD T-scores between –1.0 SD and –2.5 SD at the lumbar spine)	BMD at the lumbar spine at 24 months	Bone et al., 2008 Amgen data on file (20040132 [DEFEND] CSR)
20040135 (HALT) Phase 3 registration trial for the HALT indication	• Denosumab (60 mg) Q6M • Placebo Q6M For 24 months, then observational follow-up for a further 24-month follow-up	252 women with non-metastatic breast cancer undergoing aromatase inhibitor therapy, with BMD T-scores between –1.0 and –2.5 SD at the lumbar spine, total hip or femoral neck	BMD at the lumbar spine at 12 months	Ellis et al., 2008

Trial no. (Acronym) Phase	Interventions	Population	Primary outcome measure	Primary reference
20050179 Phase 2	• Denosumab (60 mg) Q6M + placebo for alendronate QW • Alendronate (70 mg) QW + placebo for denosumab Q6M • Placebo for denosumab Q6M and placebo for alendronate QW For 12 months	247 postmenopausal women between 50 and 70 years of age with low BMD (BMD T-score between –2.0 SD and –3.0 SD (inclusive) at the lumbar spine or total hip	Cortical thickness at the distal radius at 12 months	Seeman et al., 2009b (abstract) Amgen data on file (20050179 CSR)
20010223 Phase 2	• Denosumab (6 or 14 mg) Q3M, or (14, 60, or 100 mg) Q6M for 24 months; then (60 mg) Q6M for 24 months • Denosumab (210 mg) Q6M for 24 months then placebo for 24 months • Denosumab (30 mg) Q3M for 24 months then placebo for 12 months then denosumab (60 mg) Q6M for 12 months • Alendronate QW for 24 months then discontinued; followed for a further 24 months • Placebo for denosumab for 48 months	412 postmenopausal women with a BMD T-score of −1.8 SD to −4.0 SD at the lumbar spine or −1.8 SD to −3.5 SD at the femoral neck or total hip (inclusive)	Lumbar spine BMD at 12 months	McClung et al., 2006 Lewiecki et al., 2007 Amgen data on file (20010223 CSR)
20050172 Phase 2	• Denosumab (14, 60 or 100 mg) Q6M • Placebo Q6M For 12 months	212 Japanese postmenopausal women ≤ 80 years of age with BMD T-score < −2.5 SD and ≥ −4.0 SD at lumbar spine or < −2.5 SD and ≥ −3.5 SD at femoral neck or total hip	Lumbar spine BMD and treatment-emergent adverse events at 12 months	Amgen data on file (20050172 CSR)
20060237 Extension of 20050141 Phase 3b	Denosumab (60 mg) Q6M vial Denosumab (60 mg) Q6M pre-filled syringe For 12 months	311 women completing trial 20050141	Development of anti-denosumab antibodies at 6 months	Amgen data on file (20060237 CSR)
20050233 Extension of 20010223 Phase 3	Denosumab (60 mg) Q6M for 4 years (a total of up to 8 years, including the 4 years in study 20010223)	200 women completing trial 20010223	Incidence of adverse events over 4 years follow-up	Miller et al., 2009 (interim analysis at 2 years)

BMD, bone mineral density; BPs, bisphosphonates; CSR, clinical study report; PMO, postmenopausal osteoporosis; Q3M, every 3 months; Q6M, every 6 months; QW, once weekly; RCT, randomised controlled trial; SD, standard deviation.

Patients in all trials received daily calcium and vitamin D supplementation.

Table A2 List of RCTs and extension studies expected to report new data in the next 12 months

Trial no. (Acronym) Phase	Interventions	Population	Primary outcome measure	Date expected to report
20050233 Extension of 20010223 Phase 3	• Denosumab (60 mg) Q6M for 4 years (a total of up to 8 years, including the 4 years in study 20010223)	200 women completing trial 20010223	Incidence of adverse events over 4 years follow-up	[redacted]
20080747 Extension of 20050179 Phase 3b	None Discontinuation of denosumab Discontinuation of placebo	Women completing study 20050179 (75 planned)	Cortical thickness at the distal radius	[redacted]
20040132 (DEFEND) Phase 3	• Denosumab (60 mg) Q6M • Placebo Q6M For 24 months then discontinued for a further 24-month follow-up	332 postmenopausal women with osteopenia (BMD T-scores between –1.0 SD and –2.5 SD at the lumbar spine) completing 24 months in trial 20040132	BMD at the lumbar spine at 24 months	[redacted]
20080287 Enrolling from several studies Phase 2	None (discontinuation of previous denosumab therapy)	15 women completing 20050179, 20050141, 20060237, 20030216 (not going into 20060289) and ongoing into 20080747	Qualitative bone histology	[redacted]
20060232 (DAPS) Phase 3b	• Denosumab (60 mg) Q6M for 1 year followed by alendronate (70 mg) QW for 1 year • Alendronate (70 mg) QW for 1 year followed by denosumab (60 mg) Q6M for 1 year	250 postmenopausal women, naïve to BPs, with BMD T-score ≤ −2.0 SD and ≥ −4.0 SD at the lumbar spine, total hip or femoral neck	Adherence to treatment at 12 months	[redacted]
20060289 Extension of 20030216 Phase 3	Open-label denosumab (60mg) Q6M For up to 84 months	Women completing study 20030216	Safety	[redacted]

BMD, bone mineral density; BP, bisphosphonate; Q6M, every 6 months; QW, once weekly; SD, standard deviation.
Patients in all trials received daily calcium and vitamin D supplementation.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Denosumab is expected to be available for purchase in the UK beginning April 2010.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Denosumab does not currently have a marketing authorisation for any indication anywhere in the world.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Denosumab is not currently subject to any other health technology assessments in the UK. [redacted]

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A3 Unit costs of technology being appraised

Pharmaceutical formulation	Solution for injection, 1 mL, in pre-filled syringe Each mL of solution contains 60 mg denosumab, 0.013 mmol or 0.3 mg sodium and 47 mg sorbitol (E420). For a full list of excipients, see section 9.1.1
Acquisition cost (excluding VAT)	£183 per pre-filled syringe providing 6 months of treatment
Method of administration	Single sc injection Q6M into the thigh, abdomen or back of arm
Doses	60 mg (1 mL)
Dosing frequency	One injection Q6M
Average length of a course of treatment	Continuous
Average cost of a course of treatment	£366 per year of treatment
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	None
Q6M, every 6 months; sc, subcutaneous.	

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigations are needed for selection of patients for denosumab treatment other than those used currently in routine clinical practice for PMO.

Administration of denosumab should be performed by an individual who has been adequately trained in injection techniques (see denosumab draft SPC, section 9.1.1). Administration may be performed during a regular follow-up visit.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Patients receiving denosumab will not need monitoring over and above usual clinical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Patients must be adequately supplemented with calcium and vitamin D while being treated with denosumab (see section 9.1.1).

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. It is usually an age-related disease and can affect both sexes, but women are at greater risk because the decrease in oestrogen production after menopause accelerates bone loss to a variable degree (NICE, 2008a).

The WHO operational definition defines an osteoporotic woman on the basis of a bone mineral density (BMD) measurement (spine or hip) showing a BMD T-score below –2.5 standard deviations (SD). The term 'severe or established osteoporosis' habitually denotes a T-score below –2.5 SD in the presence of one or more fragility fractures. Osteopenia is defined as a BMD T-score between –1.0 SD and –2.5 SD. Fracture risk is also driven by parameters, including bone size and shape, bone turnover, microarchitecture, damage accumulation (microfracture) and collagen structure, all playing a role in bone strength. The use of independent risk factors for fractures (e.g., age, family history of fracture, low BMI, sedentarity, risk for falls) combined with BMD values provides a global assessment of future fracture risk, helping to identify women who should benefit from a treatment to prevent the occurrence of osteoporotic fractures (European Medicines Agency, 2005).

It is estimated that there are 180,000 osteoporosis-related symptomatic fractures annually in England and Wales. Of these, 70,000 are hip fractures, 25,000 are clinical vertebral fractures and 41,000 are wrist fractures (NICE, 2008a).

Fragility fracture is the clinically apparent and relevant outcome in osteoporosis. It is often referred to as a low-trauma fracture; that is, a fracture sustained as the result of a force equivalent to that of a fall from a height equal to, or less than, that of an ordinary chair. In the absence of fracture, osteoporosis is asymptomatic and often remains undiagnosed. Osteoporotic fragility fractures occur most commonly in the vertebrae, hip and wrist, and are associated with substantial disability, pain and reduced quality of life (NICE, 2008a).

In women aged over 50 years, the lifetime risk of a vertebral fracture is estimated to be one in three, and that of a hip fracture one in five. Postmenopausal women with an initial fracture are at substantially greater risk of subsequent fractures. For

instance, a woman with a vertebral fracture has a relative risk of 4.4 for a further vertebral fracture, 2.3 for a hip fracture and 1.4 for a wrist fracture compared with a woman with no prior fracture (NICE, 2008a).

Osteoporosis is a chronic condition characterised by bone fragility resulting in bone fracture; bone fracture is associated with pain and reduced quality of life. After a hip fracture, a high proportion of women are permanently unable to walk independently or to perform other activities of daily living and, consequently, many are unable to live independently. Hip fractures are also associated with increased mortality; estimates of the relative mortality risk vary from 2 to greater than 10 in the 12 months following hip fracture. However, it is unclear to what extent this can be attributed to fracture alone as opposed to pre-existing comorbidity (NICE, 2008a).

Vertebral fractures can be associated with curvature of the spine and loss of height and can result in pain, breathing difficulties, gastrointestinal problems and difficulties in performing activities of daily living. It is thought that the majority of vertebral fractures (50%-70%) do not come to clinical attention. Vertebral fractures are also associated with increased mortality; UK-specific data indicate a 4.4-fold increase in mortality related to vertebral fractures. However, as with hip fractures, it is unclear to what extent this may be due to comorbidities (NICE, 2008a).

In addition to increasing age and low BMD, other clinical factors have been associated with increased fracture risk. Some of these clinical risk factors are at least partly independent of BMD and include parental history of hip fracture, alcohol intake of 4 or more units per day, long-term systemic use of corticosteroids and rheumatoid arthritis. Factors that are known to be indicators of low BMD include low BMI (defined as less than 22 kg/m^2) and medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility and untreated premature menopause (NICE, 2008a). Other risk factors that are associated with increased fracture risk include a prior history of fracture, use of oral glucocorticoids and current smoking (Kanis et al., 2008a).

A full review of the risk factors associated with osteoporosis is being carried out as part of the development of the NICE clinical guideline 'Osteoporosis: assessment of

fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (NICE, 2009a).

2.2 How many patients are assumed to be eligible? How is this figure derived?

An estimated 645,000 patients will receive treatment for osteoporosis in England and Wales in 2010 (NICE 2008c, costing template updated for population projections for 2010, Office for National Statistics, 2009).

Amgen is mindful of the need to make efficient use of National Health Service (NHS) resources. Given the wide availability of generic BPs, in the UK, denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable; reasons for unsuitability include inability to comply with the special instructions for administration, a contraindication or intolerance. An estimated 6.8% of all women receiving osteoporosis treatments in England and Wales (approximately 43,900 patients) receive drugs other than oral BPs (data for 2009, IMS, 2009; CSD, 2009: see Table A6). This group of patients is expected to be eligible for denosumab treatment.

Denosumab may also be appropriate in some diagnosed patients that are currently untreated because they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for other interventions as recommended by NICE in TA160 and TA161 (NICE 2008a, 2008b). The number of patients in this group is difficult to estimate; however it is reasonable to anticipate that approximately 20% to 30% of diagnosed patients that are unsuitable for oral BPs fall within this category. The number of untreated patients in this group is estimated as between 11,000 and 18,800 (calculated assuming that the 43,900 patients represent 70% to 80% of the total population for whom oral BPs are unsuitable; i.e. the number of untreated patients in this group = 43,900/0.80*0.20 to 43,900/0.70*0.30).

The total number of patients expected to be eligible for denosumab treatment in England and Wales in 2010 is therefore estimated as approximately 54,900 to 64,700.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

A NICE clinical guideline is under development: Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk (NICE, 2009a).

Two technology appraisals have been performed:

- Alendronate, etidronate, risedronate, raloxifene and strontium for the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160 [NICE, 2008b])
- Alendronate, etidronate, risedronate, raloxifene, strontium and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (TA161 [NICE, 2008a])

Subgroups that were addressed are summarised in Table A4.

Table A4 Specific subgroups addressed in NICE Guidelines and Technology Appraisals

Guideline/ Technology Appraisal	Subgroups considered
Clinical Guideline Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk (Guideline in development, currently 'suspended') (NICE, 2009a Scope; 6 June 2003)	The following groups will be considered in the guideline: a) Individuals with low BMD (a diagnosis of osteoporosis by bone densitometry). b) Individuals with radiographic evidence of osteopenia and/or vertebral deformity. c) Individuals with previous osteoporotic fragility fracture (resulting from low trauma). d) Individuals receiving prolonged oral corticosteroid therapy. e) Individuals with secondary causes of osteoporosis. These include coeliac disease, chronic liver disease, chronic renal failure, hyperparathyroidism, hypercortisolism, hyperthyroidism and transplant recipients. This category also includes individuals with compromised physical function resulting from factors such as rheumatoid arthritis, neurological conditions or spinal paralysis from various causes. f) Women with untreated hypogonadism, including postmenopause, primary hypogonadism, premature menopause, secondary amenorrhoea (for example, following anorexia nervosa, or associated with extreme levels of exercise or certain forms of oral contraceptives), and early hysterectomy. g) Men with primary or secondary hypogonadism. h) Individuals with other risk factors, including advancing age, maternal history of osteoporotic hip fracture, family history of osteoporosis, or low BMI. Propensity to fall is a recognised risk factor for osteoporotic fracture that is being examined within the remit of the falls guideline and cross-reference will be made to this guideline.
TA160 Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women Guidance, October 2008 (NICE, 2008b)	Alendronate was recommended for women who have an independent clinical risk factor for fracture and a BMD T-score of −2.5 SD or below. Women younger than 65 years must also have at least one additional indicator of low BMD. Women aged 70 years or older may have an indicator of low BMD rather than a clinical risk factor; those with two or more indicators of low BMD or clinical risk factors may receive alendronate without a DXA scan. Risedronate and etidronate were recommended as alternative options for postmenopausal women for whom alendronate is unsuitable[a], and have a specified combination of BMD T-score, age and number of independent clinical risk factors for fracture. Strontium was recommended as an alternative option for postmenopausal women for whom alendronate and either risedronate or etidronate is unsuitable[a], and have a specified combination of BMD T-score, age and number of independent clinical risk factors for fracture. A subgroup analysis in women over the age of 74 years who had a BMD T-score of −2.4 SD or below was considered for strontium (Guidance section 4.3.3, post hoc analysis). Patients with osteopenia (BMD T-score between –1 SD and –2.5 SD below peak BMD) and those with long-term corticosteroid use were not considered in the guidance.

Guideline/ Technology Appraisal	Subgroups considered
TA161 Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women Guidance, October 2008 (NICE, 2008a)	Alendronate was recommended for women who have a BMD T-score of −2.5 SD or below. Women aged 75 years or older may receive alendronate without a DXA scan. Risedronate and etidronate were recommended as alternative options for women for whom alendronate is unsuitable[a], who also have a specified combination of BMD T-score, age and number of independent clinical risk factors for fracture. Strontium and raloxifene were recommended as alternative options for women for whom alendronate and either risedronate or etidronate is unsuitable[a], who also have a specified combination of BMD T-score, age and number of independent clinical risk factors for fracture. Teriparatide was recommended as an alternative option for women aged 65 years or older for whom alendronate and either risedronate or etidronate is unsuitable[a] or has not produced a satisfactory response, or who have a contraindication to, or are intolerant of, strontium, and who also have a specified combination of BMD T-score and number of fractures. A subgroup of women over the age of 74 years who had a BMD T-score of −2.4 SD or below was considered for strontium (Guidance section 4.3.3, post hoc analysis). A subgroup of women aged 55-64 years who have a BMD T-score of –4 SD or below and more than two fractures was considered for teriparatide (Guidance section 4.3.33). Patients with osteopenia (BMD T-score of between –1 SD and –2.5 SD below peak BMD) and those with long-term corticosteroid use were not considered.

BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; SD, standard deviation.

[a] Unsuitable means are that the patient is unable to comply with the special instructions for the administration, or has a contraindication or is intolerant of the treatment.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The current clinical pathway of care for women with PMO, as recommended in NICE TA160 and TA161, is summarised in Table A5. In this context, denosumab may be used instead of strontium, raloxifene or no treatment, as indicated in Table A5.

Table A5 Current clinical pathway of care recommended for women with postmenopausal osteoporosis illustrating the proposed use of denosumab

Patient characteristics	Recommended treatment	NICE Guidance
Postmenopausal women with an independent clinical risk factor for fracture and a BMD T-score of −2.5 SD or below[a]	Alendronate Risedronate or etidronate where alendronate is unsuitable[b]	TA160, TA161
Postmenopausal women for whom alendronate and either risedronate or etidronate is unsuitable[b] and who are not at sufficiently high risk of fracture to be eligible for strontium or raloxifene	No treatment **or denosumab**	TA160, TA161
Postmenopausal women for whom alendronate and either risedronate or etidronate is unsuitable[b]	Strontium **or denosumab**	TA160
Postmenopausal women who have osteoporosis and have sustained a clinically apparent osteoporotic fragility fracture for whom alendronate and either risedronate or etidronate is unsuitable[b]	Strontium or raloxifene **or denosumab**	TA161
Postmenopausal women aged 65 years or older who have osteoporosis and have sustained a clinically apparent osteoporotic fragility fracture and for whom alendronate and either risedronate or etidronate is unsuitable[b], or who have a contraindication to, or are intolerant of strontium, or who have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate	Teriparatide	TA161

BMD, bone mineral density.

[a] Women younger than 65 years must also have at least one additional indicator of low BMD. Women aged 70 years or older may have an indicator of low BMD rather than a clinical risk factor; those with two or more indicators of low BMD or clinical risk factors may receive alendronate without a dual-energy x-ray absorptiometry (DXA) scan.

[b] Unsuitable means that the patient is unable to comply with the special instructions for the administration, or has a contraindication or is intolerant of the treatment. Patients must also have a specified combination of BMD T-score and number of independent clinical risk factors for fracture.

Source: NICE TA160 (NICE, 2008b); NICE TA161 (NICE, 2008a).

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Despite the existence of the National Service Framework for Older People since 2001 (Department of Health, 2001) and NICE guidance (NICE, 2004, 2008a, 2008b), a large proportion of patients with PMO do not receive appropriate medication for bone protection. In the national audit conducted by the Royal College of Physicians (2007), only 28% of fragility fracture patients had been started on the relevant medication for bone protection by 12 weeks after fracture (Royal College of Physicians, 2007, 2009). The audit reported 'an unacceptable degree of variation across the NHS, and that an inadequate service is being provided by most local health services in hospital care and in prevention of future falls and fractures.'

Treatment is dominated by generic alendronate and, to a lesser extent, other oral BPs. Strontium and raloxifene are received by approximately 3% and 2% of treated patients, respectively, while teriparatide, intravenous (iv) ibandronate, zoledronate, calcitonin and calcitriol are each received by less than 1% of treated patients (IMS, 2009; CSD, 2009; see Table A6).

However, persistence and compliance with oral BPs is poor (Berecki-Gisolf et al., 2008), primarily as a result of the strict and complex dosing regimen (Reginster and Rabenda, 2006) and side effects of treatment (Sewerynek et al., 2009). Between a third and a half of all medicines prescribed for long-term conditions are not taken as recommended (NICE, 2009b). In the case of oral BPs, the percentage of patients discontinuing treatment within 1 year has been reported as at least 42% (Gallagher et al., 2008; Blouin et al., 2007; Cotte et al., 2008), and the median duration of BP treatment has been estimated to be as low as 1.2 years (Berecki-Gisolf et al., 2008; Roughead et al., 2009). [redacted] Non-adherence should not be seen as the patient's problem; it represents a fundamental limitation in the delivery of health care (NICE, 2009b). Poor adherence is associated with reduced effectiveness (Penning-van Beest et al., 2008), increased morbidity (Adachi et al., 2007; Siris et al., 2009a) and increased medical costs (Warriner and Curtis, 2009). Patients prefer once-weekly BPs over

daily treatment; however, compliance and persistence remain suboptimal in many patients receiving once-weekly or monthly therapy (Sambrook, 2006; Cooper et al 2006).

2.6 Please identify the main comparator(s) and justify their selection.

Osteoporosis treatments prescribed in England and Wales are presented in Table A6.

Table A6 Osteoporosis treatments prescribed in England and Wales (2009)

Drug	Percentage of treated patients
Alendronate (oral)	71.6%
Risedronate (oral)	15.8%
Ibandronate (oral)	4.3%
Etidronate (oral)	1.5%
Strontium (oral)	2.8%
Raloxifene (oral)	2.2%
Teriparatide (sc)	0.1%
Ibandronate (iv)	0.6%
Zoledronate (iv)	0.7%
Calcitonin (oral)	0.2%
Calcitriol (oral)	0.2%

iv, intravenous; sc, subcutaneous.

Patient shares were estimated from IMS Health Incorporated (IMS) sales data with the exception of etidronate and calcitriol, which were estimated from the CSD primary care medical records database. Patient shares were estimated from IMS regional sales analyses and hospital pharmacy audit data by dividing total sales by a compliance factor (assumed to be 60% for iv ibandronate and 100% for iv zoledronate), price and days of therapy.

Source: IMS 2009; CSD 2009.

Standard care (interventions used in 1% or more of treated patients) includes oral BPs, strontium and raloxifene. Teriparatide has been recommended by NICE in specific groups of patients (NICE 2008a), but is used in only 0.1% of treated patients. All other interventions are used in less than 1% of patients and have not been assessed by NICE.

Denosumab is expected to be an appropriate option where oral BPs are unsuitable. Some patients within this group may currently receive no treatment because they are not at sufficiently high risk of fracture to be eligible for other treatments. The primary comparators are therefore strontium, raloxifene and no treatment. Comparisons with iv BPs (ibandronate and zoledronate) and teriparatide are considered secondary comparators as these management strategies are not standard care and the mode of administration of iv BPs limits their use to a secondary care setting. Furthermore,

the mode of administration of iv BPs limits their use to a secondary care setting. Comparisons with oral BPs are presented in appendices (section 9.15) for completeness. Calcitonin and calcitriol are each used in only 0.2% of patients. Calcitriol has been appraised by NICE, but the efficacy evidence base did not support its inclusion in final recommendations. Although calcitonin was licensed for the prevention and treatment of PMO at the time of the previous NICE appraisals, the evidence for its efficacy was not reviewed. Comparisons with calcitonin and calcitriol will not be presented.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

There are no specific therapies that may be prescribed to manage adverse reactions. Disutilities and costs associated with adverse reactions are described in sections 6.4.8 and 6.5.7, respectively.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Denosumab should be administered by an individual who has been adequately trained in injection techniques. The administration may be performed within a routine healthcare consultation. The cost of a general practitioner (GP) visit is estimated as £37 (11.7-minute visit, Personal Social Services [PSS] unit costs of health and social care GP services) (Curtis, 2008).

No additional tests or investigations are needed for selection or monitoring of patients for denosumab treatment other than those used currently in routine clinical practice for PMO. In common with other osteoporosis therapies, patients must be adequately supplemented with calcium and vitamin D while being treated with denosumab (denosumab draft SPC, section 9.1.1).

2.9 Does the technology require additional infrastructure to be put in place?

Denosumab is a cold-storage product; a standard refrigerator is required.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Women with a disability may be unable to access treatments recommended in current NICE guidance (NICE 2008a, 2008b); for example, if they are unable to comply with the special instructions for administration of oral BPs.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No equity or equalities issues are anticipated for the appraisal of denosumab.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

No issues relating to equity or equalities have been addressed in the clinical and cost-effectiveness analyses.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

Table A7 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Intervention	Denosumab	Denosumab 60 mg Q6M	Licensed dose
Population	Postmenopausal women at risk of having an osteoporotic fragility fracture	Postmenopausal women at risk of having an osteoporotic fragility fracture	Not applicable
Comparator(s)	Management strategies without the use of denosumab, which may include: • BPs (such as alendronate, etidronate, ibandronate, risedronate, zoledronate) • Selective oestrogen receptor modulators (such as raloxifene) • Strontium • Parathyroid hormone analogues • Calcitriol • Calcitonin	Primary comparators: strontium, raloxifene and no treatment (placebo) Secondary comparators: teriparatide, iv ibandronate and zoledronate Supplementary comparators: alendronate, risedronate, etidronate and oral ibandronate are included in appendices for completeness (section 9.15)	Strontium and raloxifene have been recommended by NICE and are used in more than 1% of patients receiving treatment Some patients currently receive no treatment because oral BPs are not suitable and they are not at sufficiently high risk of fracture to be eligible for other treatments Teriparatide and iv BPs are each used in less than 1% of patients. Teriparatide has been recommended by NICE; iv ibandronate and zoledronate have not been assessed by NICE Denosumab is not expected to compete with oral BPs in clinical practice[a] Calcitonin and calcitriol are each used in only 0.2% of patients. Calcitriol has been appraised by NICE but the efficacy evidence base did not support its inclusion in final recommendations. Although calcitonin was licensed for the prevention and treatment of

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			postmenopausal osteoporosis at the time of the previous NICE appraisals, the evidence for its efficacy was not reviewed
Outcomes	The outcome measures to be considered include osteoporotic fragility fracture, BMD, mortality, HRQL and adverse effects of treatment	The outcome measures considered include osteoporotic fragility fracture, BMD,[b] mortality, HRQL and adverse effects of treatment	Not applicable
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and PSS perspective	The cost effectiveness of denosumab is expressed in terms of incremental cost per QALY The time horizon for estimating clinical and cost effectiveness is patients' lifetimes to reflect any differences in costs or outcomes between the technologies being compared Costs are considered from an NHS and PSS perspective	Not applicable
Other considerations	Guidance will only be issued in accordance with the marketing authorisation If the evidence allows, the following subgroups will be considered: • People with risk factors for fracture • Site of fracture • Women with a disability which prevents them from using specific technologies	The submission is in accordance with the marketing authorisation • The economic analysis explores alternative scenarios for underlying risk of fracture	• We do not anticipate subgroup analysis for patients with prior fracture at specific sites. However, analyses exploring alternative scenarios for underlying risk of re-fracture will be presented • We do not anticipate subgroup analysis for patients with a disability; however this issue could be captured within equity considerations
	Consideration should be given to: • Approach of fracture risk assessment	• Two approaches are explored for fracture risk in the economic	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	• Assessment of probability of fracture • Cost of fracture risk assessment • Continuation of treatment	analysis. Absolute risk is estimated from published epidemiological data. In a scenario analysis, fracture risk is estimated using FRAX® for previously untreated patients • Assessment of the probability of fracture is performed in the model based on the underlying risk (see above) and relative risk estimates estimated via systematic review and meta-analysis • Continuation of treatment is in line with previous NICE technology assessments in osteoporosis • The cost of fracture risk assessment for all osteoporosis therapies is assumed to consist of a once yearly GP visit and a bone mineral density measurement once every second year.	

BMD, bone mineral density; BP, bisphosphonate; GP, general practitioner; HRQL, health-related quality of life; iv, intravenous; NHS, National Health Service; PSS, Personal and Social Services; Q6M, every 6 months; QALY, quality-adjusted life year; SERM, selective oestrogen receptor modulator.

[a] Oral BPs are supplementary comparators because denosumab is not expected to compete with them in clinical practice; denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable.

[b] BMD data are presented as supporting evidence in the clinical evidence section but were not utilised in the cost-effectiveness model.

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s).

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

In September 2008, a series of evidence reviews for osteoporosis medicines developed by the National Collaborating Centre for Nursing & Supportive Care (NCCNSC) was published on the NICE website (NCCNSC, 2008). These reviews were commissioned as part of the development of a NICE clinical guideline that has been in development since 2002. Although the reviews have not been formally signed off by the Guideline Development Group, they represent the most recent reviews of evidence in this therapy area.

To address the information needs of the decision problem as outlined in the draft scope for this appraisal, a review was implemented that aimed to update the NCCNSC reviews by supplementing them with additional data from beyond June 2008 and including consideration of any new medicines that may have been approved or may have been seeking approval via the regulatory process since the NCCNSC reviews were completed. A pre-specified protocol was therefore developed, guided by the NCCNSC review and using similar search strategies.

The following databases were searched:

- MEDLINE® In-process and other non-indexed citations and MEDLINE®: 1950 to present via OVID
- EMBASE: 1980 to 2009 Week 16 via OVID

- Cochrane Central Register of Controlled Trials via Wiley Interscience
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) via OVID

Searches for studies investigating all comparators (primary, secondary and supplementary) were performed on 28 April 2009; searches for denosumab studies were performed on 8 July 2009. Searches were updated on 17 September 2009 for denosumab to identify the recent FREEDOM NEJM publication and 4 November 2009 to identify an additional selective estrogen receptor modulator (SERM) (bazedoxifene) identified from the original search. There were no date limits applied to the searches performed on 28 April 2009, 8 July 2009, and 4 November 2009, but the search on 17 September 2009 was limited to 2009 only; the entire database searched in each case. Study design filters suggested by the Scottish Intercollegiate Guidelines Network (SIGN) were applied (SIGN, 2009) for MEDLINE, EMBASE and CINAHL. No search filter was used for the Cochrane Central database as this is a trial database.

5.2 Study Selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1 summarises study inclusion and exclusion criteria. Studies were first screened based on the title and abstract; those that did not match the eligibility criteria were excluded. Full-text copies of all studies were then screened. At each screening stage, the studies were assessed in parallel independently by two individual reviewers, with a third independent reviewer resolving any discrepancies.

Table B1 Eligibility criteria used in search strategy

Inclusion criteria	**Population** Patients at risk of osteoporotic fractures, who may or may not have had a previous fracture, including people with osteoporosis, osteopenia or normal bone mineral density. Also included were studies in people with glucocorticoid-induced osteoporosis and those in women, in men or in women and men. **Interventions** Denosumab, alendronate, risedronate, ibandronate, zoledronate, etidronate, strontium, teriparatide, raloxifene, parathyroid hormone (1-84) and lasofoxifene, and bazedoxifene. Combination therapies were included. **Study design** Randomised controlled trials. Quasi-randomised studies (e.g., where the randomisation was based on date of birth or allocation by alternation) were included if there was no other evidence. **Outcomes** Studies reporting mixed trauma and non-trauma fracture were included. **Other** English language articles were included. No limits were imposed on publication date.
Exclusion criteria	**Population** Studies including patients with other underlying conditions that make them susceptible to factures were excluded (e.g., postmenopausal women with systemic lupus erythematosus and patients with kidney transplant). **Interventions** Dose-finding and formulation studies were excluded unless there was a placebo or an active control arm. Interventions given for less than 12 months. **Study design** Reviews and editorials. In vitro and in vivo studies. Quasi-randomised studies (e.g., where the randomisation was based on date of birth or allocation by alternation) unless there was no other evidence. Fewer than 10 patients in each study arm. Study period of less than 12 months after intervention administration. **Outcomes** Studies reporting fractures associated with major trauma (e.g., road accidents). **Other** Non-English language articles were excluded.

The inclusion and exclusion criteria described in Table B1 were based on the NCCNSC review. Differences in eligibility criteria compared to the NCCNSC review included:

1. Intervention list (this review includes specific interventions as listed in Table B1)
2. Inclusion for this search of studies that only included BMD as an outcome

3. Exclusion for this search of dose finding studies (however, no studies were in fact excluded for this reason).
4. Inclusion of studies with unlicensed doses

In addition, the NCCNSC review only included studies of licensed doses, and this review did not exclude on this basis.

The search strategies used including all search terms: textwords (free text), subject index headings (for example, Medical Subject Headings [MeSH]) and the relationship between the search terms (for example, Boolean) are outlined in Section 9.2. The NCCNSC review included a list of interventions, but this was not included in the search strategy whereas this review included a treatment facet.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o = 1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

In the original searches performed on 28 April 2009 and 8 July 2009, there were 5,929 citations retrieved from the literature databases and from manual searches of bibliographies. Of these citations, 1,839 were identified as duplicates and were excluded. Following the first screening stage, 543 potentially relevant citations were identified. Full-text reports of these references were retrieved for detailed evaluation, and 161 were excluded at the second screening stage. Reasons for exclusion are presented in Figure B1. A total of 382 reports representing 200 studies met the inclusion criteria after the second screen, 5 of which reported studies investigating denosumab.

In the first updated search performed on 17 September 2009, there were 321 citations retrieved from the literature databases and from manual searches of bibliographies. Of these citations, 94 were identified as duplicates and were excluded. Following the first screening stage, 42 potentially relevant citations were identified. Full-text reports of these references were retrieved for detailed evaluation, and 21 were excluded at the second screening stage. Reasons for exclusion are

presented in Figure B1. A total of 21 reports representing 11 studies met the inclusion criteria after the second screen, 1 of which reported studies investigating denosumab.

In the second updated search performed on 4 November 2009, there were 87 citations retired from the literature databases and from manual searches of bibliographies. Of these citations, 24 were identified as duplicates and were excluded. Following the first screening stage, 3 potentially relevant citations were identified. Full-text reports of these references were retrieved for detailed evaluation, and 2 were excluded at the second screening stage. Reasons for exclusion are presented in Figure B1. A total of one report representing one study (secondary citation) met the inclusion criteria after the second screen, none of which reported studies investigating denosumab.

Combining the included studies from the original review and the updates, 404 reports representing 211 studies were included plus 193 linked secondary studies.

Study selection for meta-analysis, adjusted indirect comparison and mixed treatment comparison in postmenopausal women with osteoporosis

Study eligibility

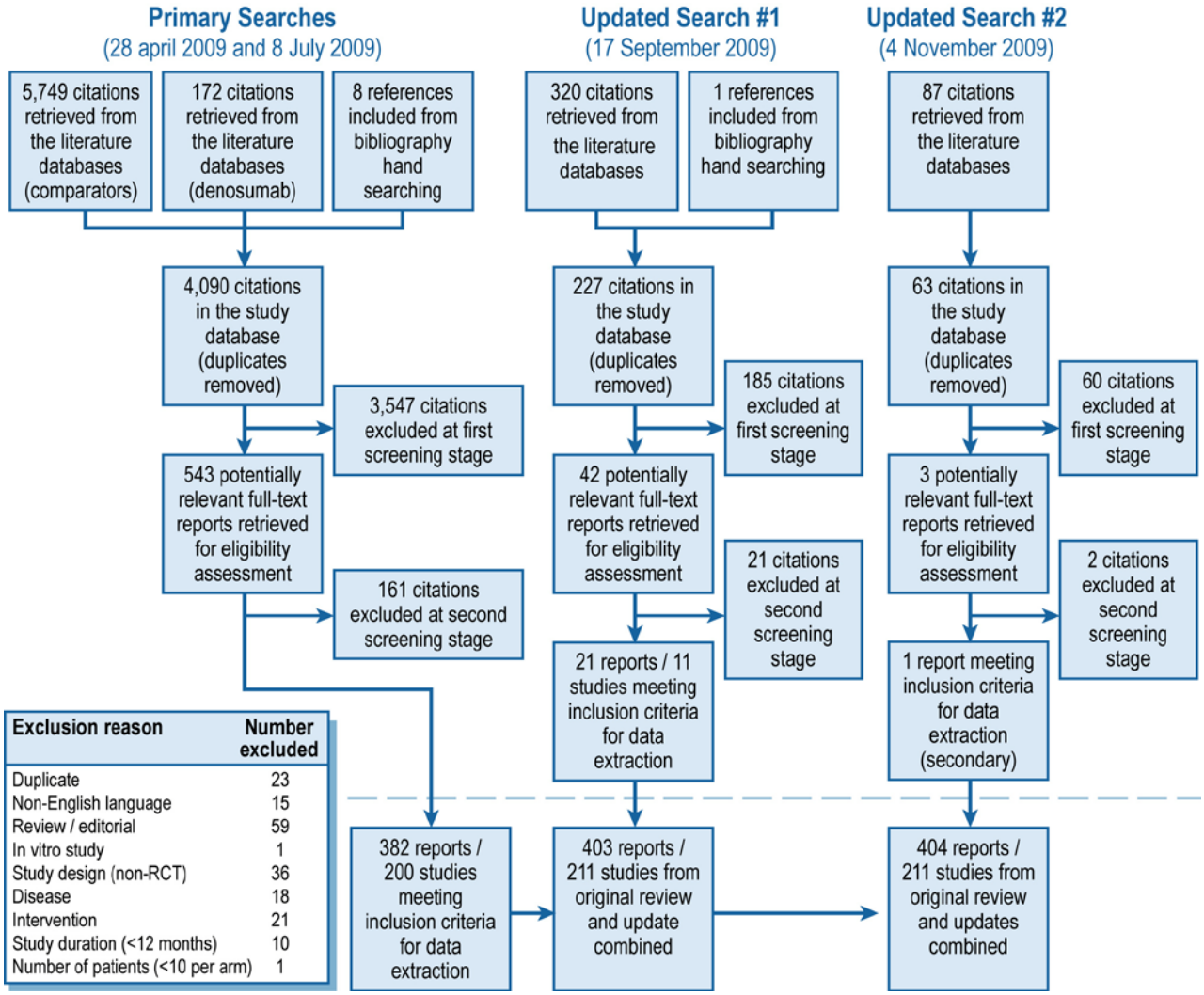
A broad list of studies was identified from NCCNSC review which is beyond the scope of a meta-analysis and IC in relation to denosumab. Therefore, a separate procedure was performed to exclude additional studies which are not in scope of a meta-analysis, IC and MTC when evaluating denosumab. Specific categories for further exclusion revolved around the following:

1. Publication type and study design
2. Study population
3. Intervention
4. Comparator
5. Outcome

Many studies met more then one criteria for exclusion. To logically provide rationale for exclusion, a hierarchy based on the above categories was used to exclude

studies using publication type and study design as the first reason for exclusion, followed by study population, intervention, comparator, and outcome. Details of study exclusion for evaluation in the meta-analysis and IC are described below and summarised in Figure B2.

Figure B1 Study identification, inclusion and exclusion: primary systematic review



RCT, randomised controlled trial.

Publication type and study design

Additional exclusion of studies based on blinding was performed after the primary systematic review described above. In the original inclusion criteria, eligible studies included parallel-group RCTs with placebo-controlled and head-to-head trials of primary interest. Studies with open-label design were excluded for meta-analysis and IC. Additionally, only studies for which full publications could be extracted were selected for evaluation, therefore, abstract only data was excluded. Of the 211

studies identified from the systematic review based on the NCCNSC review, 17 citations were found to be open-label or data was only reported in abstract form and were excluded. Reasons for exclusion are presented in Figure B2.

Population

The population of interest for meta-analysis and IC was postmenopausal women only (osteopenia or osteoporosis). Study participants must be postmenopausal women with osteoporosis at risk of osteoporotic fractures, who may or may not have had a previous fracture. According to the World Health Organization, osteoporosis is defined as BMD T-score
≤ –2.5 SD, osteopenia as T-score between –2.5 and –1.0 SD and people with normal BMD as a T-score within 1 SD of zero. This analysis will exclude all studies with postmenopausal patients at high risk for both primary and secondary fractures (e.g., systemic lupus erythematosus, inflammatory bowel disease), as well as those studies evaluating men or both men and women, evaluating glucocorticoid-induced osteoporosis and patients previously treated without a predefined washout period. Of the 211 studies identified from the systematic review based on the NCCNSC review, 52 citations were identified as evaluating men, glucocorticoid-induced osteoporosis, or high-risk groups and were excluded.

Intervention

The studies selected for analysis included studies that examined interventional drug classes for the treatment of PMO as defined in the primary systematic review described in Section 5.2.1. Studies evaluating only interventions not listed below (including hormone replacement therapy [HRT], calcitonin, vitamin D, calcium, PTH [1-84], lasofoxifene, and bazedoxifene) were excluded. The primary systematic review included all doses, licensed and unlicensed, but for the purposes of this meta-analysis, IC, and MTC, only studies using on-label dosing for PMO as defined by the British National Formulary (BNF) and European Medicines Agency below were included. This method follows the same methodology used within the NCCNSC osteoporosis evidence review published in October 2008. The only exception to this rule was ibandronate, as limited data are available of ibandronate versus placebo at the labeled doses listed below.

1. Denosumab

a. The denosumab dose is 60 mg every 6 months by subcutaneous administration.

2. Bisphosphonates
    a. Alendronic acid
        i. For the prevention of PMO, the alendronic acid dose is 5 mg/day. For treatment of PMO and osteoporosis in men, this is a dose of 10 mg/day or (in PMO) 70 mg once weekly.
    b. Disodium etidronate
        i. For the treatment of osteoporosis in postmenopausal women and for the prevention, the disodium etidronate dose is 400 mg/day for 14 days, then calcium carbonate 1.25 g/day (500 mg/day elemental calcium) for 76 days.
    c. Risedronate sodium
        i. For the prevention of osteoporosis in postmenopausal women, the risedronate dose is 5 mg/day. For the treatment of PMO to reduce risk of vertebral or hip fractures, the dose is 5 mg/day or 35 mg once weekly.
    d. Ibandronic acid
        i. For the treatment of PMO, the ibandronic acid dose is 150 mg by mouth, once a month, or 3 mg over 15–30 seconds by intravenous injection, once every 3 months.
    e. Zoledronic acid
        i. For the treatment of PMO, the zoledronic acid dose is 5 mg over at least 15 minutes by intravenous infusion, once a year. Trade name: Aclasta
3. Strontium
    a. The strontium dose is 2 g/day in water, preferably at bedtime.
4. Parathyroid hormone (teriparatide)
    a. The teriparatide (PTH 1-34) dose is a 20 microgram/day subcutaneous injection, for the treatment of osteoporosis in postmenopausal women at increased risk of fractures; the maximum duration of treatment is 18 months. Trade name: Forsteo.
5. Selective estrogen receptor modulators
    a. Raloxifene

i. For treatment of PMO, the raloxifene dose is 60 mg/day.

Additionally, studies that evaluate only a combination of therapies in which two active treatments were combined were also excluded.

Of the 211 studies identified from the systematic review based on the NCCNSC review, 37 citations were identified as evaluating interventions not included for meta-analysis, IC and MTC, evaluated off-label doses or evaluated a combination of two active treatments and were excluded.

Comparator

Specific studies identified in the primary systematic review described in Section 5.2.1 were selected based on comparators representing placebo or an active control. However, selected interventions frequently were compared to interventions not selected for evaluation in the meta-analysis and IC. Therefore these studies were selected for exclusion. Of the 211 studies identified from the systematic review based on the NCCNSC review, 16 citations were identified as evaluating a comparator not included for meta-analysis and IC and did not include a placebo control and were excluded.

Outcome

Studies reporting at least one of the following fragility fracture outcomes of interest as a primary, secondary, exploratory or adverse event were included. Fracture data that could not be extracted, fractures such as clinical fractures or fractures of other sites not listed above, and studies where other outcomes were evaluated such as BMD and bone turnover markers without fractures reported were excluded.

Fragility fractures are those associated with low trauma, which is defined as the result of a force equivalent to the force of a fall from a height equal to or less than that of an ordinary chair. Fragility fractures are also referred to as osteoporotic fractures. Studies that report major trauma-related fractures were excluded; fracture as a result of mixed trauma and non-trauma will be included.

The incidence of fracture outcome should have been measured in a dichotomous way, as the number of patients with a fracture. Studies recording only the number of fractures were not included unless there was sufficient information to calculate the

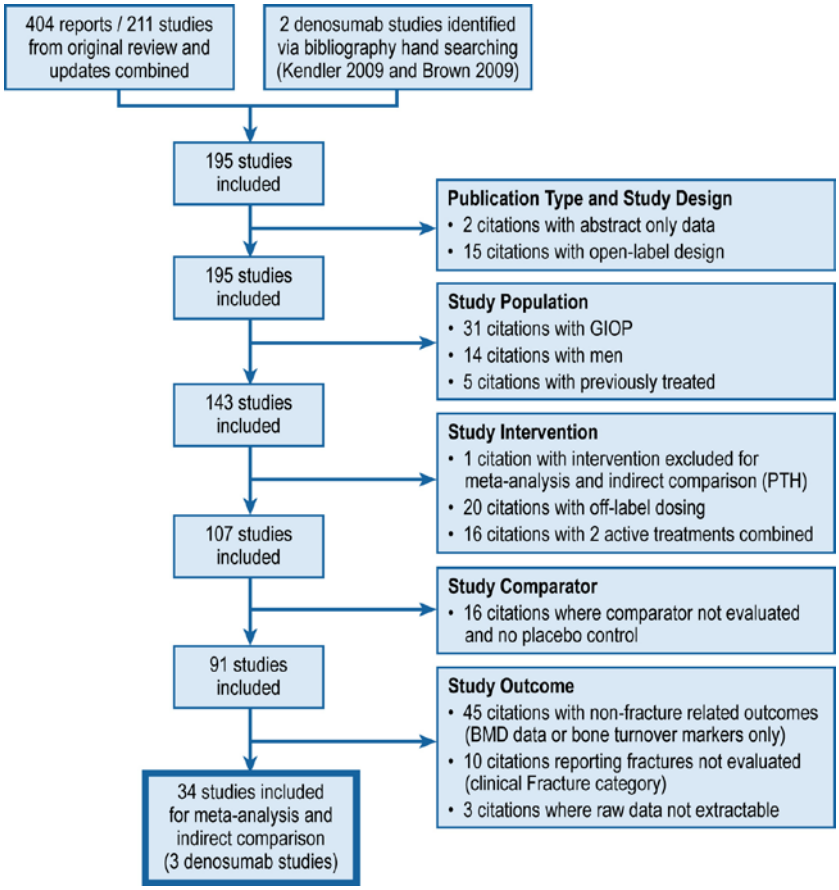
number of patients with at least one fracture. Studies evaluating the five fracture types listed below were included in the meta-analysis and indirect comparison:

1. Morphometric vertebral
    a. Fractures identified radiographically (x-ray) which include symptomatic and asymptomatic fractures and are evaluated using semiquantitative assessment.
    b. Semiquantitative assessment is based on training of the readers (joint reading of about a hundred radiographs with an expert) and use of a written protocol: vertebrae were graded from T4 to L5 on visual inspection and without direct morphometric measurement as normal (grade 0), mildly deformed (grade 1, approximately 20%-25% reduction of anterior, middle and/or posterior height), moderately deformed (grade 2, approximately 25%-40% reduction in any height), and severely deformed (grade 3, approximately 40% reduction in any height). A vertebral body was considered to be fractured if graded 1 or higher.
2. Clinical vertebral
    a. Fractures that cause sufficient discomfort for the patient to bring them to the attention of a health professional and/or are identified by x-ray.
3. Hip
    a. Specific studies do not differentiate hip and pelvis fractures, but will be included for meta-analysis and IC.
4. Non-vertebral
        i. All studies evaluating the category of non-vertebral fractures will be evaluated. However, specific studies evaluate the category via different definitions leading to potential bias (all non-vertebral fracture or six most common non-vertebral fractures).
5. Wrist fracture
    a. Defined based on study categorization.

Of the 211 studies identified from the systematic review based on the NCCNSC review, 58 citations were identified as not evaluating selected fracture types or were

unable to extract data and IC and did not include a placebo control and were excluded.

Figure B2 Study exclusion for trials to be analysed in meta-analysis, adjusted indirect comparison and mixed treatment comparison



BMD, bone mineral density; GIOP, glucocorticoid-induced osteoporosis.

Selected studies versus NCCNSC selected studies

A separate comparison of selected studies for inclusion in the meta-analysis was also performed against those studies included in the NCCNSC review. The NCCNSC review presented a number of meta-analyses by intervention across different populations. They also performed a number of sensitivity analyses. For comparison to the studies selected in this meta-analysis, studies were only compared for postmenopausal women and those included in the primary meta-analysis.

Alendronate

Four studies evaluating alendronate were excluded from this review that was included in the NCCNSC review. When evaluating alendronate versus placebo for

morphometric vertebral, a single study (Carfora et al., 1998) was not included in this meta-analysis that was included in the NCCNSC review. This study was excluded as the publication was not in English. A second study by Lindsay et al. (1999) that evaluated non-vertebral fractures and wrist fractures was also excluded as this assessed alendronate combined with HRT versus HRT alone. As this study evaluated two active treatment combined and included a comparator not selected for evaluation; the study was excluded from this analysis. A third study by Evio et al. (2004) also evaluated two active treatments assessing alendronate versus alendronate plus HRT and was excluded from the analysis. A fourth study was excluded, the Fracture Intervention Trial Long-term Extension (FLEX) study (Black et al., 2006), as this trial only evaluated overall number of fractures and was a 5 year extension study evaluating patients previously treated with alendronate.

Ibandronate

Two studies evaluating ibandronate were excluded from this review that was included in the NCCNSC review. Eisman et al. (2008) and Reginster et al. (2006) evaluated on-label doses of ibandronate versus off-label doses of ibandronate thus excluding them from evaluation. Additionally, both studies only evaluated clinical fractures which were not a selected fracture type included in this evaluation.

Zoledronate

One study was excluded from this review that was included in the NCCNSC review. Lyles et al. (2007) was excluded as this study included both men and women for morphometric vertebral, non-vertebral and hip fractures.

Strontium

One study was excluded from this review that was included in the NCCNSC review. Meunier et al. (2002) (STRontium Administration for Treatment of Osteoporosis [STRATOS]) was excluded as no available raw data could be extracted for morphometric vertebral fractures and only relative risks were available. Additionally, the-5 year Treatment of Peripheral Osteoporosis (TROPOS) study (Reginster et al., 2008) was used for this analysis, whereas the 3-year data (Reginster et al., 2006) were used in the NCCNSC review. The Reginster et al. (2008) study was used as more available raw data were available which could be used for the meta-analysis and IC. Regardless, some raw data was not available in Meunier et al. (2002)

(STRATOS) and Reginster et al. (2008) (TROPOS) and fracture incidence data was used to estimate raw fracture counts.

Teriparatide

Two studies were excluded from this review that was included in the NCCNSC review. A study by Lindsay et al. (2004) was a follow-up to the Neer et al. (2001) (FPT) study and was excluded to avoid double counting. Another study by Cosman et al. (2001), which evaluated vertebral fractures was also excluded, as this assessed teriparatide combined with HRT versus HRT alone. A third study was also excluded (Cosman et al., 2005), as this study evaluated teriparatide combined with alendronate versus alendronate alone for morphometric vertebral and non-vertebral fractures. As both of these studies evaluated two active treatments combined, and one study included a comparator not selected for evaluation (Cosman et al., 2001), the study was excluded from this analysis.

Raloxifene

One study was excluded from this review that was included in the NCCNSC review. Reginster et al. (2003) evaluated vertebral, non-vertebral and hip fractures, as this study evaluated two active treatments combined (raloxifene combined with monofluorophosphate versus monofluorophosphate alone.

Direct comparisons

Four studies evaluating ibandronate versus alendronate were excluded from this review that was included in the NCCNSC review. Reid et al. (2006), Rosen et al. (2005), Bonnick et al. (2006) and Reid et al. (2008) were excluded as these studies only evaluated overall number of fractures which was not a selected fracture type included in this evaluation. One study evaluating alendronate versus teriparatide was excluded from this review that was included in the NCCNSC review as this only evaluated all clinical fractures which was not a fracture evaluated in this analysis.

5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

In the original searches, of 382 reports meeting inclusion criteria, 182 were found to be linked to one of the remaining references. This left a total of 200 studies, 5 of which investigated denosumab. In the updated searches, of the 22 reports meeting inclusion criteria, 9 were found to be linked to one of the references identified in the original review and one was linked to a reference identified in the update. This left a total of 13 studies, 1 of which consisted of two sub-studies (Selective estrogen Menopause And Response to Therapy [SMART] trial). Section 9.2 presents linked reports.

Combining the included studies from the original review and the update, 404 reports were identified, 211 studies were included plus 193 linked secondary studies.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B2 summarises details of all RCTs. In addition to the three studies (6 reports) identified by the systematic review for denosumab, a further five RCTs are listed that were not identified (e.g., because indexing terms did not identify studies in primary search, because they were published more recently than the closing date of the searches or have not yet been published). Five extension studies investigating denosumab in postmenopausal women at increased risk of fracture: 20050233 (extension of 20010223); 20060289 (extension of 20030216); 20080747 (extension of 20050179); 20060237 (extension of 20050141); 20080287 (extension of multiple studies). Details of these studies are provided in section 9.7 (appendix 7).

Excluding denosumab studies, a total of 209 studies (398 reports) were identified for all the comparators; section 9.2 lists these.

Table B3 summarises details of the trials for all primary and secondary comparators that were included in the IC and MTC. Note that the primary comparators are strontium and raloxifene. Studies investigating oral ibandronate are included in the table since no trials investigating iv ibandronate were identified. Data for secondary comparators iv BPs (ibandronate and zoledronate) and teriparatide are presented; however, these management strategies are not standard care and the mode of administration of iv BPs limits their use to a secondary care setting. Data for the supplementary comparators (oral BPs) are presented in section 9.4 (appendix 4).

Table B2 RCTs investigating denosumab in postmenopausal women at increased risk of fracture

Trial no. (acronym)	Intervention (dosage)	Comparators (dosage)	Population	Primary study ref.
20030216 (FREEDOM)	sc denosumab 60 mg Q6M for 3 years + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	sc placebo Q6M for 3 years + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	Postmenopausal women aged 60-90 years with osteoporosis (BMD T-score < –2.5 SD at either the lumbar spine or the total hip, or at both locations, and ≥ –4.0 SD at both locations)	Amgen data on file (20030216 [FREEDOM] CSR) Cummings et al., 2009
20050141 (DECIDE)	sc denosumab 60 mg Q6M + oral placebo weekly for 12 months + daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU) supplementation	Oral alendronate weekly (70 mg) + sc placebo Q6M for 12 months + daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU) supplementation	Postmenopausal women with a BMD T-score ≤ −2.0 SD at the lumbar spine or total hip	Amgen data on file (20050141 [DECIDE] CSR) Brown et al., 2009
20050234 (STAND)	Open-label branded alendronate 70 mg QW for 1 month, then sc denosumab 60 mg Q6M + placebo for oral alendronate QW for 12 months + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	Open-label branded alendronate 70 mg QW for 1 month, then continued weekly alendronate therapy + placebo for sc denosumab Q6M for 12 months + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	Postmenopausal women aged ≥ 55 years with a BMD T-score of ≤ –2.0 SD and ≥ –4.0 SD at the lumbar spine, total hip or femoral neck	Amgen data on file (20050234 [STAND] CSR) Kendler et al., 2009
20060232 (DAPS)	sc denosumab 60 mg Q6M for 1 year (treatment period 1) followed by oral alendronate 70 mg QW for 1 year (treatment period 2) + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	Oral alendronate 70 mg QW for 1 year (treatment period 1) followed by sc denosumab 60 mg Q6M for 1 year (treatment period 2) + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	Postmenopausal women, [redacted]	Amgen data on file (20060232 [DAPS] protocol; 20060232 [DAPS] 12-month interim analysis
20040132 (DEFEND)	sc denosumab 60 mg Q6M for 24 months + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation	Placebo for 24 months + daily calcium (≥ 1 g) and vitamin D (≥ 400 IU or ≥ 800 IU) supplementation	Postmenopausal women with lumbar spine BMD T-scores between –1.0 SD and –2.5 SD	Bone et al., 2008

Trial no. (acronym)	Intervention (dosage)	Comparators (dosage)	Population	Primary study ref.
20050179 (none)	sc denosumab 60 mg Q6M (at day 1 and month 6) + placebo for oral alendronate QW for 12 months All treatment groups received daily supplementation with ≥ 500 mg elemental calcium and ≥ 400 IU vitamin D	Oral alendronate 70 mg QW for 12 months + placebo for sc denosumab Q6M Or placebo (placebo for sc denosumab Q6M + placebo for oral alendronate QW for 12 months) All treatment groups received daily supplementation with ≥ 500 mg elemental calcium and ≥ 400 IU vitamin D	Postmenopausal women aged 50-70 years with low BMD (lumbar spine or total hip T-score ≥ −3.0 SD and ≤ −2.0 SD)	Seeman et al., 2009b
20010223 (none)	Denosumab continuous treatment includes groups of 6 mg and 14 mg Q3M, and 14 mg, 60 mg and 100 mg Q6M who were switched to 60 mg Q6M dose at month 24 Denosumab 210 mg Q6M followed by placebo for the last 24 months Denosumab 30 mg Q3M followed by placebo at month 24 for 12 months followed by re-treatment with denosumab 60 mg Q6M for 12 months Calcium (1,000 mg/day) and vitamin D (≥ 400 IU/day) supplementation for all treatment groups	Alendronate Placebo Calcium (1,000 mg/day) and vitamin D (≥ 400 IU/day) supplementation for all treatment groups	Postmenopausal women with a BMD T-score of −1.8 SD to −4.0 SD at the lumbar spine or −1.8 SD to −3.5 SD at the femoral neck or total hip	McClung et al., 2006 Lewiecki et al., 2007 Beck et al., 2008 Miller et al., 2008a

Trial no. (acronym)	Intervention (dosage)	Comparators (dosage)	Population	Primary study ref.
20050172 (none)	sc denosumab 60 mg Q6M (at day 1 and month 6) Calcium (600 mg/day) and vitamin D (≥ 400 IU/day) supplementation for all treatment groups	sc injections of placebo Q6M (at day 1 and month 6) Calcium (600 mg/day) and vitamin D (≥ 400 IU/day) supplementation for all treatment groups	Postmenopausal women [redacted]	Amgen data on file (20050172 CSR)
20040135 (HALT)	sc denosumab 60 mg Q6M for 24 months	sc placebo Q6M for 24 months	Women with non-metastatic breast cancer who were undergoing aromatase inhibitor therapy	Ellis et al., 2008 Ellis et al., 2009 Amgen data on file (20040135 [HALT] CSR)
BMD, bone mineral density; BP, bisphosphonate; CSR, clinical study report; DXA, dual-energy x-ray absorptiometry; Q3M, every 3 months; Q6M, every 6 months; QW, once weekly; sc, subcutaneous; SD, standard deviation.				

Table B3 Characteristics of studies investigating denosumab, primary and secondary comparators included in the meta-analysis, indirect comparison and mixed treatment comparison

Study Name	Patient population	Blinding	Study duration	Jadad score	Regime dosing	Admin. route	Number of patients	Mean age
BONE Study Chesnut et al., 2009	Adult osteoporotic women aged between 55 to 80 years, postmenopausal for at least 5 years, with one to four prevalent vertebral fractures (T4–L4) and a BMD T-score of –2.0 to –5.0 in at least one vertebra (L1-L4) were included.	Double-blind	156 weeks	3	Ibandronate 2.5 mg QD	Oral	982	69
					Placebo	Oral	982	69
					Ibandronate 20 mg QOD for the first 24 days Q3M	Oral	982	69
DECIDE Study Brown et al., 2009	Postmenopausal women with osteoporosis (T-score ≤ −2.0 SD at the lumbar spine or total hip).	Double-blind	52 weeks	1	Alendronate	Oral	595	64.6
					Denosumab	sc	594	64.1
EFFECT International study Sambrook et al., 2004	Osteoporotic patients who were postmenopausal (defined as at least 6 months beyond the final menstrual period) with low bone density (defined by BMD at least 2.0 SD below the young normal mean at either total hip or lumbar spine) were included.	Double-blind	52 weeks	5	Alendronate 70 mg weekly	Oral	246	61.5
					Raloxifene 60 mg QD	Oral	241	61.8
EFFECT Study Luckey et al., 2004	Postmenopausal (18 months since last menstrual period) women older than 40 years (> 25 years if surgically postmenopausal) with osteoporosis as defined by a low BMD (> 2.0 SD below young normal mean bone mass for either PA lumbar spine (L1-L4).	Double-blind	52 weeks	5	Alendronate 70 mg weekly	Oral	223	63.8
					Raloxifene 60 mg QD	Oral	233	64.7
EVA Study Recker et al., 2007	Ambulatory postmenopausal women, aged between 50 and 80 years, whose last menstrual period occurred at least 2 years prior to study entry were included. Women with low bone mass (lumbar spine, or femoral neck, or total hip BMD T-score between –2.5 and –4.0 SD, inclusive).	Double-blind	44.45 weeks (mean study duration)	5	Raloxifene 60 mg QD	Oral	707	65.5
					Alendronate 10 mg QD	Oral	716	65.7

Study Name	Patient population	Blinding	Study duration	Jadad score	Regime dosing	Admin. route	Number of patients	Mean age
FPT Study Neer et al., 2001	Ambulatory women, postmenopausal for at least five years with at least one moderate or two mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine were included.	Double-blind	91 weeks (median duration of observation)	3	Teriparatide 20 mcg QD	sc	541	70
					Teriparatide 40 mcg QD	sc	552	70
					Placebo	sc	544	69
FREEDOM Study Cummings et al., 2009	Postmenopausal women with osteoporosis (BMD T-score less than –2.5 but not less than –4.0 at lumbar spine or total hip).	Double-blind	156 weeks	1	Placebo	Oral	3,906	72.3
					Denosumab	sc	3,902	72.3
HORIZON Study Black et al., 2007	Postmenopausal women aged 65 to 89 years with a BMD T-score of –2.5 SD or less at the femoral neck, with or without evidence of existing vertebral fracture, or a BMD T-score of –1.5 or less, with radiologic evidence of at least two mild vertebral fractures.	Double-blind	156 weeks	3	Zoledronic acid 5 mg once in 12 months	iv infusion	3889	73.1
					Placebo	iv infusion	3876	73
Liu et al., 2004	Postmenopausal women between 50-80 years, who were free of severe or chronically disabling conditions, had their last menstrual period at least 2 years before enrolment and had a T-score for femoral neck or lumbar spine BMD measurements ≤2.5.	Double-blind	52 weeks	4	Raloxifene 60 mg QD	Oral	102	65.5
					Placebo	Oral	102	65.1
Lufkin et al., 1998	Women aged 45 to 75 years in good health except for osteoporosis, free of any serious acute or chronic medical condition that might affect bone or calcium metabolism, fully ambulatory, and postmenopausal. All the included patients had at least one vertebral fracture at baseline.	Double-blind	52 weeks	3	Raloxifene 60 mg QD	Oral	48	69.9
					Placebo	Oral	48	68.2
					Raloxifene 120 mg QD	Oral	47	67.2

Study Name	Patient population	Blinding	Study duration	Jadad score	Regime dosing	Admin. route	Number of patients	Mean age
Michalska et al., 2006	Inclusion criteria were: ambulatory postmenopausal women, 50-80 years of age, and previous treatment with alendronate (10 mg/d) for more than 3 years. Patients had osteoporosis (T score less than –2.5, by dual-energy x-ray absorptiometry) at the lumbar spine or proximal femur.	Mixed	104 weeks	2	Placebo	Unclear	33	64.5
					Raloxifene 60 mg QD	Unclear	34	65.6
					Alendronate 10 mg QD	Unclear	33	65.4
MORE Study Ettinger et al., 1999	Adult osteoporotic (T-score ≤-2.5) females with low BMD or radiographically apparent vertebral fractures, postmenopausal for ≥ 2 years with no other severe or long-term disabling conditions. Approximately, 37% of the patients had a prevalent vertebral fracture at baseline. Study group 1 femoral neck or lumbar spine BMD T-score < −2.5 SD and study group 2: low bone mineral density and 1 or more moderate or severe vertebral fractures or 2 or more mild vertebral fractures or who had at least 2 moderate fractures, regardless of their bone mineral density.	Double-blind	208 weeks	4	Placebo (Study group 1)	Oral	1522	65
					Raloxifene 60 mg QD (Study group 1)	Oral	1490	65
					Raloxifene 120 mg QD (Study group 1)	Oral	1512	
					Placebo (Study group 2)	Oral	770	69
					Raloxifene 60 mg QD (Study group 2)	Oral	769	68
					Raloxifene 120 mg QD (Study group 2)	Oral	765	
Morii et al., 2003	Post menopausal Japanese women (who were post menopause for two or more year) with osteoporosis (L2-L4 BMD T-score of at least 2.5 SDs below the young adult mean), age no older than 80 years were enrolled in this study.	Double-blind	52 weeks	2	Placebo	Oral	100	64.3
					Raloxifene 60 mg QD	Oral	100	65.2
					Raloxifene 120 mg QD	Oral	102	64.7
MOTION Study Miller et al., 2008b	Ambulatory women aged 55 to 84 years, ≥ 5 years post-menopause with mean lumbar spine (L2 to L4) BMD T-score < –2.5 and ≥ –5.0.	Double-blind	52 weeks	4	Alendronate 70 mg weekly	Oral	859	65.6
					Ibandronate 150 mg monthly	Oral	874	65.6

Study Name	Patient population	Blinding	Study duration	Jadad score	Regime dosing	Admin. route	Number of patients	Mean age
Palomba et al., 2005	Postmenopausal ambulatory osteoporotic patients, natural post menopause (FSH >40 IU/L and 17b-estradiol < 20 pmol/L), and BMD at least 2.5 SD below the peak mean bone density at the posterior-anterior lumbar spine.	Assessor blind	52 weeks	3	Alendronate 10 mg QD	Oral	220	N/A
					Raloxifene 60 mg QD	Unclear	219	N/A
					HRT	Unclear	219	N/A
					Alendronate 10 mg QD + HRT	Unclear	220	N/A
					Alendronate 10 mg QD + raloxifene 60 mg QD	Oral	222	N/A
Silverman et al., 2008	Healthy women between the ages of 55 and 85 years were eligible if they were at least two years postmenopausal and had osteoporosis, defined as low BMD or radiographically confirmed vertebral fractures.	Double-blind	156 weeks	4	Bazedoxifene 20 mg QD	Oral	1886	66.5
					Bazedoxifene 40 mg QD	Oral	1872	66.2
					Raloxifene 60 mg QD	Oral	1849	66.4
					Placebo	Oral	1885	66.5
SOTI Study Meunier et al., 2004	Adult women aged at least 50 years, and postmenopausal for at least five years, with at least one fracture confirmed by spinal radiography (after minimal trauma), and lumbar-spine BMD ≤ 0.840 g/cm^2 (measured with Hologic instruments) were included.	Double-blind	156 weeks	2	Placebo	Oral	821	69.2
					Strontium 2 g QD	Oral	828	69.4
STAND Study Kendler et al., 2009	Postmenopausal women ≥ 55 years old with a BMD T-score of ≤ –2.0 and ≥ –4.0 who had been receiving alendronate therapy for ≥ 6 months.	Double-blind	52 weeks	1	Alendronate	Oral	251	68.2
					Denosumab	sc	253	66.9
TROPOS Study Reginster et al., 2008	Women with a femoral neck BMD ≤ 0.60 g/cm^2 (measured with Hologic instruments), corresponding to a BMD T-score less than –2.5 SD according to the centralised normative data.	Double-blind	260 weeks	4	Placebo	Oral	2537	76.8
					Strontium 2 g QD	Oral	2554	76.7

BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; N/A, not available; QD, once daily; Q3M, every 3 months; QOD, every other day; sc, subcutaneous; SD, standard deviation.

Additional studies investigating supplementary comparators only were included in the MTC. The full trial set included in the MTC is presented in section 9.4 (Appendix 4)

Studies investigating oral ibandronate are included in the table because no studies investigating iv ibandronate were identified

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

No RCTs have compared denosumab directly with any of the relevant comparators using fracture efficacy endpoints. Six RCTs have compared denosumab with alendronate using other endpoints (including BMD) as follows:

- Phase 2 RCTs:
  - 20010223/Miller et al. (2008a)
  - 20050179/Amgen data on file (20050179 CSR); Seeman et al. (2009b)
  - 20050172/Amgen data on file (20050172 CSR)
- Phase 3 RCTs:
  - 20050141 (DECIDE)/Brown et al. (2009)
  - 20050234 (STAND)/Kendler et al. (2009)
  - 20060232 (DAPS)/Amgen data on file (20060232 [DAPS] 12-month interim analysis) (phase 3b compliance, persistence and satisfaction study)

The primary clinical data for denosumab described in this submission are taken from registration trial 20030216 (FREEDOM)/Cummings et al. (2009), which compared denosumab with placebo using fracture efficacy endpoints. Additional clinical data from trial 20060289, an ongoing phase 3, open-label extension of trial 20030216 (FREEDOM), will be available once the study has been completed (the design of this study is presented in section 9.7). The six trials listed above, which compare denosumab directly with alendronate, are presented as supporting data. Trial 20050172, which compared denosumab with placebo in Japanese women with PMO using BMD efficacy endpoints, is also presented as supporting data. Long-term follow-up over a period of 6 years collected in study 20050233 (Extension of 20010223) is presented.

Trial 20060237, which compares antibody development in patients receiving the pre-filled syringe formulation of denosumab with a vial formulation, is summarised in section 9.7 (Amgen anticipates launching only the pre-filled syringe formulation in the UK).

Because no head-to-head trials have been performed that compare denosumab directly with any of the comparators using fracture efficacy endpoints, comparative efficacy has been investigated by IC (see section 5.7).

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Trial 20040132 (DEFEND)/Bone et al. (2008) enrolled patients with a BMD T-score between –1.0 SD and –2.5 SD (inclusive). Trial 20040135 (HALT)/Ellis et al. (2008) enrolled women with non-metastatic breast cancer undergoing aromatase inhibitor therapy, with BMD T-scores between –1.0 SD and –2.5 SD (inclusive). These patient groups do not have PMO as defined by the World Health Organization and have been excluded from further discussion of efficacy. Safety data from the trials are included in section 5.9.

Trial 20040135 (HALT) was not considered to be within the scope of this appraisal (see section 1.6). Safety data from the trial are included in section 5.9.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. These details should be presented in a table; the following is a suggested format.

Table B4 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Compliance and Persistence to Anti-Osteoporosis Medications in the United Kingdom using the GPRD	Anti-osteoporotic therapies used in the UK	All women in the GPRD who filled a first prescription for an anti-osteoporosis therapy some time after 1 January 1995, and who were aged ≥ 50 or who had a diagnosis to indicate premature or surgical menopause at an earlier age	• [redacted] • [redacted] • [redacted] • [redacted]	Amgen data on file (Boston Collaborative Group report, 2009)	Compliance and persistence with anti-osteoporotic therapies is pertinent to the effectiveness of the therapies in clinical practice

GPRD, General Practice Research Database; RCT, randomised controlled trial.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

See section 5.3.2 below.

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table B5 presents the design of trial 20030216 (FREEDOM). Brief descriptions of the other RCTs are presented in Table A1; full descriptions are presented in section 9.3 (appendix 3).

Table B5 Design of trial 20030216 (FREEDOM)

Trial design	**20030216 (FREEDOM)**
Location	214 centres: 83 in Western Europe (44.9% of subjects enrolled), 66 in Eastern Europe (34.7%), 48 in North America (7.4%), 10 in Latin America (11.9%) and 7 in Australia and New Zealand (1.2%).
Design	Phase 3, international, multicentre, randomised, double-blind placebo-controlled study.
Duration of study	36 months.
Method of randomisation	Subjects were randomised (1:1) in a double-blinded fashion to receive either denosumab or placebo. Randomisation was stratified by age at entry: 60-64 years, 65-69 years, 70-74 years, and ≥ 75 years.
Method of blinding (care provider, patient and outcome assessor)	• Vials containing denosumab and vials containing placebo had the same appearance. • Treatment (denosumab or placebo) was assigned to subjects using their assigned 7-digit subject identification number by an interactive voice response system; subjects, investigators and all site staff (including radiologists) did not know the identity of the investigational product administered to individual subjects.
No. of intervention(s) and comparator(s)	Denosumab 60 mg (n = 3,902). Placebo (n = 3,906).

Primary outcomes (including scoring methods and timings of assessments)	Subject incidence of new radiographic vertebral fractures: • Lateral spine radiographs were taken annually and assessed by a semiquantitative grading scale at the central imaging centre (Synarc). • A prevalent vertebral fracture was defined as a vertebral body between T4 and L4 with a semiquantitative grade of 1 or more at baseline. • A new radiographic vertebral fracture was defined as an increase of at least 1 grade in a vertebral body between T4 and L4 that was normal at baseline.
Secondary outcomes (including scoring methods and timings of assessments)	• Time to the first non-vertebral fracture and the time to the first hip fracture. • Clinical fractures were confirmed by diagnostic imaging or a radiologist's report.
Duration of follow-up	Follow-up to month 36 (patients participating in extension trial 20060289 will be followed an additional 84 months).
Source: Amgen data on file (20030216 [FREEDOM] clinical study report).	

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B6 presents eligibility criteria in trial 20030216 (FREEDOM). Eligibility criteria for other RCTs are presented in brief in Table A1, and in more detail in section 9.3 (appendix 3).

Table B6 Eligibility criteria in trial 20030216 (FREEDOM)

Inclusion criteria	Exclusion criteria
• Postmenopausal, ambulatory women between 60 and 90 years old • BMD T-score < –2.5 SD at either the lumbar spine or the total hip, or at both locations • Appropriate written informed consent provided before any study-specific procedure	• BMD T-score < –4.0 SD at lumbar spine, total hip or both locations • Oral BP treatment for osteoporosis used for: – ≥ 3 years cumulatively or – 3 months but ≤ 3 years cumulatively and last dose was < 1 year before enrollment • Intravenous BP, fluoride or strontium use for osteoporosis within the last 5 years • PTH, PTH derivatives, teriparatide, anabolic steroids, testosterone, glucocorticosteroids (> 5 mg/day of prednisone equivalent for > 10 days), systemic HRT, SERMs, raloxifene, tibolone, calcitonin or calcitriol use within the last 6 weeks • Evidence of hyper- or hypothyroidism; patients with an abnormal TSH level on thyroid treatment; current hyper- or hypoparathyroidism; current hypocalcemia; vitamin D deficiency; rheumatoid arthritis; Paget's disease; malignancy[a] within the last 5 years; bone disease that would interfere with interpretation of findings; malabsorption syndrome; height, weight or girth that would preclude accurate DXA measurements; advanced scoliosis or extensive lumbar fusion that would preclude vertebral fracture assessment; any severe, or > 2 moderate, vertebral fractures on spinal x-rays; or < 2 lumbar vertebrae (L1-L4) evaluable for DXA • Known sensitivity to mammalian cell-derived drug products

BMD, bone mineral density; BP, bisphosphonate; DXA, dual-energy x-ray absorptiometry; HRT, hormone-replacement therapy; PTH, parathyroid hormone; SD, standard deviation; SERM, selective estrogen receptor modulator; TSH, thyroid-stimulating hormone.

[a] Excluding basal cell carcinoma, cervical or breast ductal carcinoma in situ.

Source: Amgen data on file (20030216 [FREEDOM] clinical study report). Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra, Australia: Pharmaceutical Benefits Advisory Committee.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B7 presents baseline characteristics for patients randomised in trial 20030216 (FREEDOM). Most subjects (92.7%) were white. Mean (SD) age was 72.3 (5.2) years. Most subjects (94.7%) were at least 65 years of age, and 31.6% were at least 75 years of age. Mean (SD) weight and BMI were 63.80 (10.41) kg and 25.99 (4.15) kg/m^2, respectively. Baseline subject demographics were balanced across the treatment groups. Fracture risk (assessed by country-specific FRAX® algorithms [Kanis et al., 2008a] or by a combination of age, baseline BMD T-score and prevalent vertebral fracture at baseline) was balanced between the treatment groups.

Baseline characteristics for patients randomised the other RCTs are presented in section 9.3 (appendix 3).

Table B7 Baseline characteristics for patients randomised in trial 20030216 (FREEDOM)

Baseline characteristic	Denosumab 60 mg Q6M (n = 3,902)	Placebo (n = 3,906)
Age, years		
Mean (SD)	72.3 (5.2)	72.3 (5.2)
Group, n (%)		
< 70 years	1,030 (26.4)	1,028 (26.3)
70-74 years	1,637 (42.0)	1,642 (42.0)
≥ 75 years	1,235 (31.7)	1,236 (31.6)
Body mass index, kg/m^{2a}		
Mean (SD)	26.0 (4.1)	26.0 (4.2)

Region, n (%)[b]		
Western Europe	1,761 (44.8)	1,773 (45.1)
Eastern Europe	1,374 (34.9)	1,355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
BMD T-score, mean (SD)		
Lumbar spine	−2.82 (0.70)	−2.84 (0.69)
Total hip	−1.89 (0.81)	−1.91 (0.81)
Femoral neck	−2.15 (0.72)	−2.17 (0.71)
Prevalent vertebral fracture, n (%)		
Yes	929 (23.8)	915 (23.4)
No	2,864 (73.4)	2,854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)
Serum 25-hydroxyvitamin D, ng/mL[c]		
Mean (SD)	23.1 (11.7)	22.9 (11.3)
10-year fracture risk (FRAX® algorithms), mean percentage ± SD[d]		
10-year osteoporotic fracture risk with BMD	18.54 ± 10.57	18.66 ± 10.65
10-year hip fracture risk with BMD	7.24 ± 7.88	7.19 ± 7.72
Fracture risk group, n (%)[e]		
High risk[e]	1,761 (45.1)	1,752 (44.9)
Increased risk[e]	2,080 (53.3)	2,086 (53.4)
Missing	61 (1.6)	68 (1.7)

BMD, bone mineral density; Q6M, every 6 months; SD, standard deviation.

[a] The body mass index is the weight in kilograms divided by the square of the height in meters.

[b] Percentages for region are based on all subjects enrolled in the study: 3,933 in the denosumab group and 3,935 in the placebo group.

[c] Subjects with outlier values of more than 200 ng/mL were excluded from this analysis.

[d] 10-year probabilities of major osteoporotic fractures and of hip fractures based on country-specific FRAX® algorithms (Kanis et al., 2008a) using selected baseline characteristics, including country and ethnicity, age, sex (all females), body mass index, fracture history, prevalent vertebral fracture, parental history of hip fracture, current smoker, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, daily alcohol use more than 2 drinks and baseline femoral neck BMD T-score.

[e] Subjects were considered at high fracture risk if they met at least 2 of the following 3 criteria: age > 70 years; baseline BMD T-score ≤ –3.0 SD at lumbar spine, total hip or femoral neck; and prevalent vertebral fracture at baseline.

Source: Cummings et al., 2009. Adapted from Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.2). (2007). Pharmaceutical Benefits Advisory Committee, Canberra.

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of

health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary efficacy endpoint in trial 20030216 (FREEDOM) was subject incidence of new radiographic vertebral fractures during the total 36-month treatment period.

The protocol-specified secondary efficacy endpoints included the following:

- Time to first non-vertebral fracture, assessed at the time of the 36-month analysis
- Time to first hip fracture, assessed at the time of the 36-month analysis

Tertiary efficacy endpoints include the following:

- The number of subjects with new vertebral fractures during 6, 12 and 24 months of treatment
- The number of subjects with incident (new or worsening) vertebral fractures during 12, 24 and 36 months of treatment
- The number of subjects with multiple incident vertebral fractures during 12, 24 and 36 months of treatment
- The time to first clinical fracture (vertebral or non-vertebral)
- Percentage change from baseline in lumbar spine BMD at 36 months
- Percentage change from baseline in total hip, femoral neck and trochanter BMD at 12, 24 and 36 months
- Percentage change from baseline in lumbar spine, total hip, femoral neck and trochanter BMD in a subset of subjects at 1, 6, 12, 24 and 36 months
- Percentage change from baseline in distal 1/3 radius and total body BMD in a subset of subjects at 12, 24 and 36 months
- Percentage change from baseline in volumetric BMD of trabecular bone region of lumbar spine and trabecular and cortical bone regions of total hip, femoral neck

and trochanter assessed by quantitative computerised tomography (QCT) in a subset of subjects at 12, 24 and 36 months

- Percentage change from baseline in volumetric BMD of trabecular and cortical bone regions of the distal radius assessed by QCT in a subset of subjects at 1, 6, 12, 24, and 36 months
- Percentage change from baseline in bone markers (serum type 1 C-telopeptide [CTX-1], procollagen type 1 N-telopeptide [P1NP] and BSAP), intact PTH, tartrate-resistant acid phosphatase 5b (TRAP 5b), RANKL and OPG in a subset of subjects at 6, 12, 24 and 36 months (RANKL was removed from the analysis due to all results falling below the lower limit of quantification)
- Bone histomorphometric parameters in a subset of subjects at 24 and 36 months
- Bone histology (qualitative assessment of bone) in a subset of subjects at 24 and 36 months
- Three-dimensional structural parameters based on micro-CT of transiliac bone biopsy samples in a subset of subjects at 24 and 36 months
- Changes in hip structural analysis based on hip dual-energy x-ray absorptiometry (DXA) in a subset of subjects at 12, 24 and 36 months
- The number of subjects with incident breast cancer during 36 months of treatment (endpoint later removed from the analysis because no known underlying biochemical mechanism by which denosumab would affect breast cancer incidence has been demonstrated)
- Change from baseline in patient-reported outcomes (PROs) (Osteoporosis Assessment Questionnaire–Short Version [OPAQ-SV] physical function, emotional status and back pain scores, and EuroQol-5D [EQ-5D] questionnaire) at 6, 12, 18, 24, 30 and 36 months
- Change from baseline in Disability/Back Pain Questionnaire responses at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 months

Other safety endpoints included the following:

- Adverse event incidence by system organ class and preferred term
- Changes in safety laboratory analytes (serum chemistry, hematology) at each visit
- Subject incidence of anti-denosumab antibodies (yes/no)

- Change from baseline in total aortic calcification severity score at 12, 24 and 36 months in a subset of subjects
- Time to first cardiovascular endpoint (including definite or probable coronary heart disease event, congestive heart failure, stroke/transient ischaemic attack [TIA], other vascular event and any vascular event) assessed at the time of the 36-month analysis
- Incidence of non-vertebral fractures with delayed healing
- Incidence of radiographic delayed healing in distal radius fractures between treatment groups

The primary endpoints for the other RCTs are presented in Table A1; other endpoints are presented in section 9.3 (appendix 3).

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Trial 20030216 (FREEDOM) was designed to test the clinical hypothesis that denosumab, compared with control (placebo subcutaneously [sc] every 6 months), is effective in reducing the subject incidence of new radiographic vertebral fractures and the risks of non-vertebral fracture and hip fracture in postmenopausal women with osteoporosis. To test this hypothesis, the subject incidence of new radiographic vertebral fractures was compared between treatment groups using a logistical regression model adjusting for age group strata. Time to first non-vertebral fracture at other anatomical sites, including hip, was compared between treatment groups using a stratified Cox proportional hazards model with treatment group as the independent variable and age group strata as the stratified variable. The Kaplan-

Meier estimates were used to summarise the cumulative incidence of fractures at various fixed time points during the follow-up.

A fixed-sequence testing procedure was used among the three primary and secondary endpoints in the order mentioned above for multiplicity adjustment to maintain the overall significance level at 0.05.

The 36-month analysis was conducted after all subjects had the opportunity to complete the 36-month assessment.

The sample size in trial 20030216 (FREEDOM) had a power of more than 99% to detect a 45% reduction in the incidence of new radiographic vertebral fractures and to detect a 40% reduction in the risk of any non-vertebral fracture, and a power of 91% to detect a 40% reduction in the risk of hip fracture. These estimates were based on the assumption that the annual fracture rate in the placebo group over a 36-month period would be 4.0% for vertebral fractures, 3.3% for non-vertebral fractures and 1.0% for hip fractures.

Additional assumptions used in the sample size estimation to account for patients who withdrew were as follows:

- The loss-to-follow-up vertebral radiograph rate was assumed to be 5% per year.
- The rate of censoring used for non-vertebral fracture assessment, including hip, was 4% per year.
- Subjects who were lost to follow-up or withdrew before having a fracture event had their last known fracture status carried forward (Amgen data on file, 20030216 [FREEDOM] clinical study report [CSR]).

Section 9.3 (appendix 3) summarises statistical analysis and definition of study groups for the other RCTs.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned.

The following subgroup analyses were undertaken in trial 20030216 (FREEDOM). All analyses were preplanned unless stated otherwise. The primary efficacy endpoint

and the secondary efficacy endpoint of time to first non-vertebral fracture also were analysed within each of the following subgroups:

- Age (years) (≥ 65; ≥ 75; < 75; and age strata [60-64, 65-69, 70-74 and ≥ 75])
- BMI (kg/m^2) (< 25, 25 to < 30, ≥ 30, post hoc)
- Race (Caucasian and non-Caucasian)
- Geographic region (Western Europe, Eastern Europe, North America and Latin America)
- Baseline lumbar spine BMD T-score (tertiles; for new vertebral fracture only)
- Baseline total hip BMD T-score (tertiles; for time to first non-vertebral fracture only)
- Baseline femoral neck BMD T-score (≤ –2.5 SD, > –2.5 SD, post hoc)
- Baseline serum CTX-1 (tertiles)
- Prevalent vertebral fracture at baseline (yes/no)
- History of non-vertebral fracture at age ≥ 55 years (yes/no)
- Fracture risk based on age, BMD, and prevalent vertebral fracture at baseline (high risk and increased risk). A subject was considered to be at high risk of fracture if she met at least two of the following three criteria: age > 70 years; baseline BMD T-score ≤ –3.0 SD at lumbar spine, total hip or femoral neck; and prevalent vertebral fracture at baseline. A subject who did not meet at least two of those criteria was considered to be at increased risk of fracture.
- Serum 25(OH) vitamin D level (ng/mL) (≤ 20, > 20 ng/mL; for new vertebral fracture only)
- Calculated creatinine clearance (< 60 mL/min, ≤ 60mL/min, post hoc, primary endpoint, new vertebral fracture only)
- Prior use of osteoporotic medication (yes/no)

The secondary efficacy endpoint of time to first hip fracture was analysed by subgroups of fracture risk based on age, BMD and prevalent vertebral fracture at baseline.

The percentage changes from baseline in lumbar spine BMD and total hip BMD at month 36 were analysed within the following subgroups:

- Age (years) (≥ 65; ≥ 75; < 75; and age strata [60-64, 65-69, 70-74, and ≥ 75])

- Race (Caucasian and non-Caucasian)
- Geographic region (Western Europe, Eastern Europe, North America and Latin America)
- Baseline body weight (kg) (< 55, 55 to < 65, 65 to < 75 and ≥ 75)
- Baseline BMI (kg/m^2) (< 22, 22 to < 24, 24 to < 26, 26 to < 30 and ≥ 30)
- Baseline lumbar spine BMD T-score (tertiles; for lumbar spine BMD analysis only)
- Baseline total hip BMD T-score (tertiles; for total hip BMD analysis only)
- Baseline serum CTX-1 (tertiles)

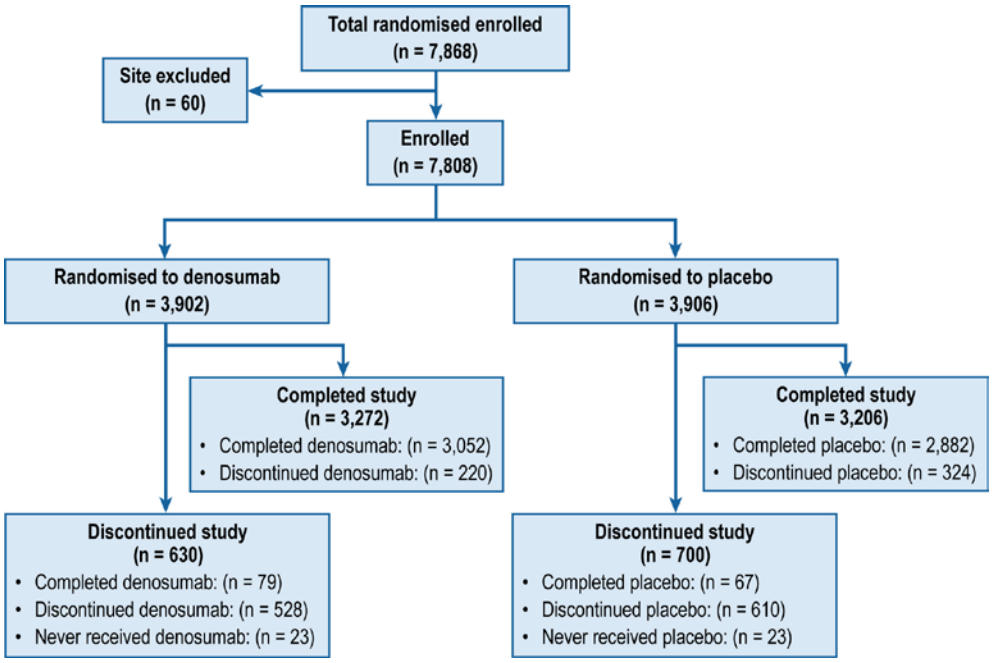
These subgroups, except for age strata, were re-examined for appropriateness and could be recategorised (due to small sample size, e.g., if < 10% of subjects are within a subgroup) before unblinding. The analyses of these subgroups were exploratory in nature. Section 9.3 (appendix 3) summarises subgroup analyses of the RCTs measuring non-fracture endpoints.

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure B3 presents a CONSORT flowchart for 20030216 (FREEDOM) that provides details of the numbers of patients who were eligible to enter the trial, underwent randomisation and were allocated to each treatment. Section 9.3 (appendix 3) presents CONSORT flowcharts for the other RCTs.

Figure B3 CONSORT flow chart for trial 20030216 (FREEDOM)



Note: BMD was measured at baseline and then annually at the hip and after 36 months at the lumbar spine. BMD of both sites was measured at baseline and at 1, 6, 12, 24, and 36 months in 441 subjects. Concentrations of two markers of bone turnover were measured in 160 subjects from fasting serum samples collected before the injection on day 1, at 1 month after the baseline injection, and before injections at 6, 12, 24, and 36 months.
Source: Amgen data on file (20030216 [FREEDOM] clinical study report).

5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?

- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

Study ID: Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM; 20030216)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Subjects were randomised in a blinded fashion using 1:1 allocation by a third party. The randomisation schedule was prepared by the sponsor before trial initiation and was based on randomly permuted blocks. Randomisation was also stratified according to 5-year age groups.	Yes
Was the concealment of treatment allocation adequate?	The treatment allocation was by interactive voice response system (IVRS) for all the centres.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics and fracture risk were reported to be similar in both groups. The T-score for lumbar spine, total hip and femoral neck and percentage of women who had vertebral fracture at baseline were similar in both groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Subjects, investigators and site personnel (care providers and outcome assessors) were blinded.	Yes
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Dropouts in the groups are reported to be similar.	No imbalances

Study ID: Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM; 20030216)		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Intention to treat analyses was performed as sensitivity analysis for primary efficacy endpoints. Subjects who were lost to follow-up, or withdrew before, or with missing radiographs having a fracture had their last known fracture status carried forward. The primary analysis for the vertebral fracture endpoint included all randomised subjects who had a baseline (or first postbaseline evaluation showing no fracture) and ≥ 1 subsequent evaluation of vertebral fracture at or before the time point under consideration. The primary analysis for the non-vertebral and hip fracture endpoints included all randomised subjects. Subjects were analysed according to their original treatment assignment, regardless of treatment received.	Yes

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Quality assessments for the other denosumab RCTs are presented in section 9.3 (appendix 3).

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Efficacy Results from trial 20030216 (FREEDOM)

The efficacy results for the fracture, BMD, bone marker and patient-reported outcome (PRO) study endpoints are presented below.

Fracture endpoint results

Table B8 presents the 36-month analysis results of the fracture endpoints evaluated in trial 20030216 (FREEDOM).

Table B8 Fracture endpoint results from trial 20030216 (FREEDOM): effect of denosumab on the risk of fracture at 36 months[a]

Outcome	Denosumab no. (%)	Placebo no. (%)	Difference in rates (95% CI)	Relative risk or hazard ratio (95% CI)[b]	*P* value
Primary endpoint					
New radiographic vertebral fracture	86 (2.3)	264 (7.2)	4.8 (3.9 to 5.8)	0.32 (0.26 to 0.41)	< 0.001
Secondary endpoints					
Non-vertebral fracture[c]	238 (6.5)	293 (8.0)	1.5 (0.3 to 2.7)	0.80 (0.67 to 0.95)	0.01
Hip fracture	26 (0.7)	43 (1.2)	0.3 (−0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04
Other fracture endpoints					
New clinical vertebral fracture	29 (0.8)	92 (2.6)	1.7 (1.1 to 2.3)	0.31 (0.20 to 0.47)	< 0.001
Multiple (≥ 2) new vertebral fractures	23 (0.6)	59 (1.6)	1.0 (0.5 to 1.5)	0.39 (0.24 to 0.63)	< 0.001

CI, confidence interval.

[a] The percentages of new and multiple new radiographic vertebral fractures are calculated for 3,702 subjects in the denosumab group and 3,691 in the placebo group who underwent spinal radiography at baseline and during at least 1 visit after baseline. The percentages of non-vertebral, hip and new clinical vertebral fractures are cumulative Kaplan-Meier estimates for 3,902 subjects in the denosumab group and 3,906 in the placebo group.

[b] Relative risks are based on the Chochran-Mantel-Haenszel method with adjustment for the age-stratification variable for vertebral fractures. Hazard ratios are based on the Cox proportional hazards model with adjustment for the age-stratification variable for non-vertebral, hip and clinical vertebral fractures.

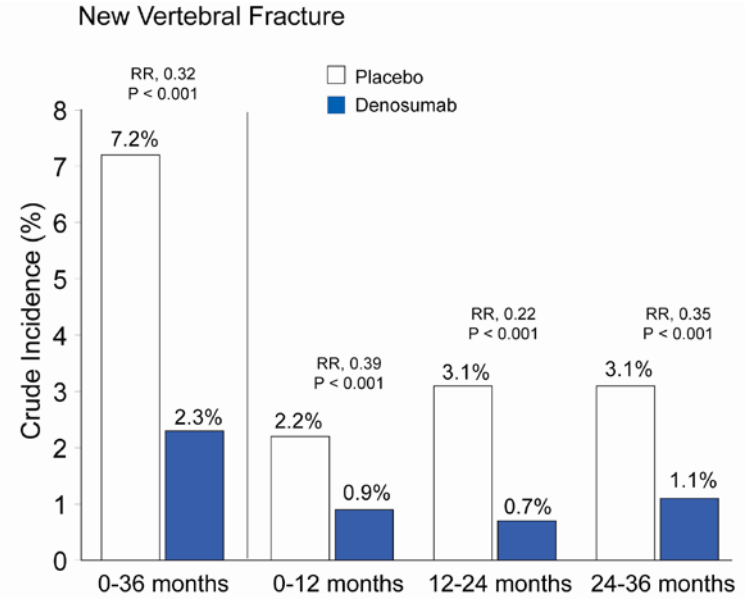
[c] A total of 28 subjects (13 in the denosumab group and 15 in the placebo group) had non-vertebral fractures associated with severe trauma and were not included in the analysis.

Note: The numerical differences in the rates for the denosumab and placebo are not equal to the presented differences in column 3 for new radiographic vertebral fractures and hip fractures because they are based on the Cox proportional hazards model stratified by age stratification variable.

Source: Cummings et al., 2009.

The calculations of percentages of new and multiple new radiographic vertebral fractures were based on the number of subjects who underwent spinal radiography at baseline and during at least one visit after baseline. The 36-month incidence of new radiographic vertebral fracture was 2.3% (86 of 3,702 subjects) in the denosumab group and 7.2% (264 of 3,691 subjects) in the placebo group, representing a 68% reduction in RR ($P < 0.001$) (Cummings et al., 2009). The reduction in risk was similar during each year of the trial (Figure B4).

Figure B4 Incidence of new radiographic vertebral fractures in trial 20030216 (FREEDOM)

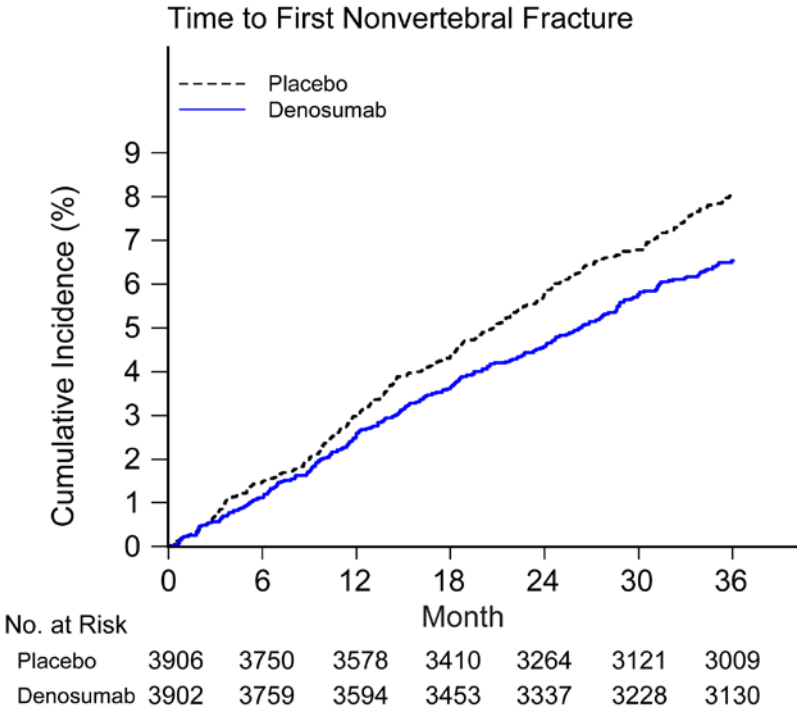


RR, relative risk.
Source: Cummings et al., 2009.

There were similar reductions in clinically diagnosed vertebral fractures (69%) and multiple new radiographic vertebral fractures (61%; $P < 0.001$ for both comparisons) (Figure B4). The calculations of cumulative incidences of non-vertebral, hip and new radiographic clinical vertebral fractures were based on Kaplan-Meier estimates of a 36-month cumulative incidence in 3,902 subjects in the denosumab group and 3,906 in the placebo group. Denosumab reduced the risk of non-vertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, as compared with 8.0% in the placebo group (HR = 0.80; 95% confidence interval [CI], 0.67 to 0.95; $P = 0.01$)—a 20% relative reduction (Figure B5).

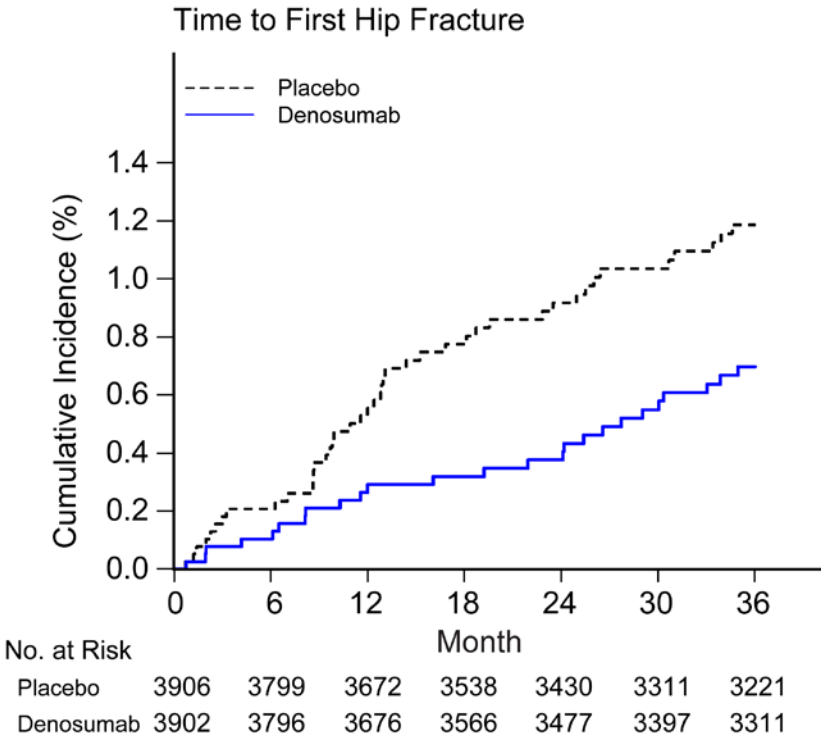
Denosumab also decreased the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (HR = 0.60; 95% CI, 0.37 to 0.97; $P = 0.04$)—a 40% relative reduction (Figure B6).

Figure B5 Cumulative incidence of time to first non-vertebral fracture in trial 20030216 (FREEDOM)



Source: Cummings et al., 2009.

Figure B6 Cumulative incidence of time to first hip fracture in trial 20030216 (FREEDOM)



[redacted]

Source: Cummings et al., 2009.

The effect of fracture risk on the efficacy of denosumab was assessed using covariate analyses. Ten-year fracture risks for major osteoporotic fracture and hip fracture were estimated using the FRAX® algorithms. Denosumab reduced the incidence of new radiographic vertebral, non-vertebral and hip fractures across subjects with a wide range of baseline 10-year fracture risk. No significant interaction between treatment and 10-year fracture risk was detected for any of the fracture endpoints. After controlling for the 10-year probability of major osteoporotic fracture, the treatment effect of denosumab remained significant for the subject incidence of new radiographic vertebral fracture (logistic regression model; odds ratio: 0.31 [95% CI, 0.24 to 0.39]; $P < 0.0001$) and for time to first non-vertebral fracture (Cox proportional hazards model; HR = 0.80 [0.67 to 0.95]; $P = 0.0108$).

Furthermore, after controlling for 10-year probability of hip fracture, the treatment effect of denosumab remained significant for time to first hip fracture (Cox proportional hazards model; HR = 0.60 [0.37 to 0.97]; $P = 0.0355$).

PRO endpoints

- Change from baseline in PRO (OPAQ-SV physical function, emotional status and back pain scores and EQ-5D questionnaire) at 6, 12, 18, 24, 30 and 36 months
- Change from baseline in Disability/Back Pain Questionnaire responses at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 months

PRO endpoint results

The results from examining the relationship between the presence of prevalent vertebral fractures and health-related quality of life (HRQL), and the relationships between number, location and severity of prevalent vertebral fractures and HRQL in women with at least one prevalent vertebral fracture in trial 20030216 (FREEDOM) are as follows:

- The presence of one vertebral fracture versus no fracture was significantly associated with worse physical function (coefficient = –1.3, standard error [SE] = 0.5), emotional status (coefficient = –2.0, SE = 0.6) and back pain (coefficient = –3.0, SE = 0.8), adjusting for covariates.

- The presence of at least two fractures versus no fracture was significantly associated with worse emotional status ($P < 0.05$) and back pain ($P < 0.05$) but not physical function.
- In women with at least one prevalent vertebral fracture (n = 1,844), no differences were found in OPAQ-SV dimensions for those with at least two (mean [SD], 2.5 [1.1]) versus one fracture (Table B9).
- Moderate or severe fractures were associated with lower scores in all OPAQ-SV dimensions ($P < 0.05$) compared with mild fractures (Table B9).
- Prevalent lumbar (L2-L4) fractures were associated with significantly lower scores in all OPAQ-SV dimensions ($P < 0.05$) compared with thoracic (T4-T9) fractures (Table B9).
- Thoracolumbar fractures (T10-L1) were associated with worse physical function ($P < 0.05$) compared with thoracic fractures (Table B9).

Table B9 Relationships between the number, severity or location of prevalent vertebral fractures and baseline OPAQ-SV scores in women with at least one prevalent vertebral fracture: trial 20030216 (FREEDOM)

	Physical function n = 1,826 $\hat{\beta}$ **(SE)**	**Emotional status n = 1,826** $\hat{\beta}$ **(SE)**	**Back pain n = 1,461** $\hat{\beta}$ **(SE)**
Models examining number of prevalent vertebral fractures[a]			
Intercept	146.4 (6.5)*	128.3 (7.3)*	93.8 (9.6)*
≥ 2 vs. 1	0.4 (0.9)	–0.5 (1.0)	–1.2 (1.3)
Models examining severity of prevalent vertebral fractures[a]			
Intercept	147.0 (6.5)*	128.9 (7.3)*	94.6 (9.6)*
Moderate or severe vs mild	–2.0 (0.8)*	–2.2 (0.9)*	–2.6 (1.2)*
Models examining location of prevalent vertebral fractures[a, b]			
Intercept	148.0 (7.1)*	128.9 (8.1)*	96.0 (10.7)*
Lumbar (L2-L4) vs thoracic (T4-T9)	–4.9 (1.4)*	–3.4 (1.6)*	–5.8 (2.0)*
Thoracolumbar (T10-L1) vs thoracic (T4-T9)	–2.2 (1.0)*	–1.5 (1.1)	–2.8 (1.5)

*$P < 0.05$.
SE, standard error.
n = Number of subjects with observed data included in the analysis of covariance model.
[a] All regression models also included age, race, region and body mass index as covariates.
[b] Women with prevalent vertebral fractures at multiple locations (thoracic, thoracolumbar or lumbar) were excluded.
Source: Silverman et al., 2009.

The effect of denosumab on HRQL and the association of all incident clinical fractures, regardless of treatment group, with HRQL in the women who participated

in trial 2003216 (FREEDOM) were assessed using the OPAQ-SV and the EQ-5D questionnaire at baseline and every 6 months for 3 years. The OPAQ-SV has 34 disease-specific questions in the following three HRQL dimensions: physical function, emotional status and back pain. EQ-5D is a generic measure with five questions and a visual analogue scale (VAS). For both measures, higher scores represent better health status. The results from this PRO assessment of HRQL from trial 20030216 (FREEDOM) are as follows:

- Among patients who completed the study, completion rates for HRQL measures at year 3 were 83% and 82% for the OPAQ-SV and the EQ-5D, respectively.
- There were no significant differences between treatment groups in HRQL measures when comparing baseline with year 3.
- Compared with women without any fractures, women with incident clinical fractures, regardless of treatment group, reported declines in two OPAQ-SV dimensions (physical function and emotional status) and in EQ-5D health index and VAS scores (all $P < 0.001$; Table B10) at year 3.
- Changes from baseline to year 3 for each OPAQ-SV dimension and both EQ-5D scores were positively correlated (all $P < 0.0001$; Table B11).

Table B10 OPAQ-SV and EQ-5D changes from baseline to year 3: trial 20030216 (FREEDOM)[a]

OPAQ-SV dimensions/ EQ-5D scores	With incident clinical fracture[b] (n = 670)		Without any incident fracture (n = 6,821)	
	n	Mean (95% CI)	n	Mean (95% CI)
OPAQ-SV: Physical function	567	–4.1 (–5.7 to –2.6)*	5,585	–0.5 (–0.9 to –0.1)
OPAQ-SV: Emotional status	566	–5.0 (–6.6 to –3.5)*	5,588	–0.8 (–1.2 to –0.4)
OPAQ-SV: Back pain	567	1.6 (–0.4 to 3.7)*	5,597	4.6 (4.0 to 5.2)
EQ-5D: Health index score	562	–0.02 (–0.04 to 0.00)**	5,535	0.01 (0.01 to 0.02)
EQ-5D: VAS score	564	–2.2 (–3.8 to –0.6)**	5,576	–0.1 (–0.5 to 0.4)

*$P \leq 0.0001$, **$P < 0.001$ compared with the group without any incident fracture; based on an analysis of covariance model adjusting for age and the respective baseline score.

CI, confidence interval ; EQ-5D, EuroQol-5D; OPAQ-SV, Osteoporosis Assessment Questionnaire–Short Version; VAS, visual analogue scale.

[a] Subjects with only morphometric vertebral fractures were not included in the analysis.

[b] Includes all subjects with clinical fractures regardless of trauma severity (excluding skull, facial, finger and toe fractures).

Source: Siris et al., 2009b.

Table B11 Spearman correlations between OPAQ-SV and EQ-5D changes from baseline to year 3 for women with incident clinical fractures: trial 20030216 (FREEDOM)[a]

	EQ-5D change from baseline			
	Health Index score		VAS score	
	n	r	n	r
OPAQ-SV change from baseline				
Physical function	562	0.47	563	0.33
Emotional status	561	0.46	562	0.37
Back pain	562	0.42	563	0.36

All $P < 0.0001$.

EQ-5D, EuroQol-5D; OPAQ-SV, Osteoporosis Assessment Questionnaire–Short Version; VAS, visual analogue scale.

[a] Subjects with only morphometric vertebral fractures were not included in the analysis. Analysis includes all subjects with clinical fractures regardless of trauma severity (excluding skull, facial, finger and toe fractures).

Source: Siris et al., 2009b.

Results of subgroups analyses

The effect of denosumab treatment on new radiographic vertebral fractures was not influenced by any of the predefined subgroups analysed ($P > 0.05$ for all potential interactions). Interaction terms for the effect on non-vertebral fracture were less than 0.05 for BMI, femoral neck BMD T-score and prevalent vertebral fracture, and greater than 0.05 for age (< 75 vs. ≥ 75 years; $P = 0.64$) and prior non-vertebral fracture ($P = 0.61$). No adjustments were made for multiplicity.

Table B12 Effect of denosumab treatment on new radiographic vertebral fractures by subgroup: trial 20030216 (FREEDOM)

Subgroup	RR (95% CI)	Interaction *P* value (Qualitative Interaction)
Age		
< 75 years	0.30 (0.22 to 0.41)	0.4822
≥ 75 years	0.36 (0.25 to 0.53)	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
Region		
Western EU, Australia, New Zealand	0.23 (0.16 to 0.34)	0.0986
Eastern EU	0.40 (0.28 to 0.59)	
Latin America	0.51 (0.26 to 1.01)	
North America	0.41 (0.16 to 1.04)	
Race		
Caucasian	0.32 (0.25 to 0.41)	0.5166
Non-Caucasian	0.44 (0.17 to 1.14)	
BMI (post hoc)		

Subgroup	RR (95% CI)	Interaction *P* value (Qualitative Interaction)
< 25 kg/m^2	0.28 (0.19 to 0.41)	0.2909
25 kg/m^2 to 30 kg/m^2	0.40 (0.28 to 0.57)	
> 30 kg/m^2	0.26 (0.13 to 0.49)	
Calculated creatinine clearance (post hoc)		
< 60 mL/min	0.41 (0.28 to 0.58)	0.1315
≥ 60 mL/min	0.28 (0.20 to 0.38)	
Prior use of osteoporosis medications		
Yes	0.31 (0.21 to 0.48)	0.8209
No	0.33 (0.25 to 0.44)	
Femoral neck BMD T-score (post hoc)		
≤ –2.5 SD	0.31 (0.22 to 0.44)	0.6398
> 2.5 SD	0.34 (0.24 to 0.47)	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Prevalent vertebral fracture		
Yes	0.34 (0.24 to 0.48)	0.9248
No	0.31 (0.22 to 0.44)	
Prior non-vertebral fracture at age ≥ 55 years		
Yes	0.38 (0.26 to 0.54)	0.3545
No	0.29 (0.21 to 0.40)	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CTX-1, serum type 1 C-telopeptide; EU, European Union; RR, relative risk; SD, standard deviation.

[redacted]

Subgroup analyses presented in the clinical study report or published reports are presented.

Source: Cummings et al., 2009 ASBMR poster; Amgen data on file (20030216 [FREEDOM] clinical study report.

Table B13 Effect of denosumab treatment on non-vertebral fractures by risk factor: trial 20030216 (FREEDOM)

Subgroup	Hazard Ratio (95% CI)	Interaction *P* value (Qualitative Interaction)
Age		
< 75 years	0.78 (0.63 to 0.96)	0.6421
≥ 75 years	0.84 (0.63 to 1.12)	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Prior non-vertebral fracture at age ≥ 55 years		
Yes	0.84 (0.65 to 1.09)	0.6052
No	0.77 (0.62 to 0.97)	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CTX-1, serum type 1 C-telopeptide; EU, European Union; SD, standard deviation.

Subgroup	Hazard Ratio (95% CI)	Interaction *P* value (Qualitative Interaction)
[redacted]		

Subgroup analyses presented in the clinical study report or published reports are presented.

Source: Cummings et al., 2009 ASBMR poster; Amgen data on file (20030216 [FREEDOM] clinical study report).

Table B14 Effect of denosumab treatment on hip fractures by risk factor: trial 20030216 (FREEDOM)

Subgroup	Hazard Ratio (95% CI)	Interaction *P* value (Qualitative Interaction)
Age		
< 75 years	0.94 (0.47 to 1.85)	0.0714
≥ 75 years	0.38 (0.18 to 0.78)	
Age strata (post hoc)		
60-64 years	0.98 (0.06 to 15.68)	0.322
65-69 years	1.24 (0.33 to 4.63)	
70-74 years	0.83 (0.36 to 1.92)	
≥ 75 years	0.38 (0.18 to 0.79)	
Femoral neck BMD T-score (post hoc)		
≤ –2.5 SD	0.53 (0.30 to 0.92)	0.5074
> 2.5 SD	0.83 (0.25 to 2.71)	
Fracture risk based on age, BMD and prevalent vertebral fracture		
High risk[a]	0.52 (0.29 to 0.91)	0.6601
Increased risk[a]	0.67 (0.24 to 1.89)	
Age (≥ 75) and baseline femoral neck BMD T-score (≤ –2.5 SD) (post hoc)		
Yes	0.40 (0.18 to 0.86)	0.1954
No	0.78 (0.40 to 1.53)	

BMD, bone mineral density; CI, confidence interval; SD, standard deviation.

[a] High risk is defined as meeting ≥ 2 of the 3 following criteria: (1) age > 70 years, (2) baseline BMD T-score ≤ –3.0 SD at lumbar spine, total hip or femoral neck and (3) prevalent vertebral fracture at baseline. Increased risk is defined as meeting < 2 of the 3 criteria described above. All other patients for whom data were available were categorised as increased risk.

[b] High risk defined as having ≥ 2 prevalent vertebral fractures or having prevalent vertebral fractures with moderate or severe severity, or meeting both criteria. Increased risk defined as not meeting the criteria described above.

Subgroup analyses presented in the clinical study report or published reports are presented.

Source: Cummings et al., 2009 ASBMR poster; Amgen data on file (20030216 [FREEDOM] clinical study report).

Efficacy results from other RCTs

The efficacy results for the primary endpoints of all other relevant denosumab RCTs are summarised in Table B15, The results for other endpoints are presented in section 9.6 (appendix 6).

Outcomes in the long term and after treatment discontinuation

The long-term efficacy of denosumab and the effects of discontinuing and restarting denosumab treatment were investigated in postmenopausal women with low bone mass in the phase 2 trial 20010223/ Miller et al., 2008a and its extension trial 20050233/Miller et al., 2009. The design of this trial is summarised in Table A1 and presented in detail in section 9.3 (appendix 3). In trial 20010223/Miller et al., 2008a, postmenopausal women with a lumbar spine BMD T-score of −1.8 SD to −4.0 SD or proximal femur BMD T-score of −1.8 SD to −3.5 SD were randomised to denosumab every 3 months (6 mg, 14 mg or 30 mg) or every 6 months (14 mg, 60 mg, 100 mg or 210 mg); placebo; or open-label oral alendronate weekly. After 24 months, patients receiving denosumab were re-allocated to receive treatment at 60 mg every 6 months for an additional 24 months, to discontinue therapy or to discontinue treatment for 12 months then re-initiate denosumab (60 mg every 6 months) for 12 months. The placebo cohort was maintained. Patients treated with alendronate discontinued alendronate and were followed. Changes in BMD and bone turnover markers (BTMs), as well as safety outcomes, were evaluated.

Overall, 262 of 412 (64%) patients completed 48 months of study. Continuous, long-term denosumab treatment increased BMD at the lumbar spine (9.4% to 11.8%) and total hip (4.0% to 6.1%). BTMs were consistently suppressed over 48 months. Discontinuation of denosumab was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within the first 12 months of treatment discontinuation. Re-treatment with denosumab increased lumbar spine BMD by 9.0% from original baseline values. Levels of BTM increased upon discontinuation and decreased with re-treatment. Adverse event rates were similar among treatment groups.

Table B15 Summary of primary endpoint results from other denosumab RCTs

Trial	Primary Endpoint	Mean percentage change from baseline	Mean percentage difference	*P* value
20050141 (DECIDE) Phase 3	Percentage change in total hip BMD from baseline to 12 months	Mean percentage change Denosumab (n = 579): 3.5 Alendronate (n = 572): 2.6	Mean percentage difference from alendronate (95% CI) 1.0 (0.7 to 1.2) (excluded the pre-specified non-inferiority margin of –1.22)	*P* < 0.0001 (in favour of denosumab)
20050234 (STAND) Phase 3	Percentage change in total hip BMD from baseline to 12 months	Mean percentage change Denosumab (n = 241): 1.90 Alendronate (n = 233): 1.05	Mean percentage difference from alendronate (95% CI) 0.85 (0.44 to 1.25) (excluded the pre-specified margin of –0.35)	*P* < 0.0001 (in favour of denosumab)
20060232 (DAPS) Phase 3b	[redacted]	[redacted]	[redacted]	[redacted]
20050179 Phase 2	[redacted]	[redacted]	[redacted]	[redacted]
20010223[b] Phase 2	[redacted]	[redacted]	[redacted]	[redacted]
20050172[b] Phase 2	[redacted]	[redacted]	[redacted]	[redacted]

Note: The interventions investigated, patient population studied, primary outcome measure and duration of follow-up are summarised in Table A1. Detailed design information are presented in section 9.3 (appendix 3) and further endpoint results are presented in section 9.6 (appendix 6).

[redacted]

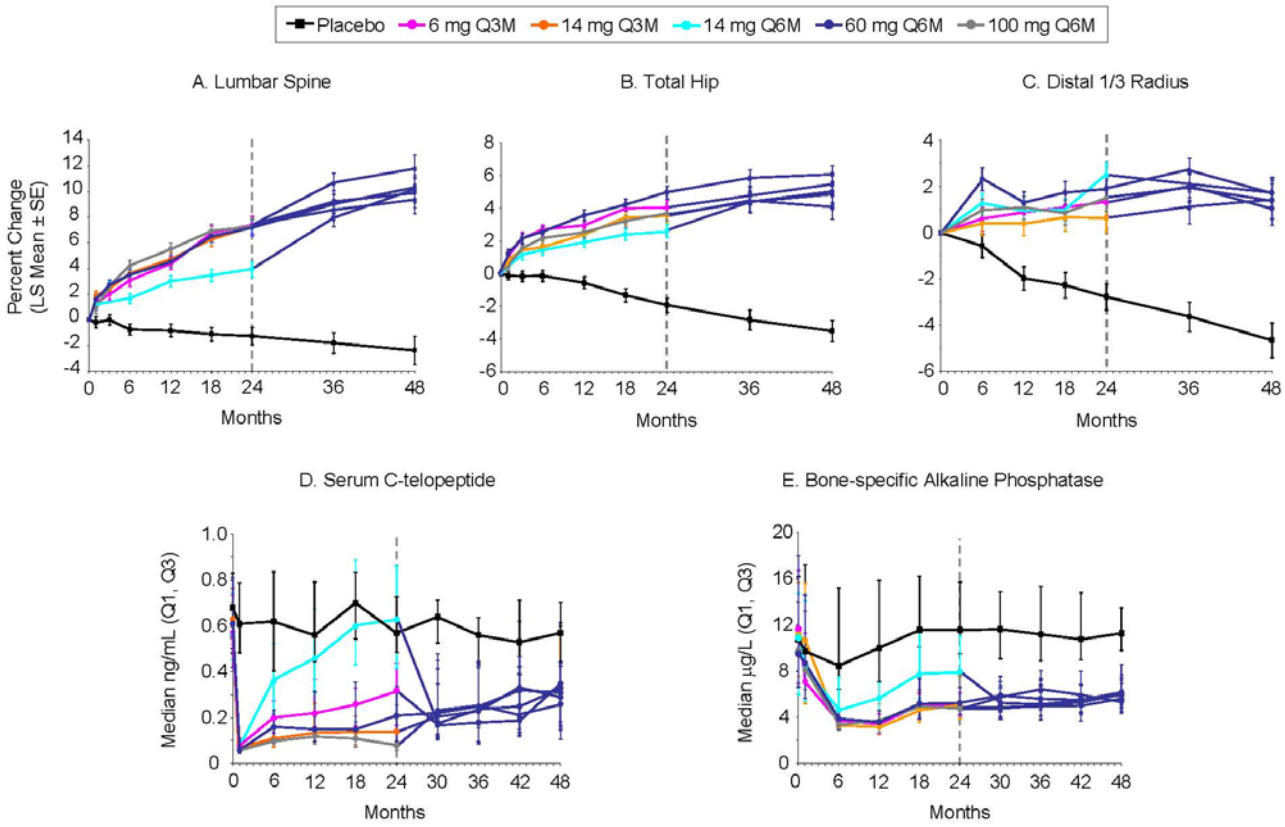
BMD, bone mineral density; CI, confidence interval, SEM, standard error of the mean

Source: Amgen data on file (20050141 [DECIDE] clinical study report; 20050234 [STAND] clinical study report; [redacted]).

Figure B7 depicts the percentage change in BMD and actual values of BTM in patients who continued denosumab treatment for 48 months.

Figure B8 depicts the percentage change in BMD and actual values of BTM in patients who discontinued denosumab treatment for the last 24 months, were re-treated with denosumab 60 mg every 6 months at month 36 or discontinued alendronate treatment.

Figure B7 Percentage change in BMD and actual values of BTM in patients who continued denosumab treatment for 48 months in trial 20010223

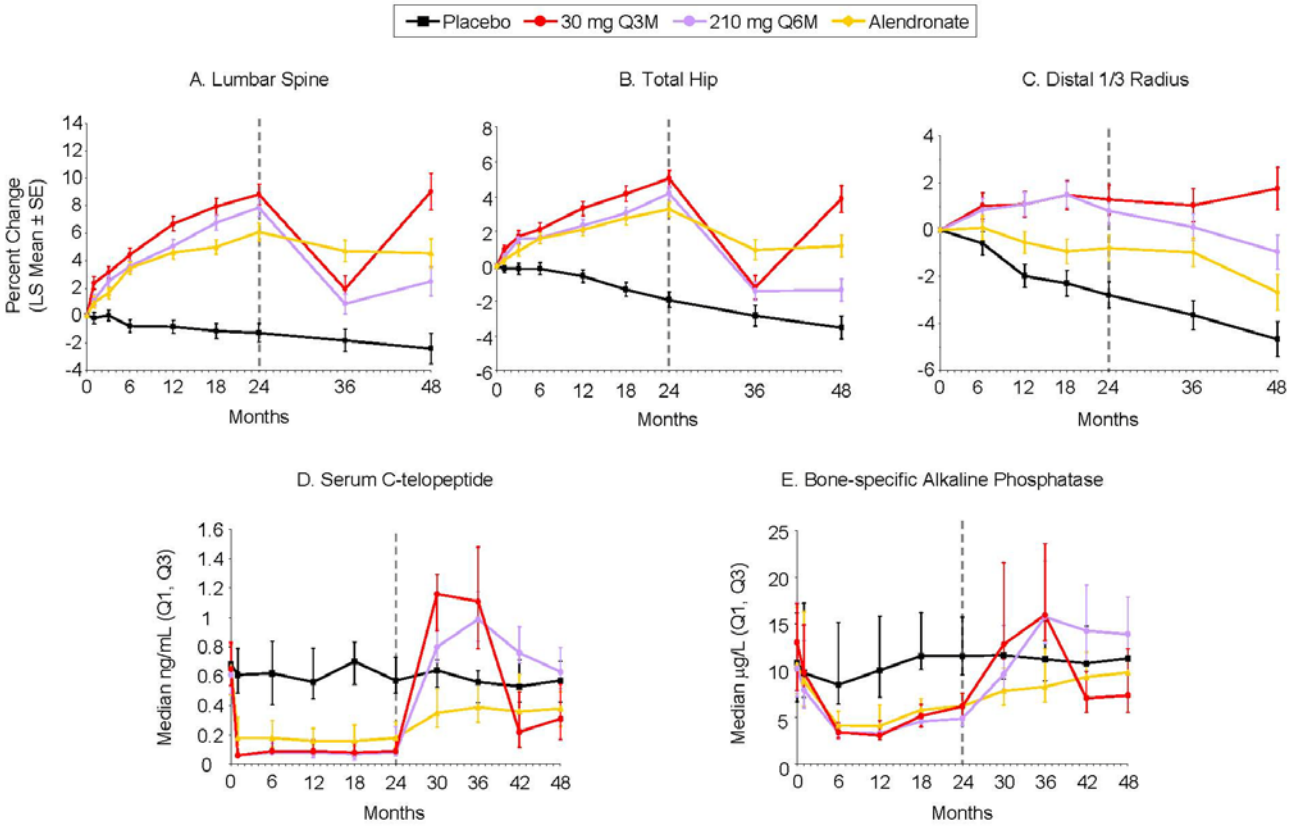


BMD, bone mineral density; BTM, bone turnover marker; LS, least squares; Q3M, every 3 months; Q6M, every 6 months; SE, standard error.

BMD values are shown as percentage change from baseline (least square mean ± SE), whereas BTM levels are shown as absolute values (median with interquartile range) at the end of each dosing cycle. The dashed line at month 24 indicates the time at which patients were re-allocated to the 60 mg Q6M dose.

Source: Miller et al., 2008a.

Figure B8 Percentage change in BMD and actual values of BTM in patients who discontinued denosumab treatment for the last 24 months (210 mg Q6M), were re-treated with denosumab 60 mg Q6M at month 36 (30 mg Q3M) or discontinued alendronate treatment in trial 20010223



BMD, bone mineral density; BTM, bone turnover marker; LS, least squares; Q3M, every 3 months; Q6M, every 6 months; SE, standard error.

BMD values are shown as percentage change from baseline (least square mean ± SE), whereas BTM levels are shown as absolute values (median with interquartile range) at the end of each dosing cycle. The dashed line at month 24 indicates the time at which dosing was re-allocated.

Source: Miller et al., 2008.

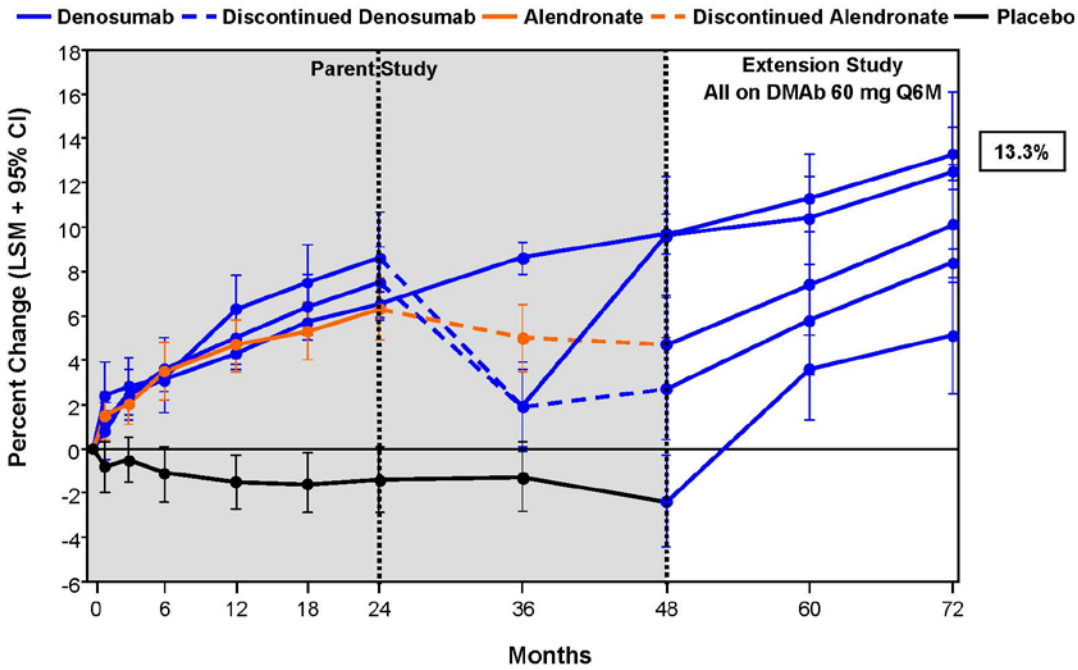
Long-term denosumab treatment led to gains in BMD and reduction of BTM throughout the course of the study. The effects on bone turnover were fully reversible with discontinuation and restored with subsequent re-treatment.

In the extension phase of this study (trial 20050233), all subjects received open-label denosumab 60 mg sc every 6 months. Results for subjects who received denosumab treatment for 6 years and those who received placebo for 4 years followed by denosumab for 2 years have been reported (Miller et al., 2009).

Of the 262 subjects who completed the parent study, 200 enrolled in the extension study, and of these, 164 (82%) had completed the first 2 years at the time of

reporting. For the 93 subjects who received 6 years of denosumab treatment, BMD at the lumbar spine increased 13.3 compared with their parent study baseline and 2.7% compared with their extension study baseline (Figure B9). For the 16 subjects in the previous placebo cohort, 2 years of denosumab treatment resulted in gains in BMD comparable to those observed during the first 2 years of 60 mg every 6 months in the parent study (Figure B9). Reductions in CTX-1 and BSAP were sustained over the course of continuous denosumab treatment. Reductions in these BTMs also were observed when the placebo group transitioned to denosumab treatment.

Figure B9 Percentage change in lumbar spine bone mineral density from parent study baseline (trial 20010223) in extension trial 20050233



CI, confidence interval; LSM, least squares mean; Q6M, every 6 months.
Source: Miller et al., 2009.

Data collected from the 4-year parent study and 2 years of the extension study demonstrated that denosumab increased BMD in subjects receiving 6 continuous years of treatment.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Section 5.2.4 includes a complete list of RCTs investigating denosumab in women with osteoporosis (Table B2) with the quality assessment of each RCT detailed in section 5.4.2. Only one denosumab trial has measured fractures as an efficacy endpoint (trial 20030216 [FREEDOM]); therefore, meta-analysis is not necessary; an IC estimating the efficacy of denosumab with respect to all the comparators in preventing fractures is presented in section 5.7.

Four trials (20050141 [DECIDE], 20050234 [STAND], 20050179 and 20010223) compared denosumab directly with alendronate using BMD endpoints evaluated by DXA. The percentage change in BMD at 12 months in the total hip, lumbar spine and femoral neck was analysed in each study. A meta-analysis of these trials was performed to provide supporting evidence (BMD data are not used in the economic analysis).

The analysis is presented in section 9.8 (appendix 8). Briefly, the meta-analysis found significant heterogeneity between studies within two endpoints (total hip and femoral neck) with no obvious explanation. The results of the random effects meta-analysis showed greater reductions in BMD for denosumab compared with alendronate in the percentage change in BMD at 12 months across all three BMD endpoints. The greatest reduction was seen in the lumbar spine (estimated mean difference denosumab minus alendronate: lumbar spine = 1.21%; 95% CI, 0.838 to 1.404; total hip = 0.723%; 95% CI, 0.247 to 1.200; femoral neck 0.604%; 95% CI, 0.119 to 1.090). and results of this meta-analysis are presented in section 9.8 (appendix 8)

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Only one denosumab trial has measured fractures as an efficacy endpoint (trial 20030216 [FREEDOM]); therefore a meta-analysis of denosumab trials for fracture endpoints is not necessary; an IC estimating the efficacy of denosumab with respect to all the comparators in preventing fractures is presented in section 5.7.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

See section 9.8 (appendix 8).

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

The studies used to inform the indirect analyses were identified from the systematic review described in sections 5.1 and 5.2.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

See section 5.2.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table B16 to Table B19 summarise the trials included in the ICs investigating the primary comparators for the following fracture types: morphometric vertebral, clinical vertebral, non-vertebral, hip and wrist. Trials are included in the primary analysis where fractures were captured as either a primary or secondary endpoint rather than through adverse event reports alone. The systematic review did not identify any ibandronate on-label trials, and it was therefore decided to include with the primary

analysis the trial comparing ibandronate 2.5 mg/day (an off-label dose) where available for completeness. Trials for oral ibandronate are shown as no data for iv ibandronate were identified. Trials for the supplementary comparators (the oral BPs) and network diagrams associated with Table B16 to Table B19.are presented in section 9.4.3 (appendix 4).

Table B16 Morphometric vertebral fracture – primary analysis

No. of trials	1	2	4	1	1	1
Trials	**20030216 (FREEDOM)**	**SOTI Study TROPOS Study**	**MORE Study (Group 1) MORE Study (Group 2) Lufkin 1998 Morii 2003**	**FPT Study**	**HORIZON Study**	**BONE Study**
Denosumab	X					
Strontium		X				
Raloxifene			X			
Teriparatide				X		
Zoledronate					X	
Ibandronate iv						
Ibandronate oral*						X
Placebo	X	X	X	X	X	X
X denotes the treatments compared. Comparators with no available trail data are greyed out. *Ibandronate oral is included because no trials were identified for ibandronate iv						

Table B17 Clinical vertebral fracture – primary analysis

No. of trials	1	1	2	1	1
Trials	**20030216 (FREEDOM)**	**SOTI Study**	**Silverman 2008 Liu 2004**	**HORIZON Study**	**BONE Study**
Denosumab	X				
Strontium		X			
Raloxifene			X		
Teriparatide					
Zoledronate				X	
Ibandronate iv					
Ibandronate oral*					X
Placebo	X	X	X	X	X
X denotes the treatments compared. Comparators with no available trail data are greyed out.					

Table B18 Non-vertebral fracture – primary analysis

No. of trials	1	2	2	1	1	1
Trials	**20030216 (FREEDOM)**	**SOTI Study TROPOS Study**	**Silverman 2008 Lufkin 1998**	**FPT Study**	**HORIZON Study**	**BONE Study**
Denosumab	X					
Strontium		X				
Raloxifene			X			
Teriparatide				X		
Zoledronate					X	
Ibandronate iv						
Ibandronate oral*						X
Placebo	X	X	X	X	X	X
X denotes the treatments compared. Comparators with no available trail data are greyed out. *Ibandronate oral is included because no trials were identified for ibandronate iv						

Table B19 Hip fracture – primary analysis

No. of trials	1	1	1	1	1
Trials	**20030216 (FREEDOM)**	**TROPOS Study**	**Lufkin 1998**	**FPT Study**	**HORIZON Study**
Denosumab	X				
Strontium		X			
Raloxifene			X		
Teriparatide				X	
Zoledronate					X
Ibandronate iv					
Ibandronate oral*					
Placebo	X	X	X	X	X
X denotes the treatments compared. Comparators with no available trail data are greyed out.					

Table B20 Wrist fracture – primary analysis

No. of trials	1	1	1
Trials	**20030216 (FREEDOM)**	**TROPOS Study**	**FPT Study**
Denosumab	X		
Strontium		X	
Raloxifene			
Teriparatide			X
Zoledronate			
Ibandronate iv			
Ibandronate oral*			
Placebo	X	X	X
X denotes the treatments compared. Comparators with no available trail data are greyed out. *No trials were identified for ibandronate oral or iv			

Section 9.4.4 includes trial summaries and network diagrams for the sensitivity analysis, including trials where fractures were only captured as adverse event summaries.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

The most appropriate analytical approach would have been to treat fractures as time-to-event data. However, this information was generally not available, so fracture incidence data (and relative risks [RRs]) were used instead.

The denominator used in the RR for the primary analysis of the morphometric vertebral fractures was the number of subjects who had an evaluable radiological assessment. For clinical vertebral, non-vertebral, hip and wrist fractures, the intention-to-treat (ITT) population was used as the denominator. The following sensitivity analyses were performed for each fracture type:

- ITT population (morphometric vertebral fractures only)
- All trials, including trials where fractures were captured as adverse events
- All trials, including trials where fractures were captured as adverse events but excluding trials with additional sources of bias.

Section 9.4.5 presents trial data included in the primary analyses. Study identifier, active/comparator treatment, fracture incidence and the population denominator are listed. Table B21 summarises the RRs for morphometric vertebral fracture, clinical vertebral fracture, non-vertebral fracture, hip fracture and wrist fracture reported in each of the studies included in the meta-analysis, IC and MTC. Note that data for all comparators (including supplementary compartors) are presented since these were included in the MTC and may contribute to the results for the primary and secondary comparators.

Table B21 Relative risk data reported by studies included in meta-analysis, indirect comparison and mixed treatment comparison

Study Name	Author Year	Treatment	Control	Morphometric Vertebral RR (95% CI)	Clinical Vertebral RR (95% CI)	Non-Vertebral RR (95% CI)	Hip RR (95% CI)	Wrist RR (95% CI)
APOTSG	Liberman, 1995	Alendronate	Placebo	0.52 (0.28 to 0.97)		0.79 (0.52 to 1.19)	0.22 (0.02 to 2.12)	0.33 (0.14 to 0.77)
BMD MN	Fogelman, 2000	Risedronate	Placebo	0.53 (0.24 to 1.17)		0.54 (0.22 to 1.33)		
BONE	Chestnut, 2004	Ibandronate Oral (2.5)	Placebo	0.51 (0.34 to 0.74)	0.54 (0.32 to 0.89)	1.11 (0.83 to 1.48)		
Bone 1997	Bone 1997	Alendronate	Placebo	0.71 (0.21 to 2.41)		0.55 (0.26 to 1.18)		
DECIDE	Brown, 2009	Denosumab	Alendronate					0.33 (0.01 to 8.18)
Dursun 2001	Durson, 2001	Alendronate	Placebo	0.79 (0.42 to 1.47)				
EFFECT	Luckey, 2004	Alendronate	Raloxifene			0.65 (0.22 to 1.94)		0.35 (0.01 to 8.42)
EFFECT INT	Sambrook, 2004	Alendronate	Raloxifene			1.18 (0.36 to 3.80)	0.33 (0.01 to 7.98)	
EVA	Recker, 2007	Alendronate	Raloxifene	1.63 (0.54 to 4.90)	6.91 (0.36 to 133.6)	0.92 (0.45 to 1.90)	0.49 (0.04 to 5.43)	0.74 (0.26 to 2.12)
FIT Fracture	Black, 1996	Alendronate	Placebo	0.53 (0.41 to 0.69)	0.45 (0.28 to 0.74)	0.81 (0.65 to 1.01)	0.49 (0.24 to 1.01)	0.53 (0.32 to 0.88)
FIT No Fracture	Cummings, 1998	Alendronate	Placebo	0.56 (0.39 to 0.80)		0.89 (0.76 to 1.04)	0.79 (0.44 to 1.44)	1.19 (0.87 to 1.62)
FOSIT	Pols, 1999	Alendronate	Placebo			0.52 (0.30 to 0.89)		
FPT	Neer, 2001	Teriparatide	Placebo	0.35 (0.22 to 0.55)		0.47 (0.25 to 0.88)	0.25 (0.03 to 2.24)	0.29 (0.06 to 1.38)
FREEDOM	Cummings, 2009	Denosumab	Placebo	0.32 (0.26 to 0.41)	0.32 (0.21 to 0.48)	0.81 (0.69 to 0.96)	0.61 (0.37 to 0.98)	0.84 (0.64 to 1.11)

Study Name	Author Year	Treatment	Control	Morphometric Vertebral RR (95% CI)	Clinical Vertebral RR (95% CI)	Non-Vertebral RR (95% CI)	Hip RR (95% CI)	Wrist RR (95% CI)
HIP old	McClung, 2001	Risedronate	Placebo			0.91 (0.76 to 1.09)	0.85 (0.60 to 1.21)	
HIP young	McClung, 2001	Risedronate	Placebo			0.78 (0.66 to 0.93)	0.60 (0.41 to 0.89)	
HORIZON	Black, 2007	Zoledronate	Placebo	0.30 (0.24 to 0.38)	0.23 (0.14 to 0.37)	0.75 (0.65 to 0.87)	0.59 (0.42 to 0.83)	
Hooper 2005	Hooper, 2005	Risedronate	Placebo	0.98 (0.42 to 2.27)		0.81 (0.25 to 2.60)		
Liu 2004	Liu, 2004	Raloxifene	Placebo		0.09 (0.01 to 1.62)			
Lufkin 1998	Lufkin, 1998	Raloxifene	Placebo	0.64 (0.30 to 1.40)		0.14 (0.01 to 2.69)		
MORE	Ettinger, 1999	Raloxifene	Placebo			0.91 (0.79 to 1.06)	1.12 (0.64 to 1.94)	0.88 (0.68 to 1.14)
MORE 1	Ettinger, 1999	Raloxifene	Placebo	0.53 (0.35 to 0.79)				
MORE 2	Ettinger, 1999	Raloxifene	Placebo	0.69 (0.56 to 0.86)				
MOTION	Miller, 2008b	Ibandronate Oral(150)	Alendronate		0.98 (0.29 to 3.38)	1.15 (0.53 to 2.46)		
Michalska 2006 1	Michalska, 2006	Raloxifene	Placebo			0.50 (0.05 to 5.25)		
Michalska 2006 2	Michalska 2006	Alendronate	Raloxifene			1.00 (0.07 to 15.33)		
Morii 2003	Morii, 2003	Raloxifene	Placebo	0.22 (0.01 to 4.43)		0.25 (0.03 to 2.20)		
Mortensen 1998	Mortensen, 1998	Risedronate	Placebo	3.00 (0.13 to 70.92)				
Palomba 2005	Palomba, 2005	Alendronate	Raloxifene	1.01 (0.26 to 3.98)				

Study Name	Author Year	Treatment	Control	Morphometric Vertebral RR (95% CI)	Clinical Vertebral RR (95% CI)	Non-Vertebral RR (95% CI)	Hip RR (95% CI)	Wrist RR (95% CI)
Pouilles 1997	Pouilles, 1997	Etidronate	Placebo			0.34 (0.01 to 8.15)		
SOTI	Meunier, 2004	Strontium	Placebo	0.64 (0.53 to 0.76)	0.65 (0.50 to 0.84)	0.92 (0.73 to 1.17)		
STAND	Kendler, 2009	Denosumab	Alendronate			1.98 (0.61 to 6.51)		1.98 (0.18 to 21.74)
Silverman 2008	Silverman, 2008	Raloxifene	Placebo		0.95 (0.45 to 2.01)	0.92 (0.69 to 1.21)		
TROPOS	Reginster, 2008	Strontium	Placebo	0.80 (0.70 to 0.92)		0.86 (0.75 to 0.99)	0.89 (0.67 to 1.18)	0.98 (0.73 to 1.31)
VERT MN	Reginster, 2000	Risedronate	Placebo	0.60 (0.44 to 0.81)		0.71 (0.47 to 1.06)	0.82 (0.34 to 1.95)	0.71 (0.37 to 1.37)
VERT NA	Harris, 1999	Risedronate	Placebo	0.64 (0.47 to 0.87)		0.63 (0.41 to 0.97)	0.80 (0.38 to 1.70)	0.64 (0.33 to 1.23)
Watts 1990	Watts, 1990	Etidronate	Placebo	0.46 (0.16 to 1.31)		3.96 (0.45 to 34.86)	2.97 (0.12 to 72.11)	4.95 (0.24 to 101.9)

CI, confidence interval; RR, relative risk.

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Indirect comparison

The initial step of the IC estimated the direct comparisons for each comparator (primary, secondary and supplementary) with a common control (i.e., placebo). Meta-analysis of the RR of each comparator versus the common control was carried out within SAS® v9.1 using the same method described in section 5.6. Cochran's Q test was used to assess heterogeneity along with the I^2 statistic to assess the degree of heterogeneity. Results are presented as forest plots, including the global hypothesis U test (based on the fixed effects model) along with the weight (%) that each individual study exerts in the meta-analysis. A continuity correction for zero fracture events was added by adding 0.5 to the fracture count in both arms. For trials that had zero events in both arms, the trial was excluded from the analyses.

The next step of the IC estimated adjusted ICs using the approach of Bucher et al. (1997) adopted for RR as the measure of treatment effect. The indirect estimate of denosumab versus comparator was adjusted according to the results of their direct comparisons with a common control (i.e., placebo) using both a fixed effect and random effects meta-analysis. Each IC of denosumab versus comparator is estimated separately within the adjusted IC framework.

For SAS code, see section 9.4.6.1.

As a sensitivity analysis, the adjusted IC analyses for the primary analysis set were repeated using absolute risk difference (RD) as a measure of treatment effect rather than RR.

Mixed treatment comparison

An MTC was undertaken to combine evidence from both direct and ICs n a single analysis that incorporates all available evidence. A Bayesian framework was taken using the methodology outlined by Ades et al. (2006). Analyses were performed with WinBUGs 1.4 and were conducted using a burn-in of 10,000 Markov chain Monte Carlo (MCMC) simulations. The posterior distribution parameter estimates for the log RR of each active versus placebo comparison and for denosumab versus active

comparisons were generated from a further 50,000 MCMC simulations. Non-informative uniform priors were used for the control group log risk, the log RR and the random effects estimate of between study variance. Estimates for the RR were calculated by back-transformation from the posterior distribution of the log RR and are presented along with 95% credible intervals together with estimates of the probability of the RR being less than one.

For WinBUGs code, see section 9.4.6.2.

5.7.6 Please present the results of the analysis.

The direct estimates of each comparator vs. placebo from the direct meta-analysis (i.e., the initial step of the adjusted IC) are presented first, followed by the results of the adjusted IC results. Results of the primary analysis are then presented for the MTC and differences between the adjusted IC and the MTC are described where notable differences exist.

Direct comparison of each comparator versus placebo

Table B22 presents the results of the random effects meta-analysis for all fracture endpoints for each direct comparison versus placebo. Sections 9.4.7.1 to 9.4.7.3 present complete results of all the direct comparisons. Results of the sensitivity analyses using risk differences as a measure of treatment effect instead of RR are presented in section 9.4.7.6.

Note that data are shown for the primary active comparators (strontium and raloxifene), and secondary comparators (the iv BPs, ibandronate and zoledronate, and teriparatide). Data for the supplementary comparators (the oral BPs) are presented in section 9.4.11 (appendix 4).

Table B22 Direct comparison of each comparator with placebo: random effects model (primary analysis)

Comparison	Morphometric Vertebral RR (95% CI)	Clinical Vertebral RR (95% CI)	Non-Vertebral RR (95% CI)	Hip RR (95% CI)	Wrist RR (95% CI)
Denosumab	**0.325 (0.256 to 0.412)**	**0.316 (0.208 to 0.478)**	**0.813 (0.689 to 0.959)**	**0.605 (0.373 to 0.983)**	0.842 (0.638 to 1.110)
Primary comparators					
Strontium	**0.720 (0.574 to 0.904)**	**0.646 (0.499 to 0.838)**	**0.877 (0.777 to 0.990)**	0.890 (0.671 to 1.180)	0.979 (0.731 to 1.312)
Raloxifene	**0.648 (0.539 to 0.781)**	0.451 (0.053 to 3.817)	0.658 (0.163 to 2.653)		
Secondary comparators					
Teriparatide	**0.347 (0.218 to 0.553)**		**0.469 (0.252 to 0.875)**	0.251 (0.028 to 2.242)	0.287 (0.060 to 1.377)
Zoledronate	**0.300 (0.239 to 0.376)**	**0.225 (0.137 to 0.370)**	**0.750 (0.649 to 0.867)**	**0.589 (0.419 to 0.827)**	

CI, confidence interval; RR, relative risk.
RR < 1 favours comparator. Statistically significant comparisons (at the 5% level) are highlighted in bold.

The results of the placebo controlled trials were consistent with the conclusion for the individual comparators that they are effective at preventing morphometric vertebral fractures. The RRs were all statistically significant with the exception of etidronate. This trial (Watts, 1990) enrolled approximately 100 subjects per arm; the small trial size contributed to the variability and the wide CI (see section 9.4.7.3).

The results for the placebo controlled trial show that the RRs were all statistically significant with the exception of raloxifene, and that they prevent clinical vertebral fractures (see section 9.4.7.3).

For non-vertebral fracture, with the exception of etidronate and ibandronate oral 2.5 mg, the results of the placebo controlled trials showed that the RR were below one. For some comparisons, the CIs only marginally exclude one. The CI for raloxifene, etidronate and ibandronate oral 2.5 mg includes one showing that the RR is not statistically significant.

The results for the placebo controlled trials show that RRs for denosumab, zoledronate and risedronate all significantly reduce the risk of hip fractures. Strontium, teriparatide, alendronate and etidronate did not show that they reduce the risk of hip fractures.

The results of the placebo controlled trials show that none of the comparators' reductions in the risk of wrist fractures were statistically significant (see section 9.4.7.3).

Indirect comparison: denosumab versus comparator

The results of the adjusted indirect comparison are provided for all fracture endpoints in Table B23. Complete results of all the indirect comparison including the sensitivity analyses and results of the fixed effect meta-analysis are presented in sections 9.4.7.4 and 9.4.7.5. Results of the sensitivity analyses using RD as a measure of treatment effect instead of RR are presented in section 9.4.7.6.

Data are shown for the primary active comparators (strontium and raloxifene), and secondary comparators (the iv BPs, ibandronate and zoledronate, and teriparatide). Data for the supplementary comparators (the oral BPs) are presented in section 9.4.11 (appendix 4).

Table B23 Adjusted indirect comparisons of denosumab versus each comparator: random effects model (primary analysis)

Comparison	Morphometric Vertebral RR (95% CI)	Clinical Vertebral RR (95% CI)	Non-Vertebral RR (95% CI)	Hip RR (95% CI)	Wrist RR (95% CI)
Primary comparators					
Denosumab vs. strontium	**0.451 (0.324 to 0.627)**	**0.488 (0.299 to 0.796)**	0.927 (0.755 to 1.138)	0.680 (0.388 to 1.192)	0.860 (0.575 to 1.286)
Denosumab vs. raloxifene	**0.501 (0.370 to 0.678)**	0.700 (0.079 to 6.165)	1.235 (0.304 to 5.029)		
[redacted]					

CI, confidence interval; RR, relative risk.
RR < 1 favours denosumab. Statistically significant comparisons (at the 5% level) are highlighted in bold.

The results of the adjusted indirect comparison showed that against strontium and raloxifene, denosumab had a statistically lower risk of morphometric vertebral fracture (RR, 0.451 to 0.501). [redacted]

The results of the adjusted indirect comparison showed that denosumab has a statistically significant lower risk of clinical vertebral fracture than strontium.

Table B24 [redacted]

[redacted]

Table B25 [redacted]

[redacted]

[redacted]

[redacted]

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

[redacted]

[redacted]

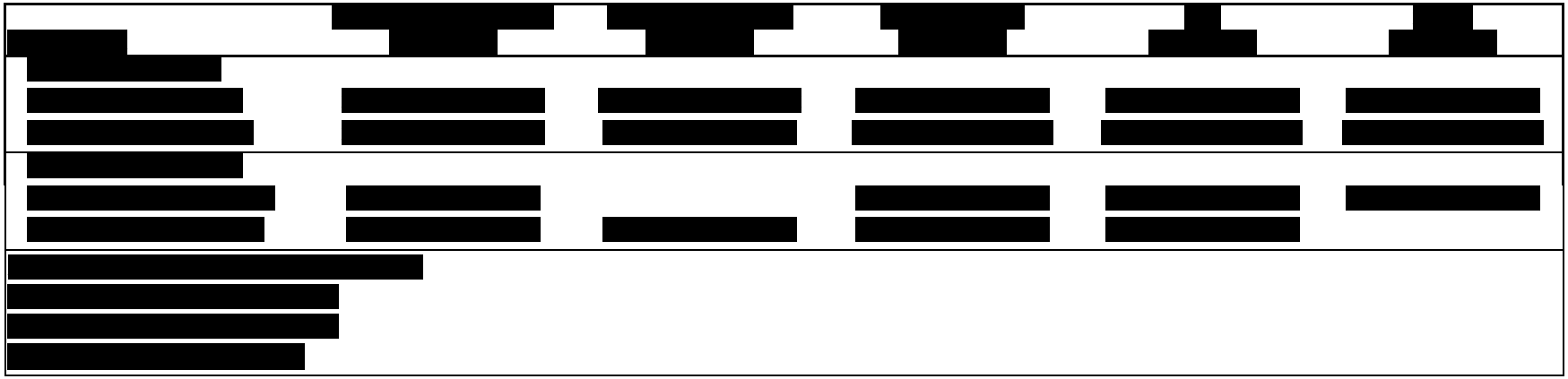
[redacted]

[redacted]

[redacted]

Table B26 [redacted]

Table B27 [redacted]



[redacted]

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered, please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

[redacted]

[redacted]

Table B28

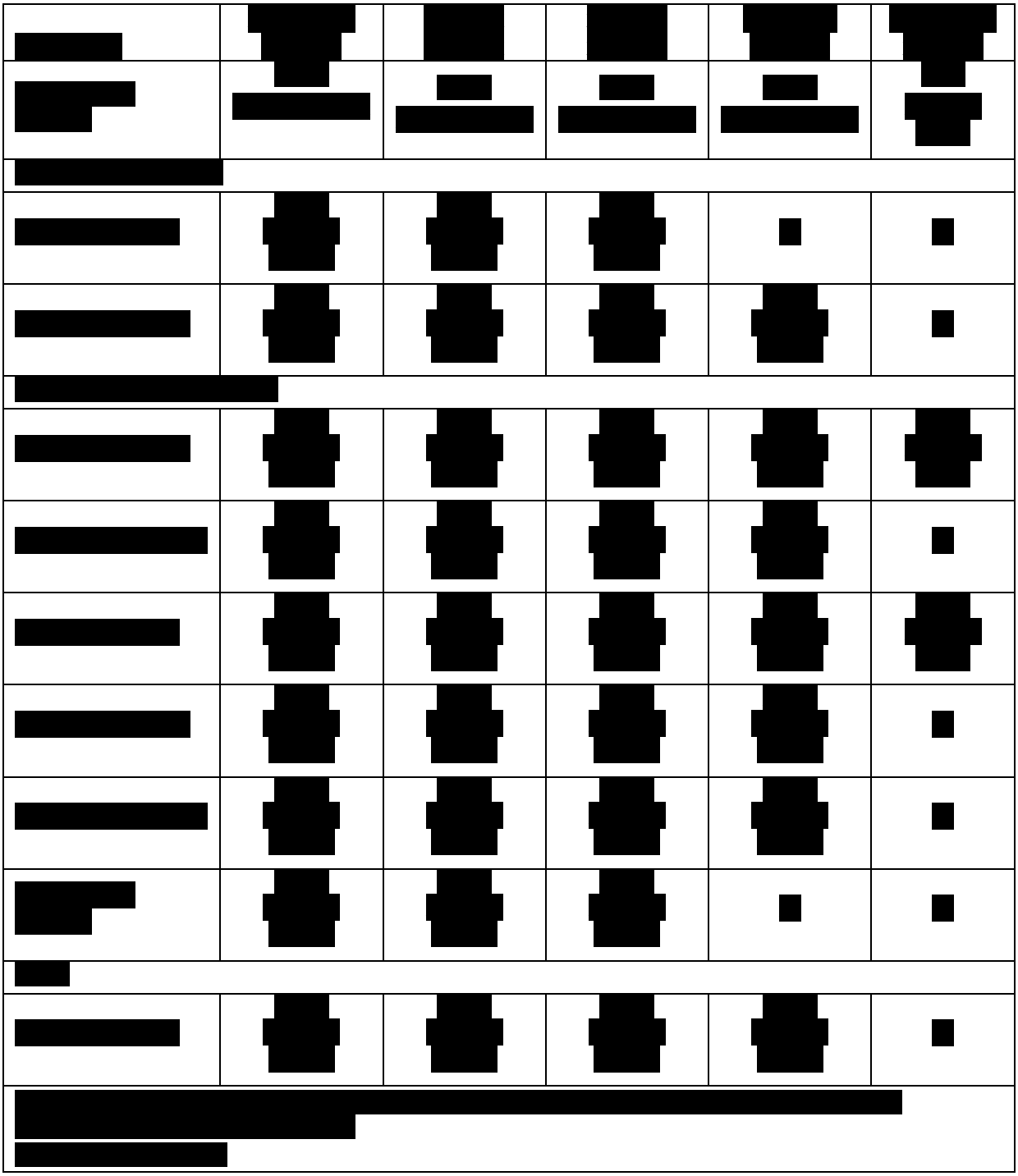


Table B29

Table B30

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

None of the denosumab PMO trials were designed primarily to assess safety outcomes.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

In trial 20030216 (FREEDOM) there were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of adverse events, serious adverse events or discontinuation of study treatment because of adverse events (Table B31). Similarly, there were no

significant differences in the overall incidence of cancer, cardiovascular events or either adverse or serious adverse events of infection. Four cases of opportunistic infections were reported in the denosumab group and three in the placebo group. Seventy subjects(1.8%) died in the denosumab group and 90 (2.3%) in the placebo group ($P = 0.08$).

No cases of osteonecrosis of the jaw occurred in either group. Delayed fracture healing was reported for two subjects in the denosumab group and four subjects in the placebo group, and one case of non-union of a humerus fracture was reported in the placebo group. There were no fractures of the femoral shaft in the denosumab group and three such fractures in the placebo group (0.1%). There were no reports of hypocalcemia in the denosumab group and three events (0.1%) in the placebo group. Decreases in serum calcium to levels below 8.0 mg/dL occurred in four subjects in the denosumab group and five in the placebo group. Local reactions after injection of a study drug occurred in 33 subjects (0.8%) in the denosumab group and 26 subjects (0.7%) in the placebo group. Neutralising antibodies to denosumab did not develop in any of the subjects.

Eczema was reported in 3.0% of subjects in the denosumab group and 1.7% in the placebo group ($P < 0.001$). Falls that were not associated with a fracture were reported in 4.5% of subjects in the denosumab group and 5.7% in the placebo group ($P = 0.02$). Flatulence was reported more frequently in the denosumab group (2.2%) than in the placebo group (1.4%, $P = 0.008$). Twelve subjects (0.3%) in the denosumab group reported serious adverse events of cellulitis, as compared with one subject (< 0.1%) in the placebo group ($P = 0.002$). There were no significant differences in the overall incidence of adverse events of cellulitis, with 47 (1.2%) in the denosumab group and 36 (0.9%) in the placebo group.

A summary of adverse events in trial 2003216 (FREEDOM) is presented in Table B31. *P* values are for descriptive purposes only; no adjustments were made for multiplicity and trial 2003216 (FREEDOM) was not powered to detect differences between treatment groups in incidence of adverse events.

Table B31 Summary of adverse events in trial 20030216 (FREEDOM)

	Placebo (N = 3,776) n (%)	Denosumab 60 mg Q6M (N = 3,886) n (%)	*P* value[a]	Hazard ratio (95% CI)[e]
All	3,607 (93.1)	3,605 (92.8)	0.91	NA
Serious	972 (25.1)	1,004 (25.8)	0.61	NA
Fatal	90 (2.3)	70 (1.8)	0.08	0.76 (0.55 to 1.03)
Leading to study discontinuation	81 (2.1)	93 (2.4)	0.39	1.14
Leading to discontinuation of a study drug	202 (5.2)	192 (4.9)	0.55	0.94
Adverse events				
Infection	2,108 (54.4)	2,055 (52.9)	0.17	0.96
Cancer	166 (4.3)	187 (4.8)	0.31	1.11
Hypocalcemia	3 (0.1)	0 (0.0)	0.08	0.00
Osteonecrosis of the jaw	0 (0.0)	0 (0.0)	N/A	NA
Serious adverse events				
Cancer	125 (3.2)	144 (3.7)	0.28	1.14
Infection	133 (3.4)	159 (4.1)	0.14	1.19
Cardiovascular event	178 (4.6)	186 (4.8)	0.74	1.02 (0.83 to 1.25)
Stroke	54 (1.4)	56 (1.4)	0.89	1.02 (0.70 to 1.48)
Coronary heart disease	39 (1.0)	47 (1.2)	0.41	1.17 (0.77 to 1.79)
Peripheral vascular disease	30 (0.8)	31 (0.8)	0.93	1.00 (0.60 to 1.65)
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98	0.99
Adverse events occurring in at least 2% of subjects[b]				
Eczema	65 (1.7)	118 (3.0)	< 0.001	1.81
Falling[c]	219 (5.7)	175 (4.5)	0.02	0.79
Flatulence	53 (1.4)	84(2.2)	0.008	NA
Serious adverse events occurring in at least 0.1% of subjects[d]				
Cellulitis (including erysipelas)	1 (< 0.1)	12 (0.3)	0.002	11.84
Concussion	11 (0.3)	1 (< 0.1)	0.004	NA

MedDRA, Medical Dictionary for Regulatory Activities; N/A = not applicable; Q6M, every 6 months.

N = Number of subjects who received ≥ 1 dose of investigational product; n = Number of subjects reporting ≥ 1 event; NA = Not available.

[a] *P* values are based on the log-rank test, except for between-group comparisons of deaths and cardiovascular events, which were based on the Cox proportional hazards model with adjustment for the baseline cardiovascular risk score.

[b] $P \leq 0.05$ for the between-group comparison. Among terms listed in MedDRA, the incidence of adverse events corresponding to 58 MedDRA-preferred terms was at least 2% in either study group.

[c] This category excludes falls that occurred on the same day as a fracture.

[d] $P \leq 0.01$ for the between-group comparison. There were 152 MedDRA-preferred terms of serious adverse events that had an incidence of at least 0.1% in either group.

[e] Hazard ratios < 1 favour denosumab and are based on the Cox proportional hazards model

Source: Cummings et al., 2009; Amgen data on file (20030216 [FREEDOM] clinical study report.

Table B32 to Table B34 summarise safety data from all placebo-controlled phase 3 trials in postmenopausal women at increased risk of fracture. Section 9.9 presents data for trials in patients receiving hormone ablation therapy. A summary of safety across both licensed indications is included in the denosumab draft SPC (section 9.1.1).

Table B32

Table B33 [redacted]

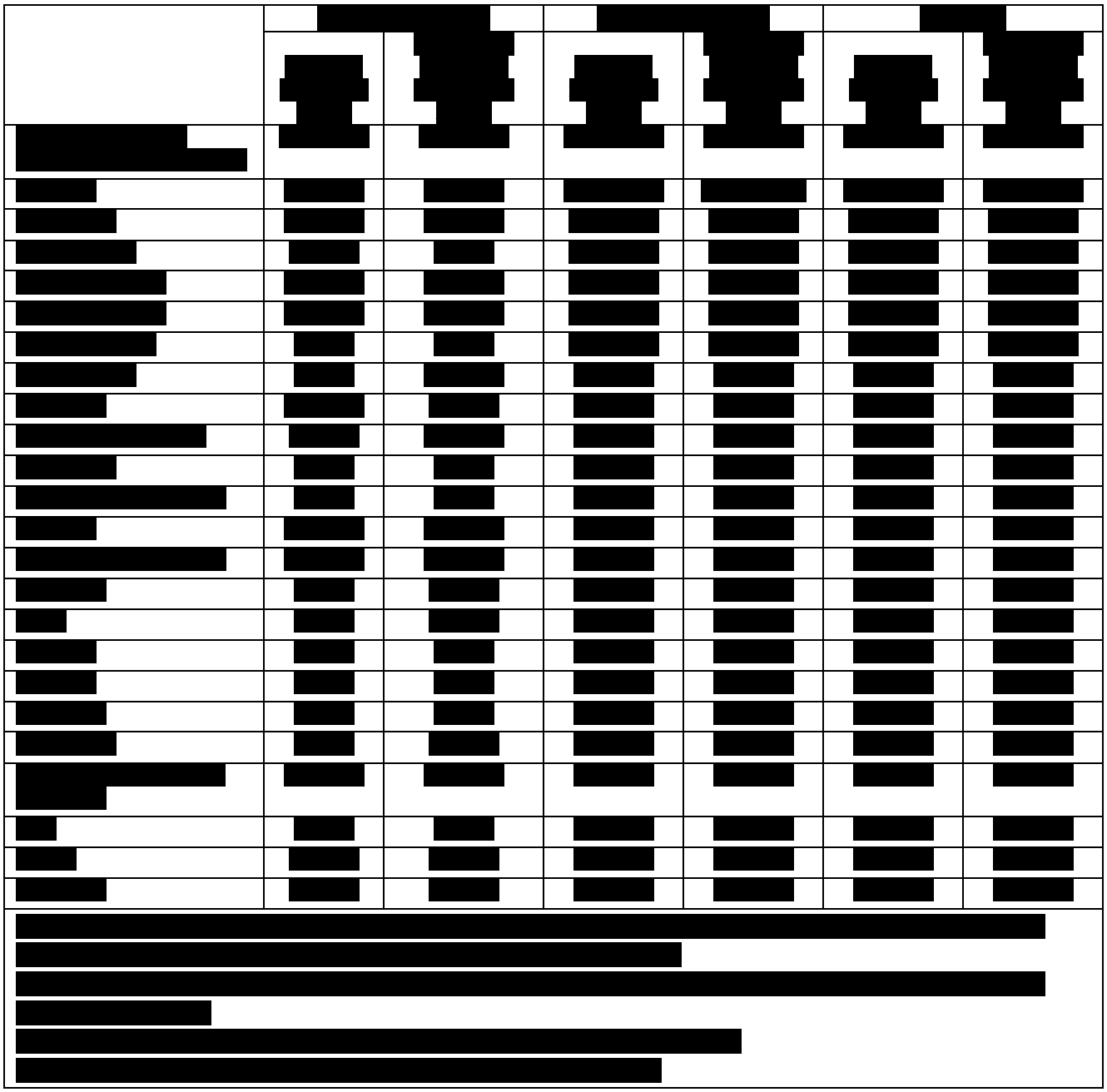


Table B34 [redacted]

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Overview of denosumab safety

Safety data for denosumab are available from approximately 14,000 subjects who participated in 30 denosumab clinical studies (11,000 postmenopausal women with low bone mass or osteoporosis, 252 women receiving aromatase inhibitor therapy for breast cancer and 1,468 men receiving androgen deprivation therapy for prostate cancer) and includes up to 5 years of denosumab exposure.

The overall incidences of adverse events, serious adverse events and adverse events leading to treatment withdrawal were generally similar between denosumab and placebo groups.

Few subjects (< 1%) permanently discontinued denosumab treatment due to treatment-related adverse events over the 2- to 3-year duration of the key phase 3 studies.

Denosumab administration was associated with mild (i.e., median serum calcium decreases from baseline ≤ 3%), transient decreases in serum calcium, which had no apparent clinical significance. Decreases in serum calcium to ≤ 7.5 mg/dL occurred with 0.04% incidence in both treatment groups. (Calcium and vitamin D supplementation was provided as standard-of-care in phase 3 denosumab study protocols.)

Extensive evaluations of cardiovascular data, including electrocardiograms (ECGs), cardiovascular adverse events and serious adverse events, external adjudication of all cardiovascular serious adverse events and an aortic calcification substudy using lateral spine x-rays, revealed no evidence of cardiovascular risk with denosumab administration.

Subject incidences of infection adverse events (non-serious and serious events combined) were generally balanced between the treatment groups; small differences were observed in the incidence of skin infections, predominantly cases of cellulitis reported as serious adverse events. When the four pivotal trials (20030216 [FREEDOM], 20040132 [DEFEND], 20040135 [HALT], and 20040138) were pooled in the combined safety analysis set, the small differences (i.e., ≤ 0.5% higher in the denosumab group) noted in individual studies in certain serious adverse events (e.g., cellulitis and erysipelas in trial 20030216 [FREEDOM] or diverticulitis in trial 20040138) were not evident (i.e., combined incidences of cellulitis: 0.2% denosumab, 0.1% placebo; erysipelas: 0.2% denosumab, < 0.1% placebo; and diverticulitis: 0.3% denosumab, 0.1% placebo).

Subject incidences of malignancy adverse events were generally balanced between treatment groups.

No adverse effects of denosumab on bone safety were observed. Fracture healing complications were infrequent, and the subject incidence of such events was balanced between treatment groups. No events of positively adjudicated osteonecrosis of the jaw were observed. Bone histology was normal following

treatment with denosumab, either in treatment-naïve subjects or in subjects previously treated with alendronate (i.e., trial 20050234 [STAND]).

Denosumab did not result in increased incidence of hypersensitivity reactions or potential clinical sequelae of hypersensitivity.

Eczema adverse events were more frequent in denosumab-treated postmenopausal women relative to placebo. Among subjects with postmenopausal bone loss (i.e., trials 20030216 [FREEDOM] and 20040132 [DEFEND]), eczema adverse events occurred in 3.1% of denosumab-treated subjects compared with 1.7% of placebo-treated subjects; the incidence of these events was balanced among subjects with bone loss due to androgen deprivation of aromatase inhibitor therapy (1.2% denosumab, 1.4% placebo).

No alterations in the safety profile of denosumab and no further reductions in serum calcium were observed following transition from alendronate to denosumab therapy. Therefore, the safety profile of denosumab was similar between subjects who were treatment-naïve to osteoporosis therapy and those who had been treated previously with BP therapy.

The safety profile of denosumab appeared stable, with extended exposure of up to 5 years in duration.

The effects of denosumab on BMD and bone turnover markers were reversible. BMD and bone markers returned to near pre-treatment levels after discontinuation of therapy. There was no evidence of significant reductions below baseline levels in any subject. Bone resorption and formation remained coupled.

No evidence of adverse effects or increased risk for fracture relative to placebo were observed, and the overall adverse event rates remained consistent and well balanced between denosumab and placebo treatment groups during the off-treatment periods.

Comprehensive clinical immunology evaluations indicated that denosumab poses little risk for immunogenicity. Samples tested from > 8,000 denosumab-treated subjects (i.e., from all studies included in this marketing application) indicated that

binding anti-denosumab antibodies were observed in < 1% of subjects after administration of denosumab. With follow-up testing of these subjects, the anti-denosumab antibodies typically did not persist. There was no evidence of altered safety or efficacy profiles associated with antibodies in these subjects. To date, no denosumab-treated subject has tested positive for neutralising antibodies in a cell-based bioassay.

Overview of comparator safety

Table B35 summarises adverse events associated with all the comparator interventions.

Table B35 Summary list of adverse events by comparator

Intervention	Key adverse events
Primary comparators	
Strontium	Gastrointestinal events (nausea, diarrhoea), allergic reactions, venous thromboembolism
Raloxifene	Hot flushes, venous thromboembolism, heart disease
Secondary comparators	
Teriparatide	Nausea, limb pain, headache, dizziness
Ibandronate (iv)	Flu symptoms, rash, osteonecrosis of the jaw
Zoledronate	Flu symptoms, atrial fibrillation, osteonecrosis of the jaw
Supplementary comparators	
Oral BPs	Gastrointestinal events

BP, bisphosphonate.
Source: National Osteoporosis Society, 2009.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Summary of efficacy: primary evidence for denosumab

In trial 20030216 (FREEDOM), denosumab given subcutaneously twice yearly for 36 months was associated with a significant reduction in the risk of new radiographic vertebral, non-vertebral and hip fractures in women with osteoporosis when compared with placebo.

- The RR for new radiographic vertebral fracture was 0.32 (95% CI, 0.26 to 0.41; *P* < 0.001). The cumulative incidence was 2.3% in the denosumab group versus 7.2% in the placebo group (a relative decrease of 68%).
- The HR for non-vertebral fracture was 0.80 (95% CI, 0.67 to 0.95; *P* = 0.01). The cumulative incidence was 6.5% in the denosumab group versus 8.0% in the placebo group (a relative decrease of 20%).
- The HR for hip fracture was 0.60 (95% CI, 0.37 to 0.97; P = 0.04). The cumulative incidence was 0.7% in the denosumab group versus 1.2% in the placebo group (a relative decrease of 40%).

To adjust for multiplicity and maintain the overall significance level at 0.05, the primary endpoint of new radiographic vertebral fracture was required to achieve significance before the next endpoints in the sequence (non-vertebral fracture and hip fracture) could be tested.

The reduction in the risk of new radiographic vertebral fracture was similar in each year of the trial: year 1, RR = 0.39 (*P* < 0.001); year 2, RR = 0.22 (*P* < 0.001); year 3, RR = 0.35 (*P* < 0.001).

The effect of denosumab treatment on new radiographic vertebral, non-vertebral or hip fractures did not differ significantly in any of the pre-specified subgroups analysed (*P* > 0.05 for all potential interactions) with the exception of baseline CTX-1 for the new radiographic vertebral fracture endpoint (*P* = 0.0036) and prevalent vertebral fracture for the non-vertebral fracture endpoint (*P* = 0.0377). The qualitative interaction term was not significant in both of these analyses (*P* = 0.7500 and 0.3574, respectively). In post hoc analyses, significant interactions were detected for the non-vertebral fracture endpoint with BMI (*P* = 0.0134) and femoral neck BMD T-score (*P* = 0.0229). The qualitative interaction term was not significant in both of these analyses (*P* = 0.5262 and 0.5000, respectively). No adjustments were made for multiplicity in either the pre-specified or post hoc analyses.

The treatment effect of denosumab on fracture risk reduction remained significant after controlling for the 10-year probability of major osteoporotic fracture (odds ratio for new vertebral fracture = 0.31; 95% CI, 0.24 to 0.39; *P* < 0.0001; HR for non-vertebral fracture = 0.80; 95% CI, 0.67 to 0.95; *P* = 0.0108) and for the 10-year

probability of hip fracture (HR for hip fracture = 0.60; 95% CI, 0.37 to 0.97; *P* = 0.0355) (fracture risk based on FRAX® algorithms). In addition, the effects of denosumab were clinically relevant in subgroups of subjects with higher risk for subsequent fracture. When higher fracture risk was identified based on the three main predictors of fracture risk (age, BMD and prevalent vertebral fracture), denosumab reduced the incidence of new vertebral and non-vertebral fractures in the high-risk subgroup (RR for new vertebral fracture = 0.35; 95% CI, 0.26 to 0.47; *P* < 0.0001; HR for non-vertebral fracture = 0.88; 95% CI, 0.70 to 1.11; *P* = 0.2901). Furthermore, in post hoc analyses, denosumab showed consistent efficacy by reducing the risk of fracture in subgroups at higher fracture risk defined by other baseline characteristics: subjects with at least two prevalent vertebral fractures or having prevalent vertebral fractures with moderate or severe severity (RR for new vertebral fracture = 0.45; 95% CI, 0.29 to 0.69; *P* = 0.0002), subjects with femoral neck BMD T-score not greater than –2.5 SD (HR for non-vertebral fracture = 0.65; 95% CI, 0.51 to 0.83; *P* = 0.0006; HR for hip fracture = 0.53; 95% CI, 0.30 to 0.92; *P* = 0.0227) and subjects ≥ 75 years old (HR for hip fracture = 0.38; 95% CI, 0.18 to 0.79; *P* = 0.0067).

Summary of efficacy: ICs and MTC

In the absence of head-to-head fracture data, comparative efficacy was investigated using adjusted ICs and MTC. Overall, the results from both the adjusted IC and MTC are consistent with each other at each fracture location.

The results showed that against strontium and raloxifene, denosumab had a statistically lower risk of morphometric vertebral fracture (RR ranging from 0.451 to 0.501). No data were identified for iv ibandronate; against oral ibandronate, denosumab had a lower risk of morphometric vertebral fracture but was not statistically significant. The results for denosumab against teriparatide and zoledronate showed that they have similar efficacy in preventing morphometric vertebral fractures.

The IC showed that denosumab had a statistically significant lower risk of clinical vertebral fracture than strontium; statistically significant differences were not seen against the other comparators. However, the credible intervals for all comparators from the MTC were much wider and statistical significance could not be concluded.

No differences were suggested by the adjusted IC or the MTC in the efficacy to prevent non-vertebral, hip or wrist fractures between denosumab and all the comparators.

Outcomes after treatment discontinuation

In trial 20010223/Miller et al., 2008a, the effects of denosumab on bone turnover were fully reversible with discontinuation and restored with subsequent re-treatment. Discontinuation of denosumab was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within the first 12 months of treatment discontinuation; the percentage change in BMD from the original study baseline remained significantly superior to that for placebo at the lumbar spine, total hip and distal radius. Re-treatment with denosumab increased lumbar spine BMD by 9.0% from original baseline values, and continued to increase over a further 2 years of treatment in the extension phase of this trial (20050233)/Miller et al., 2009). Findings were similar for total hip BMD. Levels of BTM increased upon discontinuation and decreased with re-treatment.

Denosumab inhibits bone resorption by inhibiting osteoclast formation, function and survival through the same pathway as OPG, the physiologic inhibitor of RANKL. This physiological mode of action results in qualitatively normal bone with inhibited bone turnover and may lead to superior bone quality in the long term (Seeman et al., 2009b). The effects of denosumab on bone turnover are fully reversible, as evidenced by an increase in bone turnover markers and consequent decrease in BMD with discontinuation (trial 20050233/Miller et al., 2008a). Most of the change in BMD and bone turnover markers occurred during the first year off treatment, and stabilised during the second year (Miller et al., 2008a).

Reversibility is expected based on the pharmacokinetic and pharmacodynamic characteristics of denosumab and the pathophysiology of PMO. Similar patterns in BMD and bone turnover marker changes are observed after withdrawal of HRT. Several studies involving postmenopausal women who discontinued HRT showed decreases in BMD and corresponding increases in bone turnover markers during the first year off treatment (Gallagher et al., 2002; Greenspan et al., 2002; Sornay-Rendu et al., 2003; Wasnich et al., 2004), with values returning near baseline within 2 years of therapy discontinuation (Gallagher et al., 2002). The decrease in BMD

observed after discontinuation of denosumab was comparable to that gained during treatment (Miller et al., 2008a). Similarly, bone turnover marker levels of most patients returned to baseline levels after discontinuation of denosumab (Miller et al., 2008a).

Miller and colleagues hypothesised that these changes in BMD and bone turnover markers may be explained by the skeleton following its own defined mechanostat (Frost, 1987a; Frost, 1987b). It is possible that individuals have a preset level of bone density and remodelling that is influenced by a variety of genetic and biomechanical stressors on the skeleton (Ferretti et al., 2003; Frost, 2004), and treatment with osteoporosis therapies modify bone turnover and consequently bone mass. With discontinuation of reversible treatments, such as HRT and denosumab, patients tend to return to baseline levels via an increase in bone turnover and decrease in BMD.

While untreated patients with high bone turnover and low BMD have an increased risk of fracture (Garnero et al., 2000), this may not be the case for patients who discontinue reversible therapies. Data from three large observational studies involving HRT withdrawal—the National Osteoporosis Risk Assessment (NORA), Study of Osteoporotic Fractures (SOF) and the Million Woman Study—were inconclusive about excess fracture risk among patients who discontinued therapy (Banks et al., 2004; Barrett-Connor et al., 2003; Cauley et al., 1995; Yates et al., 2004). The clinical consequences of the increase in bone turnover markers and loss of BMD after denosumab discontinuation are unknown. No increase in fracture risk was observed after denosumab was discontinued (Miller et al., 2008a). However, the study was not powered to address this question.

Patients treated with alendronate who subsequently stopped treatment have shown little change in BMD at the lumbar spine, but larger decreases in BMD at the femoral neck or distal 1/3 radius (Black et al., 2006; Bone et al., 2004; Ensrud et al., 2004). Recently, it was proposed that the different binding affinities of BPs to mineralised bone may affect the distribution of BPs within cortical and trabecular bone (Russell et al., 2008). Thus, the BMD effects upon withdrawal of alendronate therapy may not be consistent at all skeletal sites.

In trial 20050233//Miller et al., 2008a, bone remained responsive with resumed denosumab treatment, as shown by an increase in BMD and corresponding suppression of bone turnover markers similar to that observed in denosumab-naïve patients (Miller et al., 2008, Miller et al., 2009). These results further demonstrate that bone remodelling remains coupled with denosumab treatment and that prior exposure to denosumab does not mitigate a subsequent bone response to denosumab.

As with all osteoporosis therapies, continued treatment is important in minimising fracture risk. Amgen's fulfilment programme is designed to maximise treatment persistence in order to maximise the benefit of treatment Patients receiving denosumab will be supported by a patient support programme, should they wish to participate, that will send reminders to both patients and their health care professional for their second and subsequent injections, as well as provide patients with information on osteoporosis management and information about their medicine.

Summary of safety

Safety data for denosumab are available from approximately 14,000 subjects who participated in 30 denosumab clinical studies, and includes up to 5 years of denosumab exposure.

In trial 20030216 (FREEDOM), there was an increase in serious cellulitis, eczema and flatulence in the denosumab group compared with the placebo group. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing or hypocalcemia, nor were there any cases of osteonecrosis of the jaw or adverse reactions to the injection of denosumab. Other adverse events associated with other osteoporosis interventions, for example atrial fibrillation, venous thromboembolism and heart disease, were not observed.

In the Integrated Safety Summary, the overall incidences of adverse events, serious adverse events and adverse events leading to treatment withdrawal were generally similar between denosumab and placebo groups. Subject incidences of infection adverse events (non-serious and serious events combined) were generally balanced between the treatment groups; small differences were observed in the incidence of skin infections, predominantly cases of cellulitis reported as serious adverse events.

When the four pivotal trials (20030216 [FREEDOM], 20040132 [DEFEND], 20040135 [HALT], and 20040138) were pooled in the combined safety analysis set, the small differences (i.e., ≤ 0.5% higher in the denosumab group) noted in individual studies in certain serious adverse events (e.g., cellulitis and erysipelas in trial 20030216 [FREEDOM] or diverticulitis in trial 20040138) were not evident.

Summary of HRQL

In trial 20030216 (FREEDOM), EQ-5D index scores were not significantly different between treatment groups at the time points assessed (the study was not powered to detect a difference in EQ-5D index scores). Changes from baseline in EQ-5D VAS scores showed declines in health status in the placebo group as compared with the denosumab group at month 12 and at month 30. These changes were not considered clinically meaningful. The EQ-5D data collected in trial 20030216 (FREEDOM) adds little of value to the available evidence describing HRQL for patients with fragility fractures since the number of assessments in patients with clinically apparent fractures was small.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The primary efficacy and safety evidence for denosumab is based on a large randomised clinical trial in which fracture data were collected over a period of 3 years, trial 20030216 (FREEDOM). Randomisation and concealment of treatment allocation were adequate and the groups were similar at baseline. The primary endpoint (new radiographic vertebral fracture) was rigorously assessed by means of annual lateral spine radiographs assessed by a semiquantitative grading scale at a central imaging centre. Clinical fractures were confirmed by diagnostic imaging or a radiologist's report. Multiplicity of the primary and two key secondary endpoints was controlled for using a pre-specified statistical testing strategy.

The efficacy of denosumab has been demonstrated in all skeletal sites at risk of osteoporotic fracture (new radiographic vertebral and non-vertebral) and specifically in the fracture site of greatest clinical and economic importance (i.e., hip fractures). The strength of the evidence across multiple skeletal sites is sufficient to support the

inclusion of specific wording in the licensed indication. The draft SPC states 'Denosumab significantly reduces the risk of vertebral, non vertebral and hip fractures' (denosumab draft SPC, section 9.1.1; CHMP positive opinion). This is not the case for all comparators. Specifically, a significant reduction in the incidence of hip fracture has not been demonstrated for raloxifene, teriparatide or iv ibandronate (SPCs for raloxifene, teriparatide and ibandronate).

The efficacy of denosumab has been demonstrated using endpoints that are directly relevant to the clinical benefits experienced by patients in practice (i.e., fracture). Supportive evidence based on BMD data are available from trial 20030216 (FREEDOM) and an additional three RCTs (20050141 [DECIDE]; 20050234 [STAND] and 20050179). BMD data are available for 6 years of continuous treatment with denosumab, and the impact of treatment discontinuation and reinitiation have been characterised.

Safety data for denosumab were available from approximately 14,000 subjects who participated in 30 denosumab clinical studies. The overall incidences of adverse events were generally similar between denosumab and placebo groups. The safety of denosumab has been assessed in well controlled RCTs and ongoing extension studies, and a postmarketing pharmacovigilance study will continue to collect long-term safety data (trials 20050233, 20060289 and the Denosumab Postmarketing Global Safety Assessment).

Limitations

The primary efficacy data for denosumab are based on a single placebo-controlled RCT; however, supportive BMD data comparing denosumab with placebo are available from trial 20050179 and data comparing denosumab with alendronate are available from three RCTs (20050141 [DECIDE], 20050234 [STAND] and 20050179).

The comparative efficacy of denosumab relative to other interventions is based on indirect and MTCs. As with any IC, differences in the methodology, outcome measurement and the populations included in the underlying studies must be carefully considered.

Heterogeneity

Between trial heterogeneity was observed within some fracture endpoints and comparators. The direct meta-analysis, IC and MTC employed a conservative approach (i.e., random effects model), which assumes that differences exist within study and between studies. Less heterogeneity was observed in the analyses of RR than analyses of RD.

Exchangeability

The indirect comparison assumes that the effect of any given treatment included in the model should be exchangeable across the other trials included in the analyses, however the strength of the exchangeability assumption is difficult to access and quantify (Sutton et al, 2008). Our analyses used RR rather than RD as the influence of study level covariates for individual trial event rates was lower for RDs than for RRs. Limited amounts of heterogeneity were observed amongst trials and estimates and there were no major signals indicating the unsuitability of the exchangeability assumption. Support for the applicability of the exchangeability assumption is provided from the generally high level of agreement between indirect comparison estimates from the different methods of analyses conducted. In the comparison of estimates among the sensitivity analyses conducted, there is little disagreement between the methods of analysis used. One isolated case of strong disagreement between the analyses of RR and RD in the Denosumab vs Strontium comparison for clinical vertebral fractures was due to large differences in the study populations. Patients in the Strontium/Placebo study experienced higher event rates than patients in the Denosumab/Placebo study. In all other comparisons there is strong support for the exchangeability assumption.

Lack of available data for all comparators

A complete data set of all fracture endpoints for all the comparators is not available. All available fracture endpoints for all comparators in the NICE Scope have been included in the adjusted indirect comparisons and MTC primary analyses. In particular, no on label ibandronate trials were identified and it was necessary to include an off-label dose (ibandronate 2.5mg/day) where available in the primary analysis for completeness.

Small trials

Trials which had zero events in both arms were excluded from the analyses. Only a small number of trials were excluded from the analyses and the exclusion of these studies does not detract from the overall estimates from these analyses.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence base for denosumab addresses all aspects of the decision problem. Trial 20030216 (FREEDOM) investigated denosumab at the licensed dose (60 mg every 6 months) in postmenopausal women at risk of having an osteoporotic fracture. The outcome measures included fragility fracture, BMD, adverse effects of treatment and HRQL. The primary efficacy evidence directly measured the clinical benefits experienced by patients in clinical practice (i.e., the reduction in the risk of osteoporotic fracture), and encompassed all skeletal sites at risk of osteoporotic fracture (new radiographic vertebral, non-vertebral and hip). Hip fractures are of major importance clinically and economically; the evidence base directly demonstrates a significant reduction in the risk of hip fractures compared with placebo.

ICs and MTCs with other treatment options have also been performed based on fracture endpoints.

The EQ-5D index scores measured in trial 20030216 (FREEDOM) provide very little relevant evidence because few assessments were made in patients with clinically apparent fracture (see section 6.4.3).

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom

treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Denosumab dose and frequency in the trials

In all of the phase 3 denosumab trials included in the submission, and in the long-term follow up study 20050233/Miller et al., 2009, denosumab was administered at the same dose and frequency as the licensed dose that will be used in clinical practice (60 mg every 6 months). Patients were instructed to take daily supplements of calcium and vitamin D, consistent with the SPC, which states that 'Patients must be adequately supplemented with calcium and vitamin D' (denosumab draft SPC, section 9.1.1).

Generalisability of denosumab trial results to the UK PMO population

The baseline characteristics of the population randomised in trial 20030216 (FREEDOM) are compared with published data for women treated for PMO in England and Wales in Table B36. Of 7,808 patients randomised in trial 20030216 (FREEDOM), 790 (10%) were enrolled in the UK. Women were between 60 and 90 years of age. The mean age was 72 years, with the majority of patients (65%) being between 70 and 80 years of age. The mean BMI was 26 kg/m^2 with the majority of patients having a BMI being between 25 kg/m^2 and 30 kg/m^2. Fifty-three percent of patients had a prior fracture and 24% had a prevalent vertebral fracture.

Data from the GPRD for patients treated for osteoporosis in England and Wales (Gallagher et al., 2008; Breart et al., 2009) suggest a similar mean age (74 years) with a wider age distribution than in trial 20030216 (FREEDOM). Gallagher et al. (2008) reported that 19.5% of patients were younger than 60 years and 3.7% were 90 years or older. The efficacy of denosumab in preventing fractures in women younger than 60 years and 90 years or older has not been investigated; however, there was no evidence of an interaction between treatment effect and age in trial 20030216 (FREEDOM). The BMI distribution reported by Gallagher et al. (2008) suggests fewer patients in the higher BMI categories than in trial 20030216 (FREEDOM); however the mean BMI reported by Breart et al. (2009) is similar to that of the FREEDOM population (25.4 and 26.0 kg/m^2, respectively). The proportion of patients with prior fracture in FREEDOM was higher than reported by Gallagher et al. (2008); this may be due to differences in the definitions of prior fracture. The

definition applied by Gallagher et al. (2008) was not reported; the proportion of patients with prevalent vertebral fracture in trial 20030216 (FREEDOM) (23.6%) was similar to the estimate reported by Gallagher et al., 2008 (27.4%).

The eligibility criteria for trial 20030216 (FREEDOM) excluded the following groups: BMD T-score < –4.0 SD at either the lumbar spine or the total hip; thyroid or parathyroid abnormalities, hypocalcemia, vitamin D deficiency, malabsorption syndrome, rheumatoid arthritis, Paget's disease and malignancy within the last 5 years. Patients receiving recent treatment with osteoporosis medications or certain other drugs affecting bone metabolism were excluded to eliminate any carryover treatment effects.

In summary, the efficacy of denosumab observed in trial 20030216 (FREEDOM) is expected to be generalisable to effectiveness in the eligible population in clinical practice.

Table B36 Characteristics of patients treated for osteoporosis in England and Wales compared with trial 20030216 (FREEDOM) population

Characteristic	20030216 (FREEDOM) (N = 7,808)	Patients treated for osteoporosis in England and Wales	
		Gallagher et al., 2008[a] (alendronate or risedronate) (N = 36,164)	Breart et al., 2009[b] (alendronate) (N = 20,084)
Age, years			
Mean ± SD	72.3 ± 5.2	NR	74.1 ± 10.3
< 60	0 (0%)		NR
60 to < 75	5,337 (68.4)		NR
≥ 75	2,471 (31.6)		NR
< 60	0 (0%)	7,047 (19.5%)	NR
60 to < 70	2,058 (26.4%)	8,413 (23.3%)	NR
70 to < 80	5,082 (65.1%)	11,355 (31.4%)	NR
80 to < 90	663 (8.5%)	7,999 (22.1%)	NR
≥ 90	5 (< 0.1%)	1,350 (3.7%)	NR
BMI, kg/m^2			
Mean ± SD	26.0 ± 4.15	NR	25.4 ± 5.2
< 20	458 (5.9%)	3,407 (9.4%)	NR
20 to < 25	2,980 (31.2%)	11,145 (30.8%)	NR
25 to < 30	3,133 (40.1%)	7,810 (21.6%)	NR
30 to < 35	1,021 (13.1%)	2,893 (8.0%)	NR
≥ 35	216 (2.8%)	1,152 (3.2%)	NR
Unknown		9,757 (27.0%)	NR

Characteristic	20030216 (FREEDOM) (N = 7,808)	Patients treated for osteoporosis in England and Wales	
		Gallagher et al., 2008[a] (alendronate or risedronate) (N = 36,164)	Breart et al., 2009[b] (alendronate) (N = 20,084)
History of fracture	4,176 (53.5)[c]	9,898 (27.4%)[d]	NR

BMI, body mass index; BP, bisphosphonate; GPRD, General Practice Research Database; NR, not reported; SD, standard deviation.

[a] Data for a cohort of female patients from GPRD (1987-2006) aged ≥ 18 years who received a prescription for alendronate or risedronate.

[b] Data for a cohort of female patients from GPRD aged ≥ 50 years who had a general practice consultation for osteoporosis or who received at least 1 prescription for alendronate sodium (Breart et al., 2009).

[c] Any historical fracture. Prevalent vertebral fracture = 1,844 (23.6).

[d] History of fracture (detail of definition not reported).

Generalisability of comparator trial efficacy results to the UK PMO population

Persistence and compliance with oral BPs is frequently low, which is likely to lead to inferior effectiveness in clinical practice compared with the efficacy observed in trials where persistence and compliance are higher. In a study of 44,531 patients in GPRD, only 58.3% of patients starting oral BP treatment continued treatment for more than 1 year, and 23.6% continued treatment for more than 5 years (Gallagher et al., 2008). The percentage of women compliant with daily or weekly oral BPs (defined as a medication possession ratio ≥ 80%) has been estimated as 37% (Sunyecz et al., 2008). [redacted] The risk of fracture was significantly higher for patients who had discontinued treatment compared with those continuing treatment (adjusted relative rate for hip or femur fracture = 1.28 [95% CI, 1.06 to 1.56]; and for osteoporotic fracture = 1.18 [95% CI, 1.06 to 1.32]) (Gallagher et al., 2008). Increased risks of osteoporotic and hip or femur fractures were found in patients with low compliance (Gallagher et al., 2008). Similar data have been reported recently from retrospective analyses of US databases (Halpern et al., 2009; Curtis et al., 2008). Halpern et al. (2009) reported that patients with a medication possession ratio of less than 0.5 had a 10.6% higher risk of fracture relative to patients with a medication possession ratio of 0.8 or higher (*P* = 0.0338). Curtis et al. (2008) reported a significantly higher incidence of hip fracture among women who discontinued BPs than among those who did not (8.43

vs. 4.67 per 1,000 person years, respectively; *P* = 0.016). Effectiveness in clinical practice may therefore be inferior to the efficacy demonstrated in trials, which may result in increased costs (Usman Iqbal et al., 2009), as well as inferior outcomes.

Each single injection of denosumab provides a guaranteed 6 months of treatment. Patients, care givers and health professionals have the assurance of effective treatment for 6 months with no concerns about maintaining compliance with a difficult administration regime. Persistence and compliance with subsequent denosumab injections have been demonstrated to be superior to that of alendronate.

[redacted]

[redacted]

Consequently, the efficacy of denosumab relative to oral agents, teriparatide and iv ibandronate as estimated by the MTC may underestimate its effectiveness relative to the same drugs in clinical practice.

The superior persistence and compliance with denosumab are a consequence of superior patient preference with the treatment. In trials 20060232 [DAPS], 20050234 (STAND) and 20050141 [DECIDE], the simple 6 monthly subcutaneous administrations of denosumab were preferred by patients to alendronate. In trials 20050234 (STAND) and 20050141 (DECIDE), significantly more patients preferred

denosumab and were satisfied with denosumab compared to alendronate. The simplicity of administration overcomes compliance difficulties, particularly for elderly patients taking multiple daily oral medications, and relieves burden on patients, carers and nursing home staff in maintaining complex administration schedules for long-term osteoporosis treatments.

Selection of eligible patients

The proposed use of denosumab within the current clinical pathway is as an option for the treatment of patients for whom oral BPs are unsuitable; reasons for unsuitability include inability to comply with the special instructions for administration, a contraindication or intolerance. Contraindications for alendronate treatment include oesophageal abnormalities, inability to stand or sit upright for at least 30 minutes and hypersensitivity to the active substance or to any of the excipients. Alendronate is not recommended for patients with impaired renal function if the glomerular filtration rate is less than 35 mL/min. Contraindications for other oral BPs include severe renal impairment (creatinine clearance < 30ml/min) for risedronate and clinically overt osteomalacia for etidronate.

Conclusion

The results of the adjusted IC and MTC showed that the efficacy of denosumab in preventing morphometric vertebral fracture was statistically significantly greater than that of strontium, raloxifene, alendronate and risedronate (RR ranging from 0.45 to 0.576). The efficacy of denosumab for morphometric vertebral fracture was numerically greater than that of oral ibandronate, but was not statistically significant. The results for denosumab against teriparatide, zoledronate and etidronate showed that they have similar efficacy in preventing morphometric vertebral fractures.

For the clinical vertebral fracture endpoint, the IC showed that denosumab had a statistically significant lower risk of fracture than strontium; statistically significant differences were not seen against the other comparators.

For the non-vertebral, hip or wrist fracture endpoints, no differences in the efficacy to prevent between denosumab and the comparators were suggested by the adjusted IC or the MTC.

The external validity of the results of trial 20030216 (FREEDOM) to patients in routine clinical practice is expected to be high. Denosumab was used in the trial, as it will be in clinical practice; no significant patient groups were excluded and the trial population characteristics are comparable with women treated for PMO in the UK. The trial data are not specific to women for whom oral BPs are unsuitable. However, as reasons for unsuitability relate to inability to comply with treatment, a contraindication or intolerance, rather than to demographic or disease characteristics, there is no evidence to suggest that efficacy in this group would differ from that in the trial population.

For the oral comparator interventions, effectiveness in clinical practice is expected to be inferior to the efficacy demonstrated in trials as a result of reduced persistence and compliance.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic literature review was performed in accordance with a pre-specified protocol. The primary objective of this review was to systematically search and identify all existing economic evaluations of denosumab for the treatment of PMO.

Searches encompassed electronic medical databases and specified internet sites. The following electronic databases were searched:

- MEDLINE (using PubMed platform)
- MEDLINE In-Process (using PubMed platform)
- EconLit
- EMBASE (using Dialog Platform)
- The Cochrane Library, including the following:
  - Economic Evaluation Database
  - Health Technology Assessment (HTA) database
  - Database of Abstracts of Reviews of Effectiveness (DARE)

No date or language restrictions were applied in the searches. Search terms included combinations of free-text terms and Medical Subject Headings (MeSH). The following three sets of terms were used:

- Health condition of interest (disease): terms for PMO
- Intervention(s): terms for denosumab
- Study type(s): terms for economic analyses (e.g., cost-effectiveness analysis)

Section 9.10 presents the complete literature search protocol, including full listings of search terms used.

The following websites were searched:

- Conference abstracts that were published from 2005 to date
  - European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ECCEO) (http://www.ecceo8.org/)
  - American Society of Bone and Mineral Research (ASBMR) (http://www.asbmr.org/meeting/abstracts.cfm)
  - International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- Relevant appraisals by NICE and the Canadian Agency for Drugs and Technologies in Health
- NHS Evidence

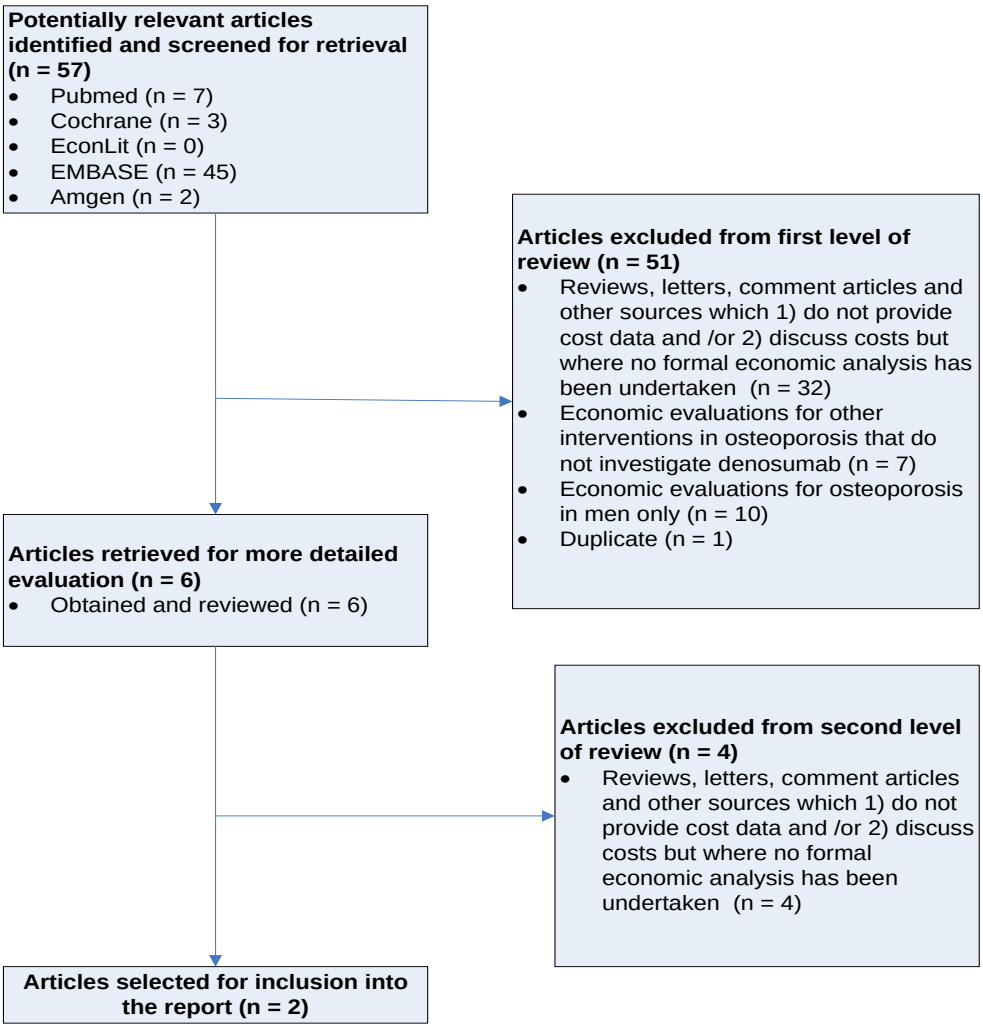
The inclusion/exclusion criteria used to identify studies of interest were based on a strategy that identified study types of interest within the population/disease condition of interest for the intervention of interest. The inclusion/exclusion criteria are as follows:

- Inclusion criteria
  - Economic evaluation studies, including studies based on models, cost analyses performed alongside clinical trials and budget-impact analyses
  - Clinical studies of denosumab that report any cost or resource use data
  - Studies of denosumab used for prevention or treatment of PMO
- Exclusion criteria
  - Reviews, letters, comment articles and other sources that discuss costs but where no formal economic analysis has been undertaken
  - General cost-of-illness or economic burden studies that do not estimate incremental cost-effectiveness or cost-utility ratios for denosumab
  - Economic evaluations for other interventions in osteoporosis that do not investigate denosumab
  - Studies evaluating osteoporosis in men

In the first-level screen, titles and abstracts of studies that were identified from the electronic databases and internet searches were reviewed using the inclusion/exclusion criteria. In the second-level screen, full texts of the studies

selected in the first-level screen were obtained for further review and the same inclusion/exclusion criteria were applied to identify relevant studies. Figure B10 presents results of the literature search and study selection process in a Quality of Reporting of Meta-analysis (QUOROM) flow chart (Moher et al., 1999).

Figure B10 QUOROM flow chart



Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Table B37 Summary of cost-effectiveness evaluations identified

Parameters	Study details	
Sources	Strom et al., 2009 ASMBR abstract; Strom et al., 2009 ECCEO presentation	Hiligsmann and Reginster, 2009; Hiligsmann and Reginster, 2009 ECCEO abstract; Hiligsmann and Reginster, 2009 ECCEO presentation
Study objective	The objective of this study was to construct a cost-effectiveness model that incorporated FRAX®, relevant cost, persistence and epidemiological data to evaluate cost-effectiveness and intervention thresholds for treatments for PMO.	The objective of this study was to assess the potential cost-effectiveness of denosumab in the treatment of women with PMO.
Study characteristics	**Analysis type:** Cost-effectiveness analysis **Model structure:** Markov cohort model **Patient population:** Women with PMO (70 years old) **Treatment comparisons:** • Denosumab compared with placebo • Denosumab compared with risedronate **Country:** UK **Perspective:** Health care perspective in the UK **Outcome measure:** Incremental cost per QALY **Time horizon:** Lifetime **Treatment period:** 5 years **Cycle length:** 6 months **Cost year and currency:** 2007 (£) **Discount rate:** 3.5% (costs and effects)	**Analysis type:** Cost-effectiveness analysis **Model structure:** Validated Markov microsimulation model **Patient population:** Women with PMO (mean age = 72.3 years) **Treatment comparisons:** • Denosumab compared with no treatment **Country:** Belgium **Perspective:** Payer perspective in Belgium **Outcome measure:** Incremental cost per QALY **Time horizon:** Death or 105 years of age **Treatment period:** 3 years **Cycle length:** 1 year **Cost year and currency:** 2006 Euros (€) **Discount rate:** 3% costs and 1.5% effects
Model assumptions	**Risk of treatment dropout** • 60% lower risk for denosumab-treated patients vs. oral risedronate-treated patients for 5-year maximum treatment duration **Declining residual treatment effect if treatment dropout occurs** • Denosumab-treated patients: maximum of 1 year after discontinuation • Risedronate-treated patients: equal to the time on treatment, up to a maximum of 5 years after discontinuation	• Offset time: base-case (linearly decline over 1.5 years) • Full adherence assumption • Drug price scenarios (hypothetical prices applied): base-case price (= €422.31 per year), base-case price + 10% and base-case price – 10% • 2 yearly physician visits and 1 BMD measurement at years 1 and 3 • No adverse events

<table>
<tr><th>Parameters</th><th colspan="2">Study details</th></tr>
<tr><td>Model inputs</td><td colspan="2">
<table>
<tr><th>Model Inputs</th><th>Denosumab</th><th>Risedronate[a]</th></tr>
<tr><td>RRR, hip</td><td>40%</td><td>26%</td></tr>
<tr><td>RRR, vertebral</td><td>68%</td><td>38%</td></tr>
<tr><td>RRR, wrist</td><td>20%</td><td>32%</td></tr>
<tr><td>RRR, other (based on non-vertebral risk and humerus risk, respectively)</td><td>20%</td><td>54%</td></tr>
<tr><td>Intervention cost (including management cost and based on a hypothetical price for denosumab and the average cost of branded products)</td><td>£305/year</td><td>£301/year</td></tr>
</table>
<table>
<tr><th>Model Inputs</th><th>Relative Risk</th><th>95% CI</th></tr>
<tr><td>Hip</td><td>0.60</td><td>0.37 to 0.97</td></tr>
<tr><td>Clinical vertebral</td><td>0.31</td><td>0.20 to 0.47</td></tr>
<tr><td>Other</td><td>0.80</td><td>0.67 to 0.95</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td>The model calculates cost-effectiveness in patient populations with any combination of the clinical risk factors through the use of FRAX®.</td><td>The model estimated the cost per QALY gained of 3 years of denosumab treatment compared with no treatment. Uncertainty was investigated using one-way and probabilistic sensitivity analyses, which were also performed to match the population in Belgium where PMO treatment is reimbursed (i.e., when BMD T-score is < 2.5 SD or there has been a prevalent vertebral fracture).</td></tr>
</table>

<table>
<tr><th>Parameters</th><th colspan="2">Study details</th></tr>
<tr><td>Results</td><td>Cost-effectiveness analysis
70-year-old women with a BMD T-score at –2.5 SD (osteoporosis threshold) without other clinical risk factors
• ICER: £14,300/QALY (denosumab vs. placebo)
• ICER: £10,700/QALY (denosumab vs. risedronate)
Intervention threshold using a willingness-to-pay of £20,000
10-year risk of major osteoporotic fracture
• ~ 8%-14% (denosumab vs. risedronate)
• ~ 10%-20% (denosumab vs. placebo)
Intervention threshold using a willingness-to-pay of £30,000
10-year risk of major osteoporotic fracture
• ~ 7%-11% (denosumab vs. risedronate)
• ~ 8%-16% (denosumab vs. placebo)</td><td>Cost per QALY gained of denosumab compared with no treatment
<table>
<tr><th>Model Price</th><th>Offset time 1.5 years</th><th>Offset time 3 years</th></tr>
<tr><td>Base-case price – 10%</td><td>€27,944</td><td>€21,063</td></tr>
<tr><td>Base-case price</td><td>€32,136</td><td>€24,711</td></tr>
<tr><td>Base-case price +10%</td><td>€36,328</td><td>€28,359</td></tr>
</table>
One-way sensitivity analysis
<table>
<tr><td>Base-case scenario</td><td>€ 32,136</td></tr>
<tr><td>Mean BMD T-score of –2.5 SD</td><td>€ 22,809</td></tr>
<tr><td>Prevalent vertebral fracture</td><td>€ 15,180</td></tr>
<tr><td>No monitoring cost</td><td>€ 26,222</td></tr>
<tr><td>0.75 time base-case fracture cost</td><td>€ 36,683</td></tr>
<tr><td>0.75 time base-case fracture disutility</td><td>€ 39,885</td></tr>
<tr><td>0.75 time base-case fracture risk</td><td>€ 46,291</td></tr>
</table></td></tr>
<tr><td>Conclusions</td><td>Given the assumptions of the model, the results of this analysis suggest that denosumab has the potential to be a cost-effective alternative to both no-treatment and risedronate in a UK setting.</td><td>• Denosumab is cost-effective compared with no treatment for postmenopausal Belgian women with low bone mass and who are similar to that included in trial 20030216 (FREEDOM)
• The cost-effectiveness of denosumab will improve when evaluated in a population more relevant for reimbursed purposes
• Further cost-effectiveness analyses are needed</td></tr>
<tr><td colspan="3">ASMBR, American Society of Bone and Mineral Research; BMD, bone mineral density; CI, confidence interval; ECCEO, European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; ICER, incremental cost-effectiveness ratio; PMO, postmenopausal osteoporosis; QALY, quality-adjusted life year; RRR, relative risk reduction; SD, standard deviation; UK, United Kingdom.
[a] Risedronate data taken from the review conducted by NICE.</td></tr>
</table>

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[3] or Philips et al. (2004)[4]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Table B38 Quality assessment of cost-effectiveness studies

Study question	Grade (yes/no/not clear/N/A)	
	UK denosumab cost-effectiveness model incorporating FRAX® and adherence	**Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women**
Study design		
1. Was the research question stated?	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	No
5. Were the alternatives being compared clearly described?	Not clear	Yes
6. Was the form of economic evaluation stated?	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	No	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	Yes
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	Yes
11. Was the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	No	Yes
13. Were the details of the subjects from whom valuations were obtained given?	No	Yes

[3] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[4] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Study question	Grade (yes/no/not clear/N/A)	
	UK denosumab cost-effectiveness model incorporating FRAX® and adherence	**Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women**
14. Were productivity changes (if included) reported separately?	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	N/A	N/A
16. Were quantities of resources reported separately from their unit cost?	No	No
17. Were the methods for the estimation of quantities and unit costs described?	No	No
18. Were currency and price data recorded?	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No	No
20. Were details of any model used given?	Not clear	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	Yes
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Yes
23. Was the discount rate stated?	Yes	Yes
24. Was the choice of rate justified?	No	Yes
25. Was an explanation given if cost or benefits were not discounted?	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No
27. Was the approach to sensitivity analysis described?	No	Yes
28. Was the choice of variables for sensitivity analysis justified?	No	Yes
29. Were the ranges over which the parameters were varied stated?	No	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes
32. Were major outcomes presented in a disaggregated, as well as aggregated, form?	No	Yes
33. Was the answer to the study question given?	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes

Study question	Grade (yes/no/not clear/N/A)	
	UK denosumab cost-effectiveness model incorporating FRAX® and adherence	**Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women**
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes
36. Were generalisability issues addressed?	No	Yes

N/A, not applicable; UK, United Kingdom.

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Note: Quality assessment of cost-effectiveness study was conducted with conference abstract and conference presentation only.

Source: Strom et al., 2009.

6.2 De novo analysis

Patients

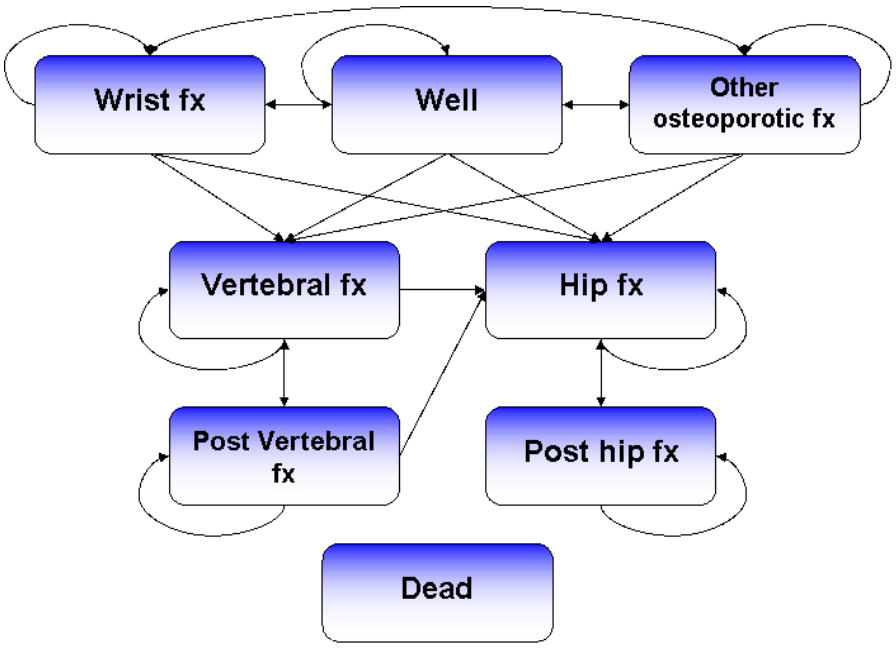
6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

Denosumab does not yet have a UK marketing authorisation for the indication detailed in this submission. On 17 December 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion for the marketing authorization of Prolia® (denosumab) for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In anticipation of the expected licensed indication, a base-case population has been defined as postmenopausal women with a starting age of 70 years old and a femoral neck T-score of –2.5 SD. Analyses are run for patients with and without prior fracture. In addition, the current model is designed such that the user may define various characteristics of the patients who populate the model. Age at treatment initiation can be varied from 50-80, T-score

from –1.0 SD to –4.0 SD, and the prevalence of vertebral fracture can take any value between 0 and 1. Subgroup analyses have also been presented for women with and without prior fracture by age and T-score.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.



See section 6.2.3 and 6.3.5 for full description of modelled clinical pathways. Other osteoporotic fracture includes other major fractures commonly associated with osteoporosis (pelvic, femur shaft, tibia, fibula, humerus, scapula, clavicle, rib and sternum).

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

Osteoporosis is a chronic disease characterised by bone fragility that can result in bone fracture. The model has been designed to capture health service costs and health consequences arising from fragility fractures. Therefore, the fracture states included in the model represent fracture types with costs and health effects for patients with osteoporosis; in particular, hip, vertebral, wrist and other common

osteoporotic fractures (pelvic, femur shaft, tibia, fibula, humerus, scapula, clavicle, rib and sternum). Two additional health states (post-hip and post-vertebral fracture) were included to account for the long-term costs and effects associated with these fractures. No long-term costs or health effects were assumed for patients with wrist or other fractures.

The model has the following additional features designed to capture other potentially important differences between therapies:

- Treatment-related adverse events (TRAEs)
- Treatment offset
- Treatment persistence
- Treatment compliance.

The model is based on a Markov cohort model approach previously used to estimate the cost-effectiveness of osteoporotic interventions in several countries (Jonsson et al., 2003; Kanis et al., 2005; Strom et al., 2007). The cycle length in the model is 6 months; a half-cycle correction is applied. The cycle length is shorter than previously employed for NICE TA160/161; however, this cycle length improves model precision whilst also aligning the model with the treatment intervals for denosumab. All patients are individually followed through the model from the age of treatment initiation to their time of death or the age of 100 years. NICE recommends that the model time horizon should reflect the period of time over which the main differences between technologies (in terms of their cost and health effects) are expected. A lifetime horizon is recommended if a treatment is expected to affect survival at a different rate to a comparator. In view of NICE recommendations, a lifetime horizon was considered appropriate for the current model due to evidence of morbidity and mortality associated with major osteoporotic fracture (see sections 6.3.1 and 6.3.2). Consequently, the main outcome measure in this analysis is the ICER measured in terms of the incremental cost per quality adjusted life year (QALY) saved.

The primary objective of the model was to quantify the expected costs and benefits of using denosumab in clinical practice and to compare these to the expected costs and benefits of alternative treatment options. The current clinical pathway of care for

women with PMO, as recommended in NICE TA160 (NICE, 2008b) and TA161 (NICE, 2008a), is summarised in section 2.4, Table A5. Denosumab is expected to be an appropriate option where oral BPs are unsuitable. It is proposed that, in this context, denosumab may be used instead of strontium or raloxifene. However, denosumab is also proposed as a treatment for patients for whom oral BPs are unsuitable, but who do not meet eligibility criteria for treatment with strontium and raloxifene, as defined in TA160/161 guidelines (according to age, T-score and clinical risk factors) (NICE, 2008b; NICE, 2008a). In these patients, it is assumed that the current appropriate comparator would be no treatment. The primary comparators are therefore strontium, raloxifene and no treatment (placebo).

Comparisons with iv BPs (ibandronate and zoledronate) and teriparatide are considered secondary comparators because these management strategies are not standard care and the mode of administration of iv BPs limits their use to a secondary-care setting. Given that denosumab is expected to be an appropriate option where oral BPs are unsuitable, comparisons with oral BPs are presented in appendices for completeness. The inclusion of oral BPs and teriparatide in the model enables the decision maker to compare the cost-effectiveness of denosumab incrementally to existing therapies, consistent with existing recommendations (NICE TA160 and TA161) (NICE, 2008b; NICE, 2008a). The model includes the following treatment options:

- Denosumab (sc)
- Primary comparators
  - Strontium (oral)
  - Raloxifene (oral)
  - No treatment
- Secondary comparators
  - Ibandronate (iv)
  - Zoledronate (iv)
  - Teriparatide (sc)
- Supplementary comparators
  - Alendronate daily/weekly (oral)
  - Etidronate (oral)

- Risedronate daily/weekly (oral)
- Ibandronate (oral)

It is acknowledged that NICE outlined a potential sequence of therapies for postmenopausal women with osteoporosis in TA160/161 (NICE, 2008b; NICE, 2008a). However, the current model has not been designed as a treatment sequencing model. Whilst in theory, a sequencing model could be used in this context, it is noted that there is no existing evidence for the clinical efficacy of denosumab or any other treatment conditional on a prior sequence of therapy. This means that clinical evidence for a second-line setting would be reliant on the same evidence as a first-line setting. A treatment-sequencing model would, as such, be no more informative than a standard modelling approach that assumed patients considered for treatment have received prior BP therapy and, hence, excludes these treatments from the analysis.

6.2.4 Please define what the health states in the model are meant to capture.

Fragility fracture is the clinically apparent and relevant outcome in osteoporosis. It is often referred to as a low-trauma fracture. In the absence of fracture, osteoporosis is asymptomatic and often remains undiagnosed. Osteoporotic fragility fractures occur most commonly in the vertebrae, hip and wrist and are associated with substantial disability, pain, reduced quality of life (NICE, 2008a) and increased mortality (Abrahamsen et al., 2009; Barrett et al., 2003; Huybrechts et al, 2006; Kanis et al., 2002a; Oden et al., 1998; Parker et al., 1999; Singer et al., 1998; Stevenson et al., 2007a; Stevenson et al., 2005a).

The model therefore consists of eight health states designed to capture the important health-service costs and health consequences arising from fragility fractures. The health states modelled include well, hip fracture, clinical vertebral fracture, wrist fracture, other osteoporotic fracture, post-hip fracture, post-vertebral fracture and dead. Other osteoporotic fracture includes other major fractures commonly associated with osteoporosis (pelvic, femur shaft, tibia, fibula, humerus, scapula, clavicle, rib and sternum).

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The bone health of untreated osteoporosis patients can continue to deteriorate, with patients facing a higher future risk of fragility fracture. A full description of osteoporosis has been provided in section 2.1.

Age, prior fracture and BMD have been identified as risk factors for fracture risk alongside other independent clinical factors. The base-case model has, therefore, been designed to vary fracture risks by patients' age, BMD (T-scores) and prior fracture, which are considered to be symptomatic of more progressive osteoporosis.

The underlying clinical pathway implemented in the model is as follows. The model structure assumes patients have a probability of sustaining a fracture, remaining healthy or dying every cycle (every 6 months). If a patient dies, she will move to the absorbing 'dead' model state. If a patient incurs a fragility fracture, she will move to the hip fracture, spine fracture, wrist fracture or other osteoporotic fracture health state depending on the fracture type.

Patients with wrist or other fractures are modelled to return to the well health state after 1 year, assuming there are no ongoing clinical costs or outcomes associated with these fracture types after a 1-year period. Patients with vertebral or hip fractures are assumed to move to the post-hip or post-vertebral fracture health states or to the dead state after 1 year and are modelled to suffer an ongoing quality of life reduction. A 6-month model cycle length was implemented in the model; therefore, four separate tunnel states were included in the model to capture outcomes for a 1-year period post fracture.

Patients in the post-vertebral fracture state may remain in this state or experience a further vertebral fracture, hip fracture or die. Post-vertebral fracture patients are not modelled to be at risk of further wrist or other fractures. Patients in the post-hip fracture state may remain in the post-hip fracture state, sustain another hip fracture or die; thus, a hip fracture patient is only at risk of sustaining a new hip fracture and is not at risk of the other fracture types. This assumption has the effect of underestimating fractures in the no treatment scenario. Further, in comparative analyses, it has the effect of underestimating vertebral, wrist and other fractures for comparators that are less effective at preventing hip and vertebral fractures. Overall, the assumption is conservative in favour of the less-effective treatment options. In comparisons with no treatment, the superior prevention of hip and vertebral fractures associated with denosumab will result in higher modelled incidence of other fracture types due to this assumption.

A function is built into the model that allows for missed fractures to be estimated (the dynamic fracture risk adjustment). This function was not used in the analyses presented for reasons of transparency. The adjusted indirect treatment comparison presented in section 5.7.6 found the following:

- No statistically significant difference in the efficacy of denosumab in preventing hip fractures against all comparators.
- Denosumab has a statistically lower risk of morphometric vertebral fracture than strontium, raloxifene, alendronate and risedronate and no statistically significant difference in risk of morphometric vertebral fracture than all other comparators.
- Denosumab has a statistically significant lower risk of clinical vertebral fracture than strontium and no statistically significant difference in risk of clinical vertebral fracture than all other comparators.

Therefore, our exclusion of the dynamic fracture risk adjustment in the analyses presented in this appraisal may be considered conservative in favour of comparators strontium, raloxifene, alendronate, risedronate and no treatment versus denosumab, and neutral for all other comparisons.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B39 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime	NICE recommends a time horizon to reflect costs and health-effect differences between therapies. A lifetime horizon is recommended for treatments that affect survival. A lifetime horizon was considered appropriate due to evidence of morbidity and mortality associated with major osteoporotic fracture (see sections 6.3.1 and 6.3.2).	Section 6.2.3
Cycle length	6 months	The cycle length improves model precision compared to annual cycles and is consistent with denosumab treatment intervals.	Section 6.2.3
Half-cycle correction	Half-cycle correction included	NICE reference case criteria	Section 6.2.3
Were health effects measured in QALYs; if not, what was used?	QALYs employed	NICE reference case criteria	Section 6.2.3
Discount of 3.5% for utilities and costs	Discount 3.5% included	NICE reference case criteria	Section 6.5.1
Perspective (NHS/PSS)	NHS/PSS perspective	NICE reference case criteria	Section 6.5.1
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Denosumab does not yet have a UK marketing authorisation for the indication detailed in this submission. Denosumab is modelled according to its anticipated marketing authorisation based on the positive opinion adopted by the CHMP on 17 December 2009. The comparators have been modelled as per their marketing authorisations.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost-effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No treatment continuation rule has been assumed. The base-case economic model assumes that patients continue osteoporosis therapy for 5 years, consistent with previous UK NICE and HTA osteoporosis models (Kanis et al., 2002b; Stevenson et al., 2007a; Stevenson et al., 2005a). This assumption is examined in a sensitivity analysis (see text below for modelled assumptions).

Adherence, Persistence and Compliance

Estimates of treatment effects applied in economic evaluations are based on efficacy observed in RCTs and, therefore, model a level of adherence apparent in clinical trial populations. However, whilst RCTs are the gold standard for comparing alternative treatments, the high internal validity required to demonstrate efficacy often comes at

the price of low external validity, and results may generalise poorly to clinical practice (Fayers et al., 1997; Franzo et al., 2005). This suggests that benefits of treatments that offer better adherence in the real-world setting may be underestimated in cost-effectiveness models if comparisons are based on clinical trial data alone. Adherence to therapy is likely to influence health economic evaluation of osteoporosis treatment due to poor adherence to some osteoporosis therapies (Kanis et al., 2004a; Klotzbuecher et al., 2000; Strom et al., 2008a). However, showing the value that improved adherence could confer is complex, and an adherence modelling framework proposed by Ström et al. (2008a) was used in the current model.

There is a wide variety of definitions for adherence in the literature. The following definitions were used for this analysis:

Adherence: General term encompassing all aspects mentioned below (i.e., persistence and compliance).

Persistence: Persistence is the duration of time from initiation to discontinuation of therapy. Patients continuing to take any amount of the medication and satisfying the number of days allowed between refills (the 'permissible gap') are considered persistent. (ISPOR Medication Compliance and Persistence Special Interest Group [Cramer et al., 2008]). Persistence can be expressed as the incidence of dropping out (withdrawing from therapy) at different time points or the proportion of the cohort still on medication after a given time since first prescription.

Compliance: Medication compliance refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking (International Society for Pharmacoeconomics and Outcomes Research [ISPOR] Medication Compliance and Persistence Special Interest Group [Cramer et al., 2008]). Compliance can be measured by the number of doses taken divided by the number of prescribed doses during a defined time period, also known as MPR.

Persistence

In the base-case analysis, the treatment duration has been set to 5 years and persistence has been assumed to be 100% for all treatments. In two sensitivity analyses, however, a proportion of patients have been modelled to withdraw from therapy. [redacted].

Table B40 Weibull parametric analysis of time to event non-persistence data for oral therapies from GPRD and for denosumab risk ratio from DAPS

	Parameter	SE	
DAPS risk ratio: Denosumab vs. Alendronate (Amgen data on file; 20060232 (DAPS) 12-month interim analysis)			
	log RR	**SE**	**RR**
[redacted]			
[redacted]			
	[redacted]		
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

d, daily; RR, relative risk; SE, standard error; w, weekly

A stepwise approach was taken to the application of improved persistence profile of denosumab over alendronate that was observed in the DAPS trial (Amgen data on file. 20060232 (DAPS) 12-month interim analysis). In the first of the sensitivity analyses, denosumab has been modelled to have the same persistence profile as oral ibandronate monthly (the least-frequently administered therapy in the GPRD study). This sensitivity analysis is considered particularly conservative given that

GPRD data clearly suggest superior persistence with less-frequently administered therapies (Table B41) and denosumab is administered once for every six administrations of ibandronate monthly.

[redacted]

Persistence has been modelled in keeping with therapy administration, which means that a patient injected with denosumab would be expected to persist for at least 6 months. Patients on oral BPs will be at risk of withdrawal from treatment earlier. It is assumed that patients treated with orally administered drugs would discontinue treatment, on average, at the mid-point of the cycle (i.e., after 3 months).

Zoledronate, ibandronate iv and teriparatide have been excluded from persistence sensitivity analyses in view of the absence of evidence on the persistence profile of these therapies.

Table B41 [redacted]

[redacted]

A dynamic offset assumption capped at 1 year has been applied to patients who discontinue their treatment. Patients who discontinue after the first cycle (6 months) receive an offset of 6 months, and patients who discontinue after the second cycle (12 months) or later receive an offset of 12 months.

Compliance

In the base-case analysis, compliance is assumed to be 100% for the 5-year treatment period for all modelled therapies. In a sensitivity analysis, a proportion of patients on oral therapies has been assumed to be poorly compliant and to incur a reduction in treatment benefit over the modelled time horizon. The sensitivity analysis on compliance assumed 100% of patients persisted with therapy.

A systematic review was undertaken to identify studies on treatment compliance in patients who received oral osteoporosis therapy (BPs, raloxifene, strontium) (Heron evidence development, 2009). The systematic review identified seven studies that reported HRs for fracture given poor compliance (Caro et al., 2004; Cotte et al., 2008; de Lusignan et al., 2006; Gothe et al., 2007; Huybrechts et al., 2006; Penning Van Beest et al., 2008; Sirus et al., 2006). Compliance was quantified in terms of the MPR defined as total number of days of medication supply divided by the number of days during the studied time period; poor compliers were assumed to have an MPR of < 80%. Patients with an MPR of < 80% are at greater risk of fracture than those with an MPR ≥ 80%. A random effects meta-analysis of these seven studies

indicated that the HR for fracture was 1.28 (1.18-1.38) (all fracture types) (Heron evidence group, 2009).

The GPRD study on persistence and compliance to oral osteoporosis therapies (oral BPs, strontium and raloxifene) (Amgen data on file, Boston Collaborative Group report, 2009) reported that 74.1% (n = 1,445) of persistent patients administered weekly alendronate complied with therapy when compliance was defined as ≥ 80% MPR.

In the sensitivity analysis on compliance, poor compliance was assumed only to apply with orally and frequently administered therapies (oral BPs, strontium, raloxifene, teriparatide). Compliance has been assumed to be 100% for denosumab patients since patients are administered six monthly injections. Patients are, therefore, modelled as complying with therapy during the 6-month period.

The reduction in efficacy for a persistent but partially compliant population compared with the efficacy observed in trials was reflected in the model using the fraction of benefit (FoB) parameter.

The FoB was estimated using the following equation:

$$FoB = 1/(P +(1-P)*F) \qquad \text{(Eq. 1)}$$

where:

P = proportion compliant

F = fracture risk in non-compliant patients

FoB was modelled to range between 0 and 1.

The proportion of patients modelled to be compliant was based on data from the GPRD study on compliance, and the fracture risk in non-compliant patients was estimated using data from pooled analyses from the systematic review.

Costs have also been downward adjusted in the sensitivity analysis on compliance to account for reduced consumption of medication. Data have been applied from a meta-analysis by Kothawala et al. (2007), who estimated that in patients with less than 80% MPR, the average MPR would be 67%. Costs have been consequently

adjusted assuming that poor compliers incur 67% of the medication costs compared to compliant patients.

It is noted that the analysis on compliance is based on MPR and does not take into account the costs and effects of patients who fill prescriptions, but who do not subsequently use the treatment. Furthermore, the reported compliance to alendronate weekly applied in this study is generally higher than estimates previously reported in published literature (Brankin et al., 2006; Gallagher et al., 2008; Rietbrock et al., 2008). Therefore, the values applied in this sensitivity analysis are considered conservative and in favour of the oral therapies versus denosumab.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided, as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

In the base-case analysis, fracture risk has been estimated from epidemiological evidence, with a sensitivity analysis undertaken using the FRAX® algorithm. FRAX® was not used in the base-case due to the lack of transparency associated with the algorithm coefficients. Therefore, in the base-case model, the risk of sustaining a hip, vertebral, wrist or other fracture has been based on three elements:

- The general population fracture risk
- The increased fracture risk associated with osteoporosis
- A risk reduction, if any, attributed to a treatment.

Fracture risk = (general population fracture incidence) * (relative risk of fracture osteoporosis) * (risk reduction from treatment)

This approach is consistent with methods used in previous NICE HTA analyses by Kanis et al. (2002a) and Stevenson et al. (2005a).

A systematic review of the literature was undertaken to identify appropriate UK studies or systematic reviews for all three fracture risk model parameters. The search was undertaken in Medline, Embase and Medline in Process during September 2009 (see section 9.14, appendix 14). The search was designed to identify data sources published since the HTA review by Kanis et al. (2002b); a publication date limit of the year 2000 was consequently applied. The search was designed to identify UK studies that could inform fracture risk parameters. However, the search criteria were broadened to UK, European or North American studies. During study selection, preference was given to UK data; where appropriate UK data were not available, alternative European or North American data were considered.

General population fracture risk

The systematic literature review identified only one UK study by Van Staa et al. (2001) that reported UK fracture incidence in a larger population, and across more fracture types, than the study by Singer et al. (1998) that was previously identified during the Kanis et al. (2002a) (Klotzbuecher et al., 2000) HTA review. This study by Van Staa et al. (2001) was a retrospective epidemiological study of fractures carried out in England and Wales using data from the GPRD database. Whilst this study includes more fracture types and is based on a larger population than Singer et al. (1998), the coverage of fracture incidence data from GPRD data may not be complete because data were collected retrospectively. Furthermore, the Van Staa et al. (2001) study had previously been identified by Kanis et al. (2002a) due to the slight overlap in search dates with the review undertaken for this submission. However, the study was not used in the previous HTA reviews by Kanis et al. (2002a), nor subsequently by Stevenson et al. (2006a). In view of all these factors, the Van Staa et al. (2001) data have not been applied in this analysis. Hip and wrist fractures were consequently estimated from Singer et al. (1998). The estimates for clinical vertebral fracture from Singer et al. (1998) were not considered reliable and, whilst Singer et al. published estimates of other fracture types, they did not report all other fracture types. UK clinical vertebral and other fracture incidence was therefore calculated by assuming that the ratio of clinical vertebral fracture and other fracture

to hip fracture in a Swedish population is similar to that of UK, Kanis et al. (2000). This approach conforms with methods previously applied for TA160/161 (NICE, 2008b: NICE, 2008a).

The relative risk of fracture associated with osteoporosis

The increased relative risk of fracture for osteoporosis patients compared to the general population has been estimated using the relative risk of fracture by Z-score. The Z-score is an estimate of the number of standard deviations below the general population mean bone mineral density (BMD) for a patient's age and sex. BMD is a term describing the amount of mineral per cubic centimetre of bone. Whilst BMD is only one of the determinants of fracture risk – accounting for approximately 15% of total fracture risk (Kanis, 2009) – the predictive ability (i.e., the increase in risk per SD decrease in BMD or gradient of risk) is comparable to that of a 1 SD increase in blood pressure for stroke and better than a 1 SD increase in serum cholesterol concentration for cardiovascular disease (Marshall et al., 2005).

The relative risk per age-matched standard deviation below the age-matched mean BMD is generally denoted as follows:

$$RR_{fx/sd.}$$

The number of age-matched standard deviations a patient is below the age-matched mean BMD is denoted by the Z-score:

$$Z_{score} = \frac{BMD_{pat} - BMD_{age-matched\ mean}}{BMD_{age-matched\ sd}} \qquad \text{(Eq. 2)}$$

The model estimated the relative risk per Z-score using population BMD estimates from the National Health and Nutrition Examination Survey (NHANES) III database, as per WHO recommendations (Strom et al., 2007) and evidence from the literature on the relative risk of fracture by Z-score.

The systematic review identified one study by Johnell et al. (2005), which reported age-dependent relative risks of hip fracture by Z-score in osteoporosis patients. This

study was a meta-analysis of 12 other studies and was the only paper that reported age-dependent values and included UK estimates (this study was not included in the NICE systematic review). The literature review did not identify any appropriate data sources for the RR of fractures by Z-score for other fracture types published post 2000. The study by Johnell et al. (2005) was consequently used to estimate the relative risk of hip fracture by Z-score.

Values for other fracture sites were estimated using a study by Marshall et al. (1996), a study that was previously identified by Kanis et al. (2002a) and also subsequently used by Stevenson et al. (2005a). The relative risk of fracture by Z-score for vertebral and wrist fracture were consequently modelled to be age independent (see section 6.3.2 for values).

Relative risk for patients with prior fractures

A history of fragility fracture is an important risk factor for further fractures and is used, in conjunction with T-scores, for clinical evaluation of osteoporosis in several countries. Therefore, it has been assumed that patients with a prior fragility fracture are at an increased risk of further fragility fractures.

The epidemiological literature review (see section 9.14, appendix 14) indicated that five UK studies reported the relative risk of fracture by prior fracture status. The estimates provided by Kanis et al. (2004a) and Van Staa et al. (2002) were considered to be the most informative. However, the study by Van Staa et al. (2002) did not report relative risk estimates and was, consequently, excluded from further review. Age-dependent relative risks for hip fracture following a prior vertebral fracture were, therefore, estimated using data from the meta-analysis of 11 previous studies (including 2 UK-based studies) by Kanis et al. (2004a). The relative risk of wrist, vertebral and other fractures given a prior vertebral fracture was estimated from Klotzbuecher et al. (2000) and was modelled to be independent of age.

The study by Klotzbuecher et al. (2000) identified in the literature review was previously employed in previous HTA analyses by Kanis et al. (2002a) and Stevenson et al. (2005a) (Stevenson et al., 2007a). However, in the current analysis, the relative risk contribution due to prevalent vertebral fracture from Klotzbuecher et al. (2000) was downward adjusted by 10%. This downward adjustment was

undertaken because the study did not control for differences in patient BMD, and current evidence suggests that patients with low BMD are more likely to have sustained a prior fracture. This means the relative risk estimates produced by Klotzbuecher et al. (2000) are likely to be confounded by BMD differences, and applying these estimates would overestimate the increase in relative risk of fracture across modelled cohorts. Kanis et al. (2004a) estimated hip fracture risk by prior fracture status controlling for BMD using Poisson regression. This study indicated that the RR without controlling for BMD would be approximately 10% lower than estimates controlling for BMD. Therefore, fracture risk for other fractures was downward adjusted by 10%, in accordance with data from the regression by Kanis et al. (2004a).

Klotzbuecher et al. (2000) reported that the risk of future hip, wrist, vertebral or other fracture, given a prior vertebral fracture, was equivalent for patients who had either a prior clinical or morphometric vertebral fracture. Therefore, estimates for the proportion of patients facing an increased risk of a fracture given a prior vertebral fracture were adjusted for the prevalence of morphometric fractures.

The RR of fracture by treatment

The RRs of fracture for each therapy for clinical vertebral, hip and wrist fracture were estimated from an indirect comparison for each treatment versus placebo where data were available (see section 5.7 for full analysis results). Where evidence was not available for a comparator, explicit assumptions were employed. It was assumed that the RR for clinical vertebral fracture was equivalent to morphometric RR data for interventions that lacked clinical vertebral fracture, whilst the RR for interventions with missing wrist and hip fracture was assumed to be 1.00.

No efficacy evidence was identified for ibandronate iv versus placebo; hence, efficacy was considered to be equivalent to ibandronate oral. Finally, it was assumed that the RR for other fracture was equivalent to 1.00 for all therapies because there was no consistent definition of other fracture across studies. This means that the current model does not capture differences in costs or health effects associated with other fractures, although it is noted that there will be some difference between therapies in the modelled ‘other’ fracture incidence and, therefore, costs and effects,

due to structural assumptions. This is because comparators with greater hip or vertebral fracture efficacy will have fewer patients moving into the post-hip or post-vertebral fracture state and will have a larger population at risk of other fracture types due to the model's structural assumptions.

The RR estimates are detailed in Section 5.7.6 (Table B23). It is noted that the clinical efficacy of strontium assumed in the current model is greater than that assumed by NICE for TA160/161. This is because the systematic review reported in sections 5.1 through 5.2.2 identified newly published 5-year data from the TROPOS study, (Reginster et al., 2008) while only 3-year data from the TROPOS study (Reginster et al., 2006) were published at the time of TA160/161. A sensitivity analysis is also presented, employing the same efficacy estimates as those used to inform TA160/161 (NICE, 2008b; NICE, 2008a).

Treatment offset

It has been assumed that patients continue to experience treatment benefit from osteoporosis therapies for a period of time after treatment is stopped (treatment carry over or treatment offset). A systematic review of RCT literature was undertaken to assess continuing bone fracture risk reduction following the cessation of long-term use of osteoporosis therapies (see section 9.16, appendix 16). This review identified only six RCTs (four for alendronate, one for zoledronate and one for denosumab), all of which reported continuing impact on BMD only, but none reported a continuing impact directly on fracture events and concluded that whilst some evidence of a carry over effect of osteoporosis anti-resorptive therapies was apparent, this effect could not be determined precisely; this conclusion has also been supported in non-RCT data (Gallagher et al., 2008) which found that patients with recently discontinued BP treatment had similar fracture risk to patients who discontinued more distantly and to patients who just started treatment, suggesting little carry over or offset effect on fracture risk. Denosumab RCT evidence supports at least 1 year of treatment offset on BMD (Miller et al., 2008). This study reported that BMD returned to baseline levels 1 year after treatment discontinuation, but remained above untreated BMD levels beyond 1 year. Thus the assumption of one year's offset with denosumab could be viewed as a conservative assumption. In view of the limited available evidence for all treatments, in the base-case analysis it has been assumed

that patients receive 1 year of treatment carry over effect. The relative risk of fracture, compared to no treatment, has been modelled to return linearly to 1.0 over the modelled offset period. In the sensitivity analysis on persistence, a dynamic offset assumption capped at 1 year has been applied to patients who discontinue their treatment. A further sensitivity analysis is presented that sets offset at 5 years for patients treated with any BP and denosumab offset fixed at 1 year.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here

As described in section 6.3.1, transition probabilities relate to the underlying general population fracture risks, the relative risk of fracture associated with osteoporosis and the relative risk associated with prior fracture.

General population fracture risk

The risks of hip and wrist fracture were estimated from Singer et al. (1998). The estimates for vertebral and other fracture types were proportioned using Swedish data from Kanis et al. (2000). The incidences of hip and wrist fractures were taken from Singer et al. (1998). Sufficient data on the risk of clinical vertebral fractures in the UK are scarce. Although there are differences in incidences, the proportionality between fracture types is similar throughout the western world. Therefore, the UK clinical vertebral fracture incidence was calculated by assuming that the ratio of clinical vertebral fracture to hip fracture in a Swedish-based study (Kanis et al., 2000) is similar to that of UK. Singer at al. (1998) have published estimates of other fractures, but did not report all fracture types (e.g., rib fractures). Therefore, the same imputation via hip fracture incidence and Swedish risk of ‘other fractures’ was made for the combined incidence of ‘other fractures’ in the UK (Singer et al., 1998; Kanis et al., 2002c). Table B42 presents a summary of the estimates of general population fracture risk.

Table B42 Extract of data used for general population fracture risk

	Risk of fractures per 10,000 persons			
Age	**Hip**	**Clinical vertebral**	**Wrist**	**Other**
50	4	10	21	24
55	5	13	33	40
60	7	12	43	28
65	13	19	53	44
70	35	50	65	100
75	62	60	70	130
80	115	72	73	195
85	223	105	90	375
90	342	142	95	469

The relative risk of fracture associated with osteoporosis

The link between BMD and fracture risk is typically measured as the risk compared to the normal population. Thus, it is a relative risk measure and it is generally calculated as the increased risk per age-matched standard deviation of BMD from the age-adjusted mean, and the risk is multiplicative rather than additive (Black et al., 2007).

Where the risk of a person with age-matched mean BMD was equal to the average relative risk of fracture, the formula for relative risk would be:

$$RR_{fx|BMD} = RR_{fx/sd}{}^{-Z_{score}} = \exp\left[\ln\left(RR_{fx/sd}\right)\times -Z_{score}\right] \quad \text{(eq. 3)}$$

However, given that BMD is normally distributed in the population, but the relative risk of fracture per standard deviation increases exponentially, individuals with BMD equal to the age-matched mean have a risk of hip fracture that is lower than average risk. Consequently, simply exponentiating the relative risk per standard deviation with the Z-score would overestimate the relative risk of fracture given that the benchmark—a person with age-matched mean BMD—has lower than average risk of fracture. A correction term approximated by eq. 4 is therefore introduced.

$$\exp\left[-\frac{\left(\ln\left(RR_{fx/sd}\right)\right)^2}{2}\right] \quad \text{(eq. 4)}$$

In order to calculate the relative risk of fracture for an individual with a specific BMD, equations (eq. 3) and (eq. 4) are multiplied, yielding:

$$\exp\left[\left[\ln\left(RR_{fx/sd}\right)\times -Z_{score}\right]-\left[\frac{\left(\ln\left(RR_{fx/sd}\right)\right)^2}{2}\right]\right] \qquad \text{(eq. 5)}$$

There are two variables in equation 5: the Z-score and the relative risk per standard deviation of BMD. In order to calculate the Z-score, age-matched BMD and age-matched standard deviations of BMD must be defined. In the model, the population values from the NHANES III database are used as recommended by WHO (Strom et al., 2007). Given that NHANES is a cross-sectional study showing mean and standard deviation BMD values for age intervals of 10 years, a regression line for mean BMD was fitted and a sample-weighted average was used for the standard deviation. Reference values for white women were used, reflecting that this group comprised the majority of the clinical trial patients. Table B43 shows the base-case Z-score estimates.

Table B43 Base-case Z-score estimates using base-case population estimates (women aged 70 years, T-score –2.5)

Description	Value	Data source
Mean general population BMD	0.65	NHANES III
BMD young population data	0.86	NHANES III
SD young population	0.12	NHANES III
Mean general population T-score	1.73	NHANES III
Model population T-score*	–2.5	Base-case population
Z-score*±	0.77	Base-case population
* Will vary with age and T-score entered into model. ± Z-score = T-score general population – T-score modelled population		

The risk per standard deviation of BMD at the hip has been taken from Johnell et al. (2005). Values from Marshall et al. (1996) are used for other fracture sites (see section 6.3.1). Table B44 shows the relative risk of fracture per standard deviation difference in BMD Z-score.

Table B44 Relative risk of fracture per standard deviation difference in BMD (Z-score)

Age	RR/SD hip	RR/SD vert	RR/SD wrist	RR/SD other
50	3.55	1.80	1.40	1.50
55	3.48	1.80	1.40	1.50
60	3.18	1.80	1.40	1.50
65	2.96	1.80	1.40	1.50
69	2.85	1.80	1.40	1.50
70	2.82	1.80	1.40	1.50
75	2.66	1.80	1.40	1.50
80	2.40	1.80	1.40	1.50
85	2.28	1.80	1.40	1.50
90	2.28	1.80	1.40	1.50
95	2.28	1.80	1.40	1.50
100	2.28	1.80	1.40	1.50

Relative risk and prior fractures

As described in section 6.3.1, a history of fragility fracture is an important risk factor for further fractures and is used in conjunction with T-scores for clinical evaluation of osteoporosis in several countries.

Relative fracture risk is measured as the risk of fracture relative to the normal population. The relative risks for hip fractures given a previous fracture by age were taken from Kanis et al. (2004a). The relative risk of wrist, vertebral and other fractures due to a prevalent vertebral fracture was estimated from Klotzbuecher et al. (2000). Klotzbuecher did not adjust estimates for BMD, and values were consequently adjusted down by 10% (Borgstrom et al., 2004; Klotzbuecher et al., 2000) (see section 6.3.1).

Since data on the relative risk of fractures for patients with prior fractures is presented as the risk relative to a population without fractures, a downward adjustment of that relative risk is required to arrive at a risk measure that is relative to the general population. The adjusted relative risk approximates:

$$RR_{frac\,adj|prev\,frac} = \frac{RR_{frac|prev\,frac}}{prev_{frac} \times RR_{frac\,adj} + \left(1 - prev_{frac}\right)} \quad \text{(eq. 6)}$$

where RRfrac| prev frac is the fracture risk of a person with a previous fracture relative to a person without a previous fracture, RRfracadj is the adjustment to

account for the fact that a proportion of the general population already have a prevalent fracture, and prevfrac is the prevalence of fracture in the normal population (Marshall et al., 2005).

The prevalence of morphometric fractures was simulated from the fracture incidence in the EVOS/EPOS study, taking post-fracture mortality into account, and was adjusted to reflect a Western European setting (Borgstrom et al., 2004) (see Table B45). This study was identified in the systematic epidemiological literature review (see epidemiological literature review in section 9,15 (appendix 15).

Table B45 Estimated vertebral morphometric fracture prevalence

Age	Prevalence
50	0.24%
55	1.44%
60	3.29%
65	6.25%
70	10.20%
75	16.00%
80	25.29%
85	38.26%
90	55.44%

Combining relative risk of fracture given BMD and prevalent fracture

In order to derive the relative risk for fracture given a patient's BMD and fracture history, equations 5 and 6 (down adjusted by 10%) are multiplied and the expression for relative risk related to BMD and fracture history is:

$$RR_{fx} = RR_{fx|BMD} \times RR_{frac\ adj|prev\ frac} \qquad \text{(eq. 7)}$$

The estimated relative risks for patients with a previous fracture are shown in Table B46.

Table B46 Relative risk of hip, vertebral, wrist and other fracture for patients with a prior fracture

Age	Hip	Vertebral	Wrist	Other
50	3.88	3.960	1.260	1.710
55	3.94	3.960	1.260	1.710
60	3.49	3.960	1.260	1.710
65	2.63	3.960	1.260	1.710
70	2.05	3.960	1.260	1.710
75	1.74	3.960	1.260	1.710
80	1.50	3.960	1.260	1.710
85	1.36	3.960	1.260	1.710
90	1.32	3.960	1.260	1.710
95	1.32	3.960	1.260	1.710
100	1.32	3.960	1.260	1.710

Risk below a T-score threshold

The model estimates the risk of fracture for a population having a T-score below a defined value. T-scores are normally distributed in the population at any given age; however, there is an exponential relationship between T-score and fracture risk. Individuals with an average T-score, therefore, have a lower than average risk of fracture. Conversely, the average fracture risk is found in individuals with a lower than average T-score (Jenssen's inequality).

To take Jenssen's inequality into account, the area under the curve of the normal distribution function was divided into 0.1 SD wide slices (i), and the contribution to the relative risk was calculated for each slice. The cumulative distribution function (F(x|σ)) can be defined as the area under the normal distribution limited by two T-score thresholds of interest (xi and xi+1):

$$F(x \mid \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \int_{x_i}^{x_{i+1}} e^{-\frac{x_i^2}{2}} dx \qquad \text{(eq. 8)}$$

The total number of slices (*g*) was reached when 6 SD below the threshold (*x*) was reached. The relative risks calculated for the midpoint of each slice with eq. 5 were then weighted by multiplying them with the relevant proportions of the cohort. Thus:

$$RR_{below} = \sum_{i=0}^{g} \left(\frac{1}{\sigma\sqrt{2\pi}} \int_{x_i}^{x_{i+1}} e^{-\frac{x_i^2}{2}} dx * RR_i \right) \qquad \text{(eq. 9)}$$

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is good evidence that the relative risk for osteoporosis fracture increases with increasing age (Borgstrom et al., 2004; Kanis et al., 2002a; Kanis et al., 2000; Singer et al., 1998; Stevenson et al., 2007a; Stevenson et al., 2005a). Age-dependent transition probabilities have consequently been employed in the model where appropriate evidence was available (see section 6.3.1).

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Intermediate outcomes have been linked to final outcomes in the model. The model assumes that a fragility fracture results in an increased risk of mortality over the subsequent 8 years (base-case). This assumption was applied because there is strong evidence in the literature that patients suffering fragility fractures are at an increased risk of mortality (Abrahamsen et al., 2009; Barrett et al., 2003; Jalava et al., 2003; Kanis et al., 2002a; Oden et al., 1998; Parker et al., 1999;Singer et al., 1998; Stevenson et al., 2007a; Stevenson et al., 2005a).

A systematic review of the literature was undertaken to identify appropriate UK studies or systematic reviews for mortality post fracture. The search was undertaken in Medline, Embase and Medline In Process in September 2009 (see section 9.14, appendix 14). The review was designed to identify data sources published since the HTA review by Kanis et al. (2002a) (Stevenson et al., 2005b). A date limit of post 2000 was consequently applied. Whilst the search was primarily designed to identify UK studies, the search criteria were broadened to include UK, European or North

American studies, with preference given to UK data, where appropriate, during study selection.

The literature review identified two studies published since 2000 that offered UK mortality estimates. One was a systematic review by Abrahamsen et al. (2009) and the other was a study by Van Staa et al. (2001). None of the UK studies reported by Abrahamsen et al. (2009) included estimates for the RR of mortality of a hip fracture (only mortality incidence post-hip fracture). Van Staa et al. (2001) reported observed and expected survival for hip fracture patients (comparing observed mortality to population life tables); however, estimates from Van Staa et al. (2001) were not age dependent. It is further noted that this study had previously been identified, but not used, during the HTA reviews by Kanis et al. (2002a) and Stevenson et al. (2005a) (Stevenson et al., 2007a).

In the previous NICE HTA analyses, the percentage of hip fractures that directly resulted in mortality up to 90 days post fracture was estimated from the Second Anglian Audit of Hip Fracture, Todd et al. (1999). It was further assumed that 33% of deaths up to 90 days post-hip fracture were unrelated to the fracture itself, 42% possibly related, and 25% directly related, based on Parker and Anand (1991). Causally related mortality from 90-365 days was assumed to be equivalent to 40% of the mortality up to 90 days, also based on Parker and Anand (1991). Mortality associated with vertebral fractures was based on a HR of 4.4 taken from a study by Jalava et al. (2003), with 28% of those deaths assumed to be causally related based on a Swedish study by Kanis et al. (2004). The mortality for patients with a humerus fracture was assumed to double (it is not clear from the reported text whether the absolute or relative risk was modelled to double), 28% of mortality was assumed to be causally related.

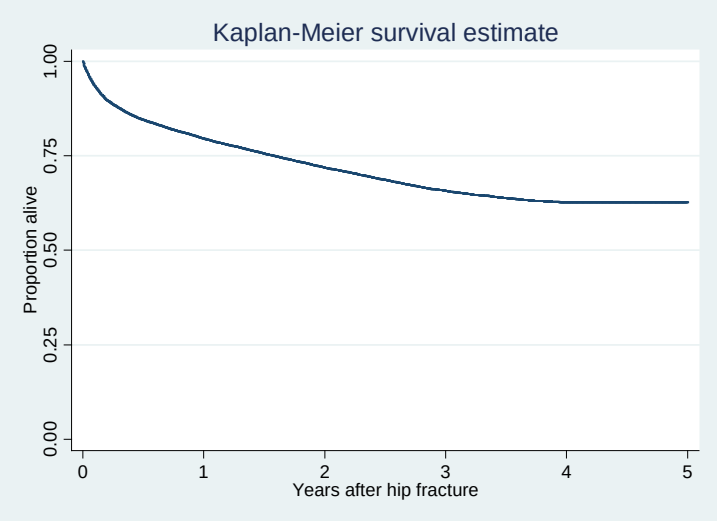
In the current analysis, Swedish national hospital registry data was obtained for mortality post-hip fracture (Statistics Sweden, 2009). The registry provided first-year mortality data for 36,551 Swedish women with an International Classification of Diseases (ICD) diagnosis for hip fracture admitted to hospital (1997-2001). Whilst it is acknowledged that UK data would generally be preferred for a UK model due to potential differences in populations and clinical practice, given its substantially larger

sample size, the Swedish registry was considered to offer more reliable estimates than those of the second Anglian Audit of Hip Fracture (sample size = 952 [Todd et al., 1999]). Swedish registry data for mortality post-hip fracture has consequently been employed in the base-case analysis.

Figure B11 plots the post-hip fracture survival curve used in the model. First-year mortality following hip fracture was estimated from the 36,551 Swedish women in the registry using ICD diagnosis code S72 for 1997-2001, using a Poisson regression model (all p-values < 0.001), shown in eq. 10:

$$y_{t_1} = e^{-6.788 + age \times 0.0603} \qquad \text{(Eq. 10)}$$

Figure B11 Hip fracture mortality estimate



Mortality in the second and following years after hip fracture was estimated based on 27,771 women with an ICD diagnosis code of S72 with the Weibull model (all p-values < 0.001), shown in eq.11:

$$y_{t_{2...5}} = 1 - \frac{e^{-(e^{(-8.125 + age \times 0.699)}(t-1)^{0.887})}}{e^{-(e^{(-8.125 + age \times 0.699)}(t-2)^{0.887})}} \qquad \text{(Eq.11)}$$

Mortality during second and following years post-hip fracture was calculated by taking the average mortality over years 2-5. Standardised mortality ratios were constructed by dividing the estimated mortalities by the Swedish female normal population mortality from 2000 (Statistics Sweden, 2009).

Mortality risks after clinical vertebral fractures were derived from a Swedish study by Johnell et al. (2004) that examined the age-dependent mortality of 2,847 women following clinical vertebral fractures. This study was considered preferable to that of Jalava et al. (2003), previously applied in the NICE analyses (NICE, 2008b; NICE, 2008a), which reported mortality for 677 women (352 of whom had morphometric fractures). The Poisson model used by Johnell et al. (2004) is shown in eq. 12:

$$y_t = e^{-4.815 - 0.631 + age \times 0.04548 - \text{years from fracture} \times 0.176} \quad \text{(Eq. 12)}$$

Mortality during the second and following years post-vertebral fracture was calculated by taking the average mortality over years 2-5. Standardised mortality ratios after clinical vertebral fractures were constructed by dividing this estimated average mortality by the Swedish female normal population mortality for 1994 (Human Mortality Database, 2009; Johnell et al., 2004). Relative risks of mortality related to hip and vertebral fractures are shown in Table B47.

No UK studies were identified for mortality associated with other fracture sites; estimates were consequently based on a US study by Barrett et al. (2003). It was assumed that women sustaining a fracture at other sites than hip and spine were at increased risk of death only within the year of fracture. Barrett et al. (2003) analysed a US sample from Medicare and reported relative risks of death 1 year after the occurrence of fracture. These relative risks were weighted by the proportions of fractures by site in the Swedish population presented in Kanis et al. (2001).

It has been assumed that 30% of the observed mortality for all fracture types is causally related. This is an assumption-based estimate derived from values previously applied in NICE economic analyses for TA160 and TA161 and has been varied in sensitivity analyses between 20% and 40%. Table B48 details relative risks of mortality following other fractures.

Table B47 Relative risks of mortality following hip and vertebral fracture

	RR of mortality compared to the normal population			
Age	Hip 1st year	Clinical vertebral 1st year	Hip 2nd and following years	Clinical vertebral 2nd and following years
50	9.79	12.07	3.62	7.94
55	8.64	10.15	3.34	6.67
60	7.69	9.04	3.11	5.94
65	6.39	7.43	2.70	4.88
70	5.54	5.98	2.44	3.93
75	4.16	4.39	1.91	2.88
80	2.92	2.75	1.39	1.81
85	2.15	1.98	1.06	1.30
90	1.63	1.36	0.83	0.89

See text (section 6.3.4) for details on data source

Table B48 Relative risks of mortality following other fractures

Fracture type	**Number of Fractures**	**Proportion of patients**	**Relative risk of death**
Rib*	340	30%	1.0
Pelvis	47	4%	1.7
Proximal humerus	352	31%	1.4
Humeral shaft	117	10%	1.2
Clavicle, scapula, sternum*	145	13%	1.0
Other femoral	52	5%	1.8
Tibia, fibula	98	9%	1.1
All	1,151	100%	1.22

See text (section 6.3.4) for details on data source

**No excess mortality reported, relative risk assumed to be equal to 1.0*

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Four clinical experts were invited to attend a face to face meeting. Clinicians were selected on the basis of their expertise in the field of osteoporosis. Two experts agreed to participate. Clinical opinion was obtained via face to face meetings and subsequent email correspondence; minutes of the face to face meeting were documented and circulated for approval. Declarations of any conflicts of interest were not sought.

Clinical expert opinion was used for general advice and feedback on key model assumptions. Clinicians were presented the economic assumptions used in NICE TA160 and TA161 (NICE, 2008b; NICE 2008a), and potential alternative assumptions that could be applied in the current model. They were asked to comment on the most clinically appropriate assumptions for the economic analysis. The parameters discussed included:

- Comparators
- Measurement of baseline fracture risk
- Mortality post fracture
- Quality of life
- Therapy and disease related adverse events

- Percentage of patients managed in a GP setting
- Persistence
- Compliance
- Duration of treatment effect.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B49 lists the key variables used in the base-case analysis of the model.

Table B49 Summary of parameters and assumptions applied in the base-case economic model

Variable	Value	Distribution (model range)	Reference
Age at treatment start (years)	70	Deterministic (55-75)	Section 6.2
T-score (SD)	≤ –2.50	Deterministic (–1.0 to –4.0)	Section 6.2
Proportion with previous vertebral fracture	0, 1	Deterministic (0-1)	Section 6.2
Discount rates for costs and effects	3.50%	Deterministic (0-6%)	Section 6.2
Treatment duration	5 years	Deterministic (5 years –lifetime)	Section 6.2
Modelling horizon	Lifetime	Deterministic (10years-lifetime)	Section 6.2
GIAE modelling oral therapies	2.35%	Deterministic	Section 6.4
Cellulitis modelling denosumab	0.3%	Deterministic	Section 6.4
Adjustment for missed fractures	No	Deterministic	Section 6.2
Persistence	No	Deterministic	Section 6.2
Compliance	No	Deterministic	Section 6.2
Number of DXA scans/year, all treatments	0.5	Deterministic	Section 6.2
Maximum offset time	1 year	Deterministic	Section 6.2
Utility			
Population utility	Age dependent	Deterministic	Section 6.4
Utility multiplier fracture	Fracture dependent	Beta	Section 6.4
Utility multiplier GIAE	0.91	Beta	Section 6.4
Utility multiplier cellulitis	0.82	Beta	Section 6.4
Costs			
Drug therapy costs	Therapy dependent	Deterministic	Section 6.5
BMD monitoring	£33	Gamma	Section 6.5
GP visit	£37	Deterministic	Section 6.5
GIAEs course H2 antagonists	£2.37	Deterministic	Section 6.5
Cellulitis hospital admission	£1,437	Lognormal	Section 6.5
Fracture HRG costs	Age dependent	Lognormal	Section 6.5
Nursing home costs per year	£25,269	Deterministic	Section 6.5

Variable	Value	Distribution (model range)	Reference
Fracture risk			
General population	Age dependent	Deterministic	Section 6.3
Relative risk fracture by BMD	Age/fracture dependent	Deterministic	Section 6.3
Relative risk fracture by prior fracture status	Age/fracture dependent	Deterministic	Section 6.3
Relative risk of fracture, all comparators vs placebo	meta-analysis	Lognormal	Section 5.7 [a] and 6.3.1[a]
Mortality post fracture	Age/fracture dependent	Deterministic	Section 6.3
Patients entering nursing home post-hip fracture	Age dependent	Deterministic	Section 6.3
Proportion of patients day case/admitted/surgery	Age independent	Dirichelet	Section 6.3

HRG, Healthcare Resource Groups; GIAE, gastrointestinal adverse event.

[a] Data sourced from meta-analyses – see Table B22 (section 5.7.6) PSA uses 95% CIs around HR

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

In the base-case, the life-time fracture risk for postmenopausal osteoporotic women is estimated based on epidemiological evidence (see sections 6.3.1 and 6.3.2). The relative risk of fracture for denosumab and other comparators versus no treatment was estimated from clinical trial data and meta-analyses versus no treatment (see section 5.7). It was assumed that the relative risk of fracture applied as soon as patients commenced therapy and remained constant over the modelled (5-year) treatment duration for persistent patients. RCT data was extrapolated over the modelled 5-year treatment period assuming that the RCT-reported relative risks of fracture versus no treatment remained constant. The treatment effect was modelled to return linearly to one following cessation of treatment, over the modelled offset period. In view of the limited available evidence in the base-case analysis, it has therefore been assumed that patients receive 1 year's treatment carry over effect. In the sensitivity analysis on persistence, a dynamic offset assumption capped at 1 year has been applied to patients who discontinue their treatment (see section 6.3.1).

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The economic analysis makes the following key assumptions:

- Osteoporosis results in an increased risk of fracture over and above the general population. Assumption reflects epidemiological data (Johnell et al., 2004; Marshall et al., 2005).
- Prior fragility fractures are associated with an increased risk of future fragility fracture for osteoporosis patients. Assumption reflects epidemiological data (Kanis et al., 2004a; Klotzbuecher et al., 2000).
- Osteoporosis treatment will reduce the risk of fragility fractures. Assumption reflects RCT data (see section 5.6)
- Patients will be treated with osteoporosis therapy over a 5-year period. Assumption consistent with previous NICE HTA analyses (Kanis et al., 2002a; Stevenson et al., 2007b; Stevenson et al., 2005a) .
- Osteoporosis treatments are associated with treatment offset or carry over equivalent to 1 year. Assumption in line with systematic review of the evidence (see section 6.3.1).
- 100% of patients will persist with therapy in the base-case analysis. This is a conservative assumption that will favour oral and frequently administered comparator therapies. A review of the literature suggests that patients may be at risk of dropping out of oral and frequently administered therapies. In a sensitivity analysis, a proportion of patients have been modelled to non-persist with treatment (Boston Collaborative Group, 2009) (see section 6.2.8).
- 100% of patients comply with therapy. This is a conservative assumption that will favour oral and frequently administered comparator therapies. A review of the literature suggests that poor compliers may be at risk of reduced treatment effect. Compliance assumption tested in sensitivity analysis (Siris et al., 2006; Caro et al., 2004) (see section 6.2.8).
- Vertebral fractures may be treated by a GP or in hospital. Other fracture types would be treated in hospital. Assumption-based estimate informed by expert clinical opinion.

- The fracture-specific hospitalisation cost will depend on whether the patient is treated as a day case, admitted to hospital (no surgery or admitted with surgery) and will be age dependent. This reflects NHS reference cost data.
- If a patient sustains a fracture, a fracture-specific reduction in utility is assigned. This reflects morbidity associated with fracture and estimates from current HRQL evidence (Johnell et al., 2004; Peasgood et al., 2009).
- Wrist fractures and other osteoporotic fractures are assumed only to have an impact on costs and HRQL during the first year after the event. This reflects current HRQL and cost evidence and is consistent with previous HTA economic analyses (Peasgood et al., 2009; Stevenson et al., 2005a; Stevenson et al., 2007a).
- Hip and vertebral fractures are assumed to have a direct impact on costs and quality of life during the first year after the fracture. Hip and vertebral fractures are assumed to have an ongoing utility penalty every year following the event. This reflects current HRQL and cost evidence and is consistent with previous HTA economic analyses (Peasgood et al., 2009; Stevenson et al., 2005a; Stevenson et al., 2007a).
- Patients are assumed to be at an increased risk of mortality following hip, vertebral and other fractures. This reflects current evidence on mortality following fracture (Abrahamsen et al., 2009; Barrett et al., 2003; Jalava et al., 2003; Johnell et al., 2004; Kanis et al., 2002a; Oden et al., 1998; Parker et al., 1999; Singer et al., 1998; Stevenson et al., 2007a; Stevenson et al., 2005a).
- Patients are at an elevated risk of entry into nursing home care following hip fracture. This reflects current UK evidence (Todd et al., 1999).
- Entry into nursing home care incurs a cost of £69 per day, reflecting current private nursing home care costs (£467 per week). This estimate reflects the most conservative weekly cost for nursing home care published in Personal and Social Services Research Unit (PSSRU) 2008 cost data and is consistent with cost estimates previously used for NICE TA160 and 161.
- Entry into nursing home does not result in a HRQL decrement. This is a conservative assumption consistent with assumptions previously applied for NICE TA160 and TA161.

- Patients using oral therapies are at increased risk of gastrointestinal adverse events and will incur a utility decrement and cost of treatment (a GP visit and a course of H2 antagonists). This assumption is consistent with previous NICE economic analyses for TA160 and TA161.
- Patients on denosumab are at risk of cellulitis, and a proportion of patients will incur a utility decrement and cost for hospital admission (Redekop et al., 2004; Department of Health, 2006). This was considered a conservative assumption included to demonstrate that inclusion of skin infections for denosumab would not result in important differences in ICER estimates.
- Patients are not modelled to be at an increased risk of venous thromboembolism, osteonecrosis of the jaw, infusion reactions, or other therapy-related adverse events. These side effects are rare, and inclusion would not be expected to result in substantial differences between therapies. This assumption is consistent with previous NICE economic analyses for TA160/161.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.
The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.
All parameters used to estimate cost-effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Osteoporosis is a chronic condition characterised by bone fragility resulting in bone fracture; bone fracture is associated with pain, reduced quality of life (NICE, 2008a) and increased mortality (Abrahamsen et al., 2009; Barrett et al., 2003; Jalava et al., 2003; Kanis et al., 2002a; Oden et al., 1998; Parker et al., 1999; Singer et al., 1998; Stevenson et al., 2007a; Stevenson et al., 2005a).

After a hip fracture, a high proportion of women are permanently unable to walk independently or to perform other activities of daily living and, consequently, many are unable to live independently. Hip fractures are also associated with increased mortality; estimates of the relative mortality risk vary from 2 to greater than 10 in the 12 months following hip fracture. However, it is unclear to what extent this can be attributed to fracture alone as opposed to pre-existing comorbidity (NICE, 2008a).

Vertebral fractures can be associated with curvature of the spine and loss of height and can result in pain, breathing difficulties, gastrointestinal problems and difficulties in performing activities of daily living. It is thought that the majority of vertebral fractures (50%-70%) do not come to clinical attention. Vertebral fractures are also associated with increased mortality; UK-specific data indicate a 4.4-fold increase in mortality related to vertebral fractures. However, as with hip fractures, it is unclear to what extent this may be due to comorbidities (NICE, 2008a).

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Osteoporosis is an asymptomatic disease until a fragility fracture occurs. Following a fragility fracture, patients will suffer a reduction in HRQL during the initial post-fracture period, and the reduction in HRQL may continue in the long term according to the fracture type (Peasgood et al., 2009).

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation
- Method of valuation
- Point when measurements were made
- Consistency with reference case
- Appropriateness for cost-effectiveness analysis
- Results with confidence intervals.

The EQ-5D questionnaire was administered to patients at baseline and every 6 months for the 3-year study duration participating in the FREEDOM denosumab trial in women with postmenopausal osteoporosis. The EQ-5D has been widely used in patient populations, including women with osteoporosis, and is consistent with the NICE reference case. It is noted that the schedule of administration of the EQ-5D in FREEDOM did not allow for measurement of health status immediately after the fracture event. Moreover, the number of fracture events with associated EQ-5D scores recorded in the FREEDOM trial was low. In view of these limitations with the FREEDOM trial data, evidence from the systematic review of the HRQL literature in osteoporosis was considered to be more reliable that the data provided by FREEDOM and was therefore applied in the economic analysis.

Statistically significant differences in HRQL between treatment groups were not demonstrated. Incident fractures were shown to be associated with poorer HRQL (see Table B50). When the impact of fractures on HRQL was assessed using the EQ-5D, subjects with any incident fractures experienced greater diminutions in EQ-5D health index scores and visual analogue scale (VAS) scores compared to those without fracture (see Table B51).

Table B50 [redacted]

[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

[redacted]

[redacted]

Table B51 Change in EQ-5D health state index score utility from baseline to visit following fracture (combined data set both treatment arms) in the FREEDOM clinical trial

Description	n	Mean	SD	Min	Q1	Median	Q3	Max
[redacted]								
[redacted]								

*Comparison Between Subjects With New Vertebral Fracture and Comparator Group of Subjects Without Fracture
EQ-5D change from baseline to the visit following the first new vertebral fracture was included for each subject with new vertebral fracture regardless of trauma severity; for each subject with new vertebral fracture, at most 3 subjects who have similar baseline characteristics and have no fracture at or before the corresponding visit were randomly selected as the comparator group.
Only includes the first new vertebral fracture that has no preceding clinical fractures during the study.
n = Number of subjects with new vertebral fractures regardless of trauma severity or number of subjects without any fractures in the comparator group from the many-to-one matching algorithm.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D
- Details of the methodology used
- Details of validation of the mapping technique.

Appropriate EQ-5D data were identified from secondary sources. Hence, mapping from one instrument to another was not undertaken in the current model.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 12, section 9.12.

A systematic review of the HRQL data was undertaken in Medline, Medline (R) In-Process, Embase, NHS Economic Evaluation Database (NHS EED) and EconLIT. The review was designed to identify quality of life studies that reported the utility associated with minimal/low/non-pathological trauma hip, vertebral (clinical and symptomatic), wrist and other fracture. Full details of the systematic review methods and results have been detailed in appendix 12, section 9.12.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

The approach taken with HRQL was to apply a series of utility 'multipliers' to a set of age-specific baseline utilities taken from UK populations norms.

To identify appropriate parameters, a literature review of HRQL studies was undertaken. Full details of the literature-review methods and results are reported in section 9.12 (appendix 12). In summary, 27 studies of potential interest were identified: one study elicited HRQL utility values using standard gamble methods (SG); three studies using time trade off (TTO); 11 studies using VAS (all except one of the studies that reported VAS also used another instrument); and 26 studies using multi-attribute utility instruments (MAUI). In the last of these categories, 21 used EQ-5D, two used Health Utilities Index (HUI) 2, one used HUI 3 and two used the Quality of Wellbeing (QWB) scale.

A systematic review and meta-analysis of HRQL utility values for osteoporosis-related conditions was also recently published by Peasgood et al. (2009). The inclusion criteria for studies within the review were similar to those used in this published review, although Peasgood et al. (2009) included a total of 28 studies (not all of these studies contributed to the final meta-analysis). The Peasgood et al. (2009) review identified five studies not included in the current review, although none of these references was used as a source of utility values for the meta-analyses by Peasgood et al. (2009). One study article included in the Peasgood et al. (2009) review was excluded from this review because it was available only in Spanish. Four other studies were excluded because they did not report utility values after a low trauma fracture. Four additional studies were identified by the current review. The first study by Ström et al. (2008b) had been referred to in the text of Peasgood et al. (2009) and shared data with another included study (Borgstrom et al., 2006a), but reported a longer follow-up period. The remaining studies was published in 2008 and 2009 and therefore appeared to have been outside the date range of the Peasgood review (Suzuki et al., 2008; Hagino et al, 2009 and Sugeno et al, 2008).

Hip fracture

The systematic review of the literature identified five studies that reported EQ-5D utility values after an osteoporotic hip fracture, provided sufficient information and met the quality assessment criteria for a meta-analysis. These studies were

Blomfeldt et al., 2005; Borgstrom et al., 2006a; Ström et al., 2008b; Murray et al., 2002; Soderqvist et al., 2006; and Tidermark et al., 2002. This evidence is consistent with that in the systematic review by Peasgood et al. (2009). Given this consistency, the utility values and utility losses associated with hip fracture were estimated from meta-analyses reported by Peasgood et al. (2009). Peasgood et al. (2009) reported a utility multiplier of 0.70 for the first year post fracture and 0.80 for second and subsequent years; these data are summarised in Table B52. It has been assumed that HRQL losses post fracture continue over the remainder of the patient's lifetime.

Table B52 HRQL (utility) multipliers relating to hip fracture based on Peasgood et al., 2009

Osteoporosis health state	Mean utility multiplier (95% CI)	Studies contributing data
Utility multipliers first year	0.70 (0.64-0.77)	Blomfeldt et al. (2005) Borgstrom F. et al. (2006a) Murray et al. (2002) Soderqvist et al. (2006) Tidermark et al. (2002)
Utility multipliers second year	0.80 (0.68-0.96)	Blomfeldt et al. (2005) Murray et al. (2002) Tidermark et al. (2002)

Clinical vertebral fracture

The systematic review of the literature did not distinguish between clinical vertebral fracture and morphometric vertebral fracture studies. However, this distinction was important for utility values appropriate for the current economic analysis. The conclusions of this review were therefore considered in the context of the current model. The systematic literature review indicated that the study by Borgstrom et al. (2006a) provided the most reliable EQ-5D values for the utility loss associated with the first year following a vertebral fracture; this conclusion was also reached by Peasgood et al. (2009). The study by Borgstrom et al, 2006a was in a hospitalised clinical vertebral fracture cohort, Ström et al. (2008b) published updated estimates based on the same dataset as Borgstrom et al. (2006a) and provided HRQL data for the second year post clinical vertebral fracture from Ström et al (2008b), based on extrapolation of 18-month data from Borgstrom et al. (2006a). The values applied for the first, second and subsequent years for hospitalised clinical vertebral fractures have therefore been modelled to be equivalent to those reported in the updated study by Ström et al. (2008b).

It is acknowledged that Borgstrom et al. (2006a) (and Ström et al., 2008b) assessed HRQL of patients attending hospital with clinical vertebral fractures (72% patients admitted). In the economic models for NICE TA160 and 161, the Appraisal Committee noted that a utility estimate for vertebral fractures from a hospitalised cohort was likely to overestimate the disutility for non-hospitalised patients and would, therefore, be unlikely to reflect an average clinical vertebral fracture cohort that would also include those patients who did not attend hospital, but were managed in a GP setting. In the current model, therefore, it has been assumed that, in the first and subsequent years following fracture, only patients attending hospital with clinical vertebral fractures incur the utility decrement for the first and second years suggested by Borgstrom et al. (2006a) and Ström et al. (2008b). Utility estimates for both the first and subsequent years post fracture were modelled on values that assumed the 4-month quality of life estimate was reached after a 1-month period. This is a more conservative assumption than taken in the meta-analysis by Peasgood et al. (2009), which reported utility multipliers based on 1-year values derived by simple linear interpolation (see Table B53). The remaining patients were assumed to be managed in a GP setting and modelled to incur a lower utility decrement.

No evidence was identified in current literature for the HRQL of patients with non-hospitalised clinical vertebral fractures (fractures managed in a GP setting). Three studies provided HRQL estimated using UK EQ-5D tariffs for morphometric fracture populations (Van Schoor et al., 2005; Oleksik et al., 2000; and Cockerill et al., 2004). Van Schoor et al. (2005) examined patients with vertebral deformities, osteoarthritis and other chronic diseases. Consequently, this study did not measure HRQL in a purely osteoporotic population. Cockerill et al. (2004) examined the HRQL of morphometric fractures in patients recruited from population registers. Patients were radiologically assessed at baseline and then at a subsequent follow up visit. Follow-up visits occurred at a median time of 3.8 years after the initial visit; HRQL questionnaires were then administered at a median time of 1.9 years after the second follow-up visit. These estimates consequently reflected the HRQL of fracture patients that occurred on average at least 1.9 years post fracture. Oleksik et al. (2000) measured HRQL in PMO women with prevalent vertebral fractures as part of

the baseline assessment of the Multiple Outcomes of Raloxifene Evaluation (MORE) study. The estimates from Oleksik et al. (2000) were considered to offer the most reliable estimates for first year post fracture, and estimates from Cockerill et al. (2004) were applied for the second and subsequent years following fracture (see Table B53). It is noted that the estimates provided by both of these studies were based on prevalent morphometric fracture populations rather than clinical fracture populations. The estimates from these studies may consequently underestimate the utility loss associated with clinical vertebral fractures managed in a GP setting, and it is therefore anticipated that the HRQL loss associated with clinical vertebral fracture will be a conservative estimate.

Data from the literature indicates that between 2% and 35% of patients with clinical vertebral fractures may be admitted into hospital in the UK (Cooper et al., 1993; Finnern et al., 2003; Stevenson et al., 2006b). This evidence, however, was considered to be of particularly poor quality. The proportion of clinical vertebral fracture patients managed in a hospital versus GP setting has, therefore, been estimated using the modelled clinical vertebral fracture predictions and Hospital Episodes Statistics (HES) data for the proportion of patients hospitalised with vertebral fracture. Clinical fracture incidence by age was estimated in the current model using data from Singer et al. (1998) and Kanis et al. (2000). English population data for each age group were then applied to estimate the total number of fractures for women over 60 years of age in England. These data were compared to the number of HES finished consultant episodes for women aged 60+ (i.e., hospital admissions in England) for vertebral fractures for the ICD diagnosis codes (S12, S22, S32, T02, T08). These methods suggested that 80% (26,614/33,160) of patients would be managed (diagnosed and treated) purely in a GP setting, and 20% (6,546/33,160) of patients would be managed (diagnosed/initially treated) in hospital. Consequently, it has been assumed that 20% of patients are managed in a hospital setting. In the base-case model, 20% of patients have, therefore, been modelled to relate to the utility data from Ström et al. (2008b) and 80% the value from Oleksik et al. (2000) and Cockerill et al. (2004), see Table B53.

Table B53 Utility multipliers for vertebral fracture

Osteoporosis health state	Utility value (95% CI)	Studies contributing data
Hospitalised patients		
Utility multipliers 1st Year	0.65 *(0.51- 0.73)	Ström et al. (2008) assuming 4-month QoL reached in 1 month
Utility multipliers 2nd Year+	0.73 *(0.62-0.82)	Ström et al. (2008b)
Non-hospitalised patients		
Utility multipliers 1st Year	0.91 (n/r)	Oleksik et al. (2000)
Utility multipliers 2nd Year+	0.99 (n/r)	Cockerill et al. (2004)

Notes
*Calculated from confidence interval reported for utility loss

Wrist fracture

The systematic review of the literature suggests that estimates provided Borgstrom et al. (2006a) (updated estimates provided in the study by Ström et al, 2008) offered the most reliable utility data for the first year following wrist fracture (see section 9.12, appendix 12). The values applied for second and subsequent years for hospitalised clinical vertebral fractures have therefore been modelled to be equivalent to those reported by Ström et al, 2008. The study reported by Dolan et al. (1999) was also included in the meta-analysis by Peasgood et al. (2009), however, this study had no pre-fracture values and a short follow-up period (48 days on average) after the initial visit to a follow-up treatment clinic, and was, therefore, considered inappropriate for inclusion. The values from Ström et al. (2008b) are detailed in Table B54 (assuming the 4-month HRQL was reached after a 1-month period). It was assumed that, after the first year post fracture, HRQL returned to baseline values.

Table B54 Utility values for wrist fracture Ström et al., 2008b

Time since fracture	Utility multiplier (95% CI)	Studies contributing data
Utility multiplier	0.934 *(0.911-0.956)	Ström et al. (2008) assuming 4-month QoL reached in 1 month

Notes
*Calculated from confidence interval reported for utility loss

Other fracture

The literature review did not identify HRQL values associated with other fracture types, and consequently, utility multipliers for wrist fracture have also been applied to patients experiencing other fracture types (pelvis, femur, rib, clavicle, sternum, scapula, tibia and fibula). These fractures are likely to incur a more substantial utility

loss than wrist fracture. Hence, it is noted that this offers a conservative approach, and the model is likely to underestimate the utility loss associated with other fracture types. It was assumed that after the first year post fracture, HRQL returned to baseline as per wrist fracture.

Osteoporosis without fracture

The systematic review of the utility literature indicated that osteoporosis without a fracture was associated with no utility loss (section 9.12, appendix 12). General UK population tariff utility values for women by age estimated using EQ-5D scores were consequently applied (Kind et al., 1998) (see Table B55).

Table B55 Utility values no fracture

Age	Utility
50	0.82
65	0.78
75	0.72
85	0.69

Nursing home residents

No reliable preference based utility value associated with becoming a nursing home resident was found in the reviewed literature. The National Osteoporosis Foundation review suggested a utility multiplier of 0.4 for nursing home residents based on the judgement of a panel of experts (National Osteoporosis Foundation, 1998). This value was not applied in the base-case analysis since it is considerably lower than the values identified for post-fracture health states in this review. No utility decrement was modelled for entry into a nursing home. This is considered a conservative assumption likely to underestimate the potential utility loss associated with hip fracture.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Given the small number of fracture events with associated EQ-5D scores recorded in FREEDOM it is difficult to make meaningful comparisons with the literature. Moreover, the schedule of administration of the EQ-5D in FREEDOM did not allow for measurement of health status immediately after the fracture event.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

The utility loss associated with gastrointestinal adverse event (GIAEs) requiring a GP consultation has been assumed to replicate 'abdominal symptoms once a day that is not always resolved with medication, certain foods, drinks and pain relievers may need to be avoided, wake up in the night once a week, and often feel anxious'. This has a time trade-off value of 0.91 in Groeneveld et al. (2001). These symptoms are assumed to last a full month. The disutility associated with GIAEs was applied only to persistent patients. These assumptions are consistent with those previously applied in NICE TA160/161.

A search of the Centre for Evaluation of Value and Risk in Health (CEA) Registry for utility values that could potentially be used for cellulitis did not identify any studies specifically reporting utility for cellulitis. Utility values were consequently estimated from a study by Redekop et al. (2004) that reported EQ-5D utility values for diabetic foot ulcers. Cellulitis is a common complication of foot ulcers, although in the absence of a foot ulcer, the utility loss would be expected to be smaller. The multiplier was assumed to be equivalent to patients with an infected ulcer (no amputation) and was estimated as 0.82 (0.79-0.85). This disutility value was applied for a 1-month period, consistent with GIAE assumptions, although it is noted that clinical opinion indicated that this was likely to overestimate the time patients suffered a reduction in QoL due to cellulitis. The application of this utility value was, therefore, considered to be a conservative assumption that would favour alternative comparators versus denosumab.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B56 summarises the quality-of-life values for cost-effectiveness analysis.

Table B56 Summary of quality-of-life values for cost-effectiveness analysis

State	Mean utility	Confidence interval	Justification
Well 50 years 60 years 70 years 80 years +	 0.82 0.78 0.72 0.69	 n/r n/r n/r n/r	General population EQ-5D tariff values for the UK. Systematic review of the literature indicated no utility loss for osteoporosis without fracture.
	Utility multiplier	**Confidence interval**	**Justification**
Hip fracture year 1	0.70	0.64-0.77	The systematic review of the literature concluded that pooled EQ-5D data reported in Peasgood et al. (2009,) were appropriate to estimate HRQL for hip fracture patients year 1 and years 2+.
Hip fracture year 2-5	0.80	0.68-0.96	
Vertebral fracture year 1 Hospitalised patients Non-hospitalised patients	 0.64 0.91	 *0.57-0.73 n/r	Estimates taken from Borgstrom et al. (2006), and Ström et al. (2008b) identified as most appropriate source of data for hospitalised clinical vertebral patients in the systematic review of literature. Oleksik et al. (2000) identified as most appropriate data source for non-hospitalised patients. Estimates from Cockerill et al. (2004) applied for years 2+ non-hospitalised patients.
Vertebral fracture year 2-5 Hospitalised patients Non-hospitalised patients	 0.73 0.99	 *0.62-0.82 n/r	
Wrist fracture	0.934	*0.911-0.956	Estimates taken from pooled analysis Ström et al. (2008) EQ-5D data for wrist fracture patients assuming 4-month utility reached after one month.
Other fracture	0.934	*0.911-0.956	Utility values for other fractures poorly or unreported. Wrist fracture utility values applied as a conservative estimate.
Dead	0	-	Utility assumed to be measured on a 0-1 scale where 0 = death
GIAEs	0.91	0.87–0.96	Groeneveld (2001) Previously employed in NICE HTA reviews. Applied for consistency
Cellulitis	0.82	0.79-0.85	Redekop et al, 2004 – assumption that utility multiplier equivalent to patients with leg ulcers

*Calculated from Strom et al, 2008 using confidence interval for utility loss.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical expert opinion was used to provide general feedback on the appropriate approach for HRQL data in a face to face meeting (see section 6.3.5). In this meeting, NICE methods previously applied for HRQL were discussed. It was noted that in TA160/161(NICE, 2008b; NICE, 2008a), data from Kanis et al. (2004b) was employed, although the utility multiplier for clinical vertebral fractures was increased in year one to be equivalent to hip fracture (0.792) since estimates were from an inpatient population and considered to be overstated by the Appraisal Committee. Clinical opinion suggested assuming an equivalent disutility for hip and vertebral fractures did not represent the difference in clinical events. All parties agreed using updated estimates from a recent systematic review would be appropriate with potential sensitivity analyses using previous NICE inputs.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Patients with hip, vertebral, wrist and other fractures have been modelled to incur a utility loss in the first year. Patients with wrist or other fractures are assumed to return to the well state and accrue utility as per population tariffs for the second and subsequent years. Patients with hip and vertebral fractures remain in the post-hip and post-vertebral health states, respectively, and incur an ongoing utility loss for the second and subsequent years.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Therapy related adverse events (TRAEs) associated with BPs and strontium include an excess rate of GIAEs and osteonecrosis of the jaw. Other TRAEs associated with strontium include an excess rate of allergic reactions and venous thromboembolism (VTE). Therapy-related adverse events associated with raloxifene include hot flushes, VTE and heart disease, whilst those associated with zoledronate include flu symptoms, atrial fibrillation, osteonecrosis of the jaw; and those associated with ibandronate include flu symptoms, rash, and osteonecrosis of the jaw. Therapy-related adverse events associated with teriparatide include nausea, limb pain, headache and dizziness (National Osteoporosis Society, 2009). However, only GIAEs were included in the economic analysis BPs and strontium, in line with previous economic models included in the NICE analyses for TA160 and 161. This is considered a conservative approach that will favour BPs and strontium versus denosumab.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life reflected age-specific female UK general population utility tariffs. Population utility tariffs were not adjusted to adjust for the potential inclusion of fracture patients in the sample population. It is acknowledged that this may result in some minor underestimation of utility values.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The utility loss associated with fracture is assumed to be greatest in the first year following fracture, with a lower ongoing fracture utility loss modelled for the second and subsequent years for vertebral and hip fracture patients. No ongoing utility loss was assumed for wrist or other fracture patients.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values in sections 6.4.3 to 6.4.8 have not been amended. Utility multipliers have been used in the analysis. Multipliers were applied because evidence suggests that the utility loss associated with fracture is multiplicative and varies according to baseline utility tariffs (Peasgood et al., 2009).

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.
All parameters used to estimate cost-effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Osteoporosis is a chronic condition characterised by bone fragility resulting in bone fracture. Therefore, costs incurred by the NHS for osteoporosis include drug therapies designed to prevent bone loss and fracture management for patients who incur a fragility fracture.

Therapy management

NHS costs for osteoporosis drug therapy management include:

- Initial screening/ GP assessment
- Bone mineral density measurement
- Pharmaceutical therapies

- Drug administration for iv therapies
- Ongoing monitoring (e.g., subsequent GP visits and BMD measurement).

Drug therapy costs have been estimated using the most recent prices from the British National Formulary (BNF) (BMJ Group, 2009) (see section 6.5.5). Cost data has been sourced from the National Schedule of Reference Costs 2007-08 - NHS Trusts and Primary Care Trusts (PCTs) combined schedule (Department of Health, 2006) and the Unit Costs of Personal and Social Services Resource Use 2008 (Curtis, 2008).

It has been assumed that iv therapy administration and bone mineral density (BMD) measurement would be undertaken in a hospital setting. NHS reference costs were, therefore, identified for iv drug administration and BMD measurement. The NHS Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures report (NHS, 2008) indicated the procedure code for administration of zoledronate was X72.3, which maps to HRG codes SB12Z and SB15Z (administration of simple iv chemotherapy agent first and subsequent attendance). In the absence of a general HRG code for iv administration, SB12Z and SB15Z were applied for administration of both iv therapies (zoledronate, ibandronate); as documented below, the administration cost for ibandronate is examined in a sensitivity analysis. The NHS reference cost for a DXA scan (RA15Z) was used for BMD measurement. A HRG for high-cost bone metabolism drugs was identified during a scoping search of NHS reference costs for the procurement and administration of teriparatide. However, BNF costs were used to estimate drug costs for teriparatide in order to be consistent across therapies.

Osteoporotic fracture treatment

It has been assumed that fragility fracture patients (except morphometric vertebral) are treated in a hospital setting. Patients with clinical vertebral fractures have been assumed to be treated in either a GP or hospital setting with a proportion of patients modelled to incur costs only for GP management.

Data from the literature indicates that between 2% and 35% patients with clinical vertebral fractures may be admitted into hospital in the UK (Cooper et al., 1993; Finneren et al., 2003; Stevenson et al, 2006b). However, this evidence was

considered of particularly poor quality as the methods were not adequately described. The fracture incidence modelled for the current analysis and HES data on the number of hospitalised vertebral fractures have, therefore, been used to estimate the proportion of vertebral fractures managed in a GP versus a hospital setting. It has consequently been assumed that 80% of clinically identified vertebral fractures are managed in a GP setting and 20% of patients are treated in hospital (see section 6.4.6). Of the 20% of patients attending hospital, it is assumed 29% are treated as a day case and discharged and 71% are admitted for inpatient care. The latter estimate was taken from the ratio of finished consultant episodes and admissions as reported in HES 2005 data for patients over the age of 60 treated in UK hospitals with ICD diagnosis codes for vertebral fractures.

The literature review of costs identified one UK cost study based on data from the general practice research database (GPRD). This reported excess costs associated with vertebral fracture diagnosis (Puffer et al., 2004; see section 9.13, appendix 13). Costs for GP management were, therefore, assumed to include medication costs for pain (co-codamol/paracetamol 30/500) and an excess of GP visits (4.69 additional visits per year) and outpatient referrals (0.51 additional referrals per year) as reported by Puffer et al. (2004).

Fracture patients treated in a hospital setting are assumed to be treated as a day case, or admitted with or without a surgical procedure. NHS reference costs for each of the following components have therefore been identified:

- Adverse event assessment
- Fracture treatment
  - Day case
  - Admitted no surgery
  - Admitted with surgery
- Outpatient management

The proportion of patients treated as a day case, admitted without surgery and admitted with surgery would depend on the severity of the fracture and individual patient characteristics (British Orthopaedic Association, 2007). It has been assumed

that all patients with hip fracture (neck of femur) undergo surgery as per British Orthopaedic Association (BOA) blue book (British Orthopaedic Association, 2007) guidelines. Vertebral fracture patients have been assumed to undergo conservative treatment (no surgery) as per expert clinical opinion (personal communication Professor Compston, September 2009). Two studies identified in the cost literature search (see section 9.13, appendix 13) reported the mean percentage of patients admitted to hospital following non-hip, non-vertebral fracture (Stevenson et al., 2006c; Bouee et al., 2006). The study by Bouee et al. (2006) reported inpatient admission rates for 112 patients from two prospective RCTs. Stevenson et al. (2006c) referenced inpatient admission rates to two previous studies, although study methods were difficult to ascertain. Only Bouee et al. (2006) additionally reported the percentage of patients treated with and without surgery for non-hip and non-vertebral fractures and, consequently, in the base-case analysis, wrist and other fractures have been modelled using data from Bouee et al. (2006) (see Table B61 and Table B62). Data from Stevenson et al. (2006b) were applied in a sensitivity analysis (with estimates for the percentage of inpatients receiving surgery taken from expert opinion, personal communication Professor Compston, October 2009) (see Table B62).

Assessment and diagnosis

NHS reference costs for adverse event assessment have been estimated from HRG code VB09Z, Category 1 investigation with Category 1-2 treatment for all fracture types, selected according to the treatment category codes associated with fracture.

Fracture treatment: day case and admitted without surgery

Patients admitted to hospital without surgery were assumed to be treated as either a day case or admitted for a longer length of stay (LoS). Costs for day case patients were based on Non-Elective Inpatient (Short Stay) NHS reference cost data, whilst costs for admitted patients were based on Non-Elective Inpatient (Long Stay) data. The details of all selected reference costs have been documented in section 9.13 (appendix 13).

A review of ICD 10 codes under HRG4 chapter listings (Department of Health, 2006) was undertaken to identify HRG codes relating to fracture diagnosis without surgical

procedure. HRG codes HD36A, B and C (pathological fracture or malignancy of bone and connective tissues) included ICD diagnosis codes for osteoporotic fractures of the shoulder, upper arm, forearm, pelvis, lower leg, ankle and other fracture sites in postmenopausal women. It was, therefore, assumed that fractures of the pelvis, rib, sternum, clavicle, scapula, humerus, tibia and fibula were associated with HD36 A, B or C. The choice between A, B or C (major complications, with complications and without complications respectively) was selected by comparing the mean LoS by fracture type reported in Hospital Episode Statistics (HES) year 2005/2006 (NHS, 2009), for the latest statistics by age at date of access, compared to the mean LoS associated with each HRG. The NHS reference cost selected therefore differed for patients aged 60-74 and 75+ (see section 9.13, appendix 13).

ICD diagnosis codes for vertebral and femur (or upper limb) fractures were not included in HD36. Vertebral fracture ICD diagnosis codes were found under a number of HRGs (HC20, HC22, HC24, HC91Z and HC92Z). However, HC20 (vertebral column injury without procedure) included fracture-related ICD codes for fatigue fracture (M48), as well as other vertebral fracture types, and was therefore considered the most appropriate HRG for osteoporosis patients with vertebral fracture and no surgical procedure. UK HES data indicated that the average LoS for fractures of the spine (S32, S12, S22) was 15.2 days and 22.5 days for women aged 60-74 and 75+, respectively (2005/2006) (see section 9.13, appendix 13). Hence HC20A was selected (vertebral column injury with major complications). ICD diagnosis codes for femur fractures without a procedure appeared only in one HRG, HA91Z (hip trauma diagnosis without procedure), and this code was therefore applied.

An excess bed day charge was applied to all fractures with HES reported mean LoS (NHS, 2009) more than 2 days greater than that of the mean. The excess bed day charge was assumed to reflect the patient population (elderly and very elderly osteoporotic patients) and was estimated using Non-Elective Inpatient (Long Stay) excess bed day data (Department of Health, 2006). The 2-day margin was chosen to allow for some discrepancy between average HRG estimates and HES reported mean LoS, and was considered a conservative approach since this is likely to result in lower cost estimates for some fracture sites.

Fracture treatment: Inpatient with surgery

A review of OPCS codes under HRG4 chapter listings (Casemix service NHS, 2008; NHS, 2008) was undertaken to ascertain HRG codes with orthopaedic procedures relating to different fracture types. Orthopaedic procedural codes for all fractures were selected according to the fracture location and then validated against HES reported LoS for patients aged 60-74 and 75+ by fracture type (2005/2006)(NHS, 2009) (see section 9.13 (appendix 13)..

UK hospital episode statistics (HES) indicated that the average LoS for neck of femur fractures (S720) was 19.2 days and 26.4 days for women aged 60-74 years and 75+ years, respectively, in 2005/2006 (NHS, 2009). In the absence of evidence on the proportion of patients likely to undergo major, intermediate or minor hip procedures, the OPCS code for intermediate hip procedures for trauma with major complications (HA13A) was selected. HA13A includes primary open and closed reduction of fracture and fixation of fractures using internal and external methods; the LoS reported for this HRG was validated with HES reported LoS for hip fracture in elderly patients. It is acknowledged that other codes could have been applied. Alternative codes may have included major hip procedures, minor hip procedures (HA12 or HA14) or hip replacement (HA11). However, data on the proportions of patients likely to undergo different procedures were not identified in our literature review; hence, a single HRG code was applied. Applying the code for intermediate hip procedures was considered a conservative approach.

Similar reviews were undertaken to select appropriate NHS reference costs for other fracture types. Major extradural spine category 1 with major complications (HC02B) was considered to offer the best reference cost for procedures resulting from a vertebral fracture. Femur and pelvis fractures were assumed to relate to the same HRG code as hip fracture (HA13A). Lower limb fractures (fibula, tibia) were assumed to relate to Major Knee Procedures Category 1 for Trauma with CC (this HRG included ICD codes for procedures on long bones, as well as knee- associated procedures). Arm and shoulder fractures (clavicle, scapula, humerus, forearm) were assumed to be included in Major Arm Procedures Category 1 for Trauma with CC (HA42B) in the absence of any other arm- or shoulder-related surgical procedure HRGs with NHS cost reference data.

Outpatient expenses

The cost for outpatient managed hip fracture was estimated as an NHS cost for hip fracture rehabilitation based on HRG VC02 and VC16Z. NHS reference costs for other fractures were based on HRG T110 (Trauma and orthopaedic first attendance and follow-up attendance). Outpatient attendance was estimated to be 2.9 visits per fracture episode for all fractures estimated from HES statistics for outpatient activity associated with T110. It is noted that HES data are unreliable for outpatient attendances, and this estimate was corroborated using clinical expert opinion (personal communication Professor Compston, September 2009). The same outpatient assumptions (rates and unit costs) were assumed for all fracture patients, including those treated as day case and inpatient with and without surgery, as well as the number of rehabilitation visits following hip fracture in the absence of an alternative preferable estimate identified in the cost literature review.

Total average fracture costs

Total average fracture costs were estimated per fracture type using a weighted proportion of patients treated in general practice and in a hospital setting (day case, admitted without surgery and admitted with surgery). Costs for accident and emergency assessment and outpatients were included for all patients treated in hospital. All costs were indexed to a 2009 cost year using the health component of the UK consumer price index (CPI) (UK National Statistics, 2009). An annual discount rate of 3.5% was used for both costs and effects as per current NICE recommendations.

Table B57 Total fracture costs for postmenopausal women aged 60-74 years

Fracture site	% of patients treated by GP	Cost of GP management per patient	Total average cost per patient. GP managed fracture	% of patients treated as hospital day case	Total average cost per patient treated as a day case	% of patients hospital admission no procedure	Total average cost per patient fracture admission no procedure	% of patients with admission surgical procedure	Total cost per patient fractures with admission and surgical procedure	Average weighted LoS for admitted patients	HES reported LoS women aged 60-64	Excess bed days	Average weighted excess bed day charge (per day)	Total fracture costs women aged 60-64
Hip	0%	£0	£0	0%	£0	0%	£0	100%	£8,217	20.27	19.20	0.00	£228	£9,165
Spine	80%	£259.89	£209	6%	£32	14%	£600	0%	£0	14.71	15.15	0.00	£34	£1,318
Forearm	0%	£0	£0	44%	£211	44%	£1,090	12%	£593	7.12	3.40	0.00	£167	£2,311
Other fracture														
Femur	0%	£0	£0	44%	£239	44%	£1,697	12%	£1,002	15.47	26.63	11.16	£109	£4,604
Pelvis	0%	£0	£0	44%	£224	36%	£1,342	20%	£1,660	15.96	15.54	0.00	£114	£3,658
Ribs	0%	£0	£0	20%	£96	80%	£1,989	0%	£0	6.88	8.50	0.00	£250	£2,617
Sternum	0%	£0	£0	65%	£312	23%	£559	13%	£619	8.04	8.50	0.00	£100	£1,806
Scapula	0%	£0	£0	65%	£312	23%	£559	13%	£613	7.27	8.00	0.00	£101	£1,799
Clavicle	0%	£0	£0	65%	£312	23%	£559	13%	£613	7.27	8.00	0.00	£101	£1,799
Humerus	0%	£0	£0	44%	£211	44%	£1,090	12%	£593	7.12	8.00	0.00	£167	£2,311
Tibia	0%	£0	£0	44%	£209	44%	£1,189	12%	£703	9.96	11.70	0.00	£122	£2,514
Fibula	0%	£0	£0	44%	£209	44%	£1,189	12%	£703	9.96	11.70	0.00	£122	£2,514

Source: data from Bouee et al., 2006.

Table B58 Total fracture costs for postmenopausal women aged 75 years plus

Fracture site	% of patients treated by GP	Cost of GP management per patient	Total average cost per patient. GP managed fracture	% of patients treated as hospital day case	Total average cost per patient treated as a day case	% of patients hospital admission no procedure	Total average cost per patient fracture admission no procedure	% of patients with admission surgical procedure	Total cost per patient fractures with admission and surgical procedure	Average weighted LoS for admitted patients	HES reported LoS women aged 60-64	Excess bed days	Average weighted excess bed day charge (per day)	Total fracture costs women aged 60-64
Hip	0%	£0	£0	0%	£0	0%	£0	100%	£8,217	20.27	26.40	6.13	£228	£10,560
Spine	80%	£260	£209	6%	£32	14%	£600	0%	£0	14.71	22.51	7.79	£34	£1,581
Forearm	0%	£0	£0	44%	£209	44%	£1,090	12%	£593	7.12	9.90	2.78	£167	£2,771
Other fracture														
Femur	0%	£0	£0	44%	£239	44%	£1,697	12%	£1,002	15.47	36.51	21.04	£109	£5,678
Pelvis	0%	£0	£0	44%	£224	36%	£1,342	20%	£1,660	15.96	20.38	4.42	£114	£4,161
Ribs	0%	£0	£0	20%	£101	80%	£2,994	0%	£0	13.53	15.10	0.00	£151	£3,651
Sternum	0%	£0	£0	65%	£331	23%	£841	13%	£619	12.31	15.10	2.79	£72	£2,319
Scapula	0%	£0	£0	65%	£331	23%	£841	13%	£613	11.54	16.60	5.06	£74	£2,483
Clavicle	0%	£0	£0	65%	£331	23%	£841	13%	£613	11.54	16.60	5.06	£74	£2,483
Humerus	0%	£0	£0	44%	£224	44%	£1,641	12%	£593	12.32	16.60	4.28	£167	£3,606
Tibia	0%	£0	£0	44%	£224	44%	£1,641	12%	£703	13.38	25.10	11.72	£122	£4,435
Fibula	0%	£0	£0	44%	£224	44%	£1,641	12%	£703	13.38	25.10	11.72	£122	£4,435

Source: data from Bouee et al., 2006.

Table B59 Total fracture costs for postmenopausal women aged 60-74 years

Fracture site	% of patients treated by GP	Cost of GP management per patient	Total average cost per patient. GP managed fracture	% of patients treated as hospital day case	Total average cost per patient treated as a day case	% of patients hospital admission no procedure	Total average cost per patient fracture admission no procedure	% of patients with admission surgical procedure	Total cost per patient fractures with admission and surgical procedure	Average weighted LoS for admitted patients	HES reported LoS women aged 60-64	Excess bed days	Average weighted excess bed day charge (per day)	Total acute care costs, including excess bed days
Hip	0%	£0	£0	0%	£0	0%	£0	100%	£8,217	20.27	19.20	0.00	£228	£9,165
Spine	80%	£259.89	£209	6%	£32	14%	£600	0%	£0	14.71	15.15	0.00	£34	£1,318
Forearm	0%	£0	£0	75%	£361	21%	£528	4%	£182	7.04	3.40	0.00	£76	£1,338
Other fracture														
Femur	0%	£0	£0	0%	£0	20%	£773	80%	£6,574	19.04	26.63	7.59	£219	£9,699
Pelvis	0%	£0	£0	0%	£0	95%	£3,551	5%	£411	13.87	15.54	0.00	£190	£4,619
Ribs	0%	£0	£0	93%	£447	7%	£174	0%	£0	6.88	8.50	0.00	£22	£802
Sternum	0%	£0	£0	93%	£447	7%	£174	0%	£0	6.88	8.50	0.00	£22	£802
Scapula	0%	£0	£0	93%	£447	7%	£165	0%	£17	6.93	8.00	0.00	£22	£810
Clavicle	0%	£0	£0	93%	£447	7%	£165	0%	£17	6.93	8.00	0.00	£22	£810
Humerus	0%	£0	£0	68%	£327	27%	£675	5%	£233	7.04	8.00	0.00	£97	£1,537
Tibia	0%	£0	£0	10%	£48	36%	£975	54%	£3,111	11.36	11.70	0.00	£208	£4,708
Fibula	0%	£0	£0	10%	£48	36%	£975	54%	£3,111	11.36	11.70	0.00	£208	£4,708

Source; data from Stevenson et al., 2006b.

Table B60 Total fracture costs for postmenopausal women aged 75 years plus (data from Stevenson et al., 2006)

Fracture site	% of patients treated by GP	Cost of GP management per patient	Total average cost per patient. GP managed fracture	% of patients treated as hospital day case	Total average cost per patient treated as a day case	% of patients hospital admission no procedure	Total average cost per patient fracture admission no procedure	% of patients with admission surgical procedure	Total cost per patient fractures with admission and surgical procedure	Average weighted LoS for admitted patients	HES reported LoS women aged 60-64	Excess bed days	Average weighted excess bed day charge (per day)	Total acute care costs, including excess bed days
Hip	0%	£0	£0	0%	£0	0%	£0	100%	£8,217	20.27	26.40	6.13	£228	£10,560
Spine	80%	£260	£209	6%	£32	14%	£600	0%	£0	14.71	22.51	7.79	£34	£1,581
Forearm	0%	£0	£0	75%	£356	21%	£528	4%	£182	7.04	9.90	2.86	£76	£1,548
Other fracture														
Femur	0%	£0	£0	0%	£0	20%	£773	80%	£6,574	19.04	36.51	17.46	£219	£11,861
Pelvis	0%	£0	£0	0%	£0	95%	£3,551	5%	£411	13.87	20.38	6.51	£190	£5,859
Ribs	0%	£0	£0	93%	£474	7%	£262	0%	£0	13.53	15.10	0.00	£13	£918
Sternum	0%	£0	£0	93%	£474	7%	£262	0%	£0	13.53	15.10	0.00	£13	£918
Scapula	0%	£0	£0	93%	£474	7%	£249	0%	£17	13.25	16.60	3.35	£13	£967
Clavicle	0%	£0	£0	93%	£474	7%	£249	0%	£17	13.25	16.60	3.35	£13	£967
Humerus	0%	£0	£0	68%	£346	27%	£1,017	5%	£233	12.70	16.60	3.90	£97	£2,284
Tibia	0%	£0	£0	10%	£51	36%	£1,346	54%	£3,111	13.11	25.10	11.99	£208	£7,603
Fibula	0%	£0	£0	10%	£51	36%	£1,346	54%	£3,111	13.11	25.10	11.99	£208	£7,603

Source: data from Stevenson et al., 2006b.

Table B61 Percentage of patients treated in secondary care (outpatient, inpatient no surgery, inpatient with surgery)

Patient	Hip	Pelvis	Rib	Wrist, leg, humerus	Clavicle, sternum
Outpatient	0%	43.9%	80.1%	43.9%	64.9%
Inpatient No surgery	0%	35.9%	19.9%	43.9%	22.5%
Inpatient Surgery	100%	20.2%	0%	12.2%	12.6%
Total	100%	100%	100%	100%	100%

Based on Bouee et al., 2006.

Table B62 Percentage of patients treated as outpatient, inpatient no surgery, inpatient with surgery

Fracture	% hospitalised Stevenson et al 2006	% of admissions treated surgically[b]
Hip	100%	100%
Spine	35%	0%
Forearm	25%	15%
Pelvis	100%	5%
Femur	100%	80%
Ribs	7%	0%
Sternum	7%	0%
Scapula[a]	7%	15%
Clavicle	7%	5%
Humerus	32%	15%
Tibia	90%	60%
Fibula	90%	60%

[a] Estimates for scapula assumed to be same as humerus

[b] Estimates obtained by personal communication from Professor Compston September 2009

Based on Stevenson et al., 2006b and clinical expert opinion

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The NHS reference costs included in the analysis are believed to be appropriate for the costing of the intervention and comparators being appraised.

NHS reference costs included for fracture management were sourced using a scoping search of ICD 10 and OPCS codes included under HRG4 chapter listings (Department of Health, 2006) to ensure that the most appropriate NHS reference costs were obtained. It is acknowledged that some NHS reference cost data for fracture management include inpatient episodes based on much younger cohorts of patients than osteoporotic populations and may, therefore, underestimate fracture costs for certain fracture types. HES data, for example, suggested that more than

50% of fractures of the spine (ICD codes S320,S321, S322, S12) and 23% of femur shaft fractures (S723, S724 and S728) were in patients under 60 years of age.

The mean LoS for fracture-related codes was consequently cross referenced to the HES-reported mean LoS by fracture type for women aged 60-74 and 75+ to ensure that costs appropriately reflected elderly osteoporotic patients. If the mean LoS were considered particularly underestimated (e.g., more than 2 days difference), excess bed day charges were applied.

Administration costs for iv therapies were considered to reflect the most appropriate cost tariffs. The scoping review of HRG codes indicated that there are no NHS reference costs specifically assigned to the administration of BPs. However, the NHS Classification of Interventions and Procedures report (NHS, 2008) indicated that the procedure code for administration of zoledronate was X72.3, which maps to HRG codes SB12Z and SB15Z (administration of simple iv chemotherapy agent first and subsequent attendance). BNF administration data suggest that iv infusion would be over a 15-30 second period for ibandronate and over *at least* a 15-minute period for zoledronate. These chemotherapy codes relate to simple chemotherapy administration only and, in the absence of a general HRG code for iv BP administration, are considered to represent the most appropriate unit costs. A previous micro-costing study in patients treated with 4mg of zoledronate for bone metastases indicated that the total nursing time for the zoledronate iv infusion would be approximately 45 minutes (IV infusion time 24 minutes) (Derhernais et al., 2001).

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, Appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice

- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic literature search for osteoporosis-related costs was conducted in Embase, Medline and Medline In-process on 14th September 2009. Full details of the literature search, including search terms employed, may be found in section 9.13 (appendix 13). The literature search was designed to identify UK cost studies or systematic reviews in osteoporosis from 2000 onwards. A date restriction was included since the search was designed to update the previous cost literature search undertaken by Kanis et al. (2002a).

Studies were included if they were considered primary cost studies or systematic reviews of cost data for osteoporosis. Studies were excluded if osteoporosis was discussed in a UK context, but costs were referenced to non-UK sources due to potential differences in population and health service practice in a non-UK setting. Studies were also excluded if they only applied cost data from previous analyses.

Search results

In total, 12 studies were identified; however, one study by Brown et al. (2001) reported costs for fractures, but did not state calculation methods or data sources and was consequently excluded. One additional paper was published prior to the year 2000 and predated our literature search; however, this study was referenced by a large number of other cost analyses in the area and was also tabulated for reference purposes (Dolan et al., 1998).

Three studies were conducted as part of systematic reviews (Kanis et al., 2002a; Cameron et al., 2000; Kanis et al., 2007). The remaining seven studies were costing studies only (Bouee et al., 2006; Burge et al., 2001; Finnern et al., 2003; Puffer et al., 2004; Stevenson et al., 2006b; Lawrence et al., 2005; Verma et al., 2009). Full details of these studies, including the country and date of each study, their applicability to UK clinical practice, cost valuations used, costs for use in economic analysis and technology costs, have been provided in section 9.13, (appendix 13).

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical expert opinion was used for general advice and feedback on resource use assumptions at a face to face meeting (see section 6.3.5 for further details). In this meeting, it was agreed that given NICE requirements, the current model should employ HRG costs for fracture outcomes. During the HRG cost scoping review, further clinical advice was sought via email correspondence on the most appropriate HRGs and a clinical expert was provided with costing methods and assumptions for a methodological review. Further clinical opinion was sought on the percentage of patients managed in a GP/inpatient setting given the lack of evidence identified during the cost literature review. This advice was obtained via email correspondence.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

The total annual cost for each drug therapy was assumed to include monitoring and administration costs, as well as drug acquisition. Procurement costs for each drug therapy were based on British National Formulary (BNF, accessed September 2009) prices with dosing information from BNF manufacturer recommendations. The mean treatment cost was estimated using a mean price per dose multiplied by the average number of doses required per year. It is noted that mean drug costs assumed no drug wastage, an assumption that would favour oral and frequently administered therapies. In the sensitivity analysis on compliance, patients who poorly complied with therapy were assumed to incur lower drug costs (see section 6.7.9).

Administration costs were assumed to be zero for patients using oral therapies. In the base-case analysis, patients administered denosumab were assumed to have the subcutaneous injection administered by their GP. One injection was assumed to be included in the annual monitoring visit; hence, costs for only one additional GP visit were included. In two sensitivity analyses, the cost of administration for one visit per year was reduced to zero (under the assumption that denosumab was self-administered) and increased to £127 (under the assumption that denosumab was administered in a secondary care setting). The latter cost was equivalent to the NHS reference cost for a first attendance face to face non-admitted specialist orthopaedic consultation (T110N), indexed to year 2009. It is noted that this latter cost may over estimate consultation costs since costs for a follow-up attendance would be lower than the first attendance costs stated. Moreover, this analysis is likely to overestimate the cost of initiating denosumab in secondary care and all subsequent administrations being in the primary care setting as the model does not allow a different cost to be set for first and subsequent administrations of denosumab.

Patients using teriparatide were also assumed to administer the drug subcutaneously through a daily home injection. Costs for only one additional GP visit were included for initiation and management of subcutaneous therapy. This is considered a conservative approach since administration costs for teriparatide were effectively considered

equivalent to those for denosumab, despite twice yearly administration for denosumab rather than the daily administration of teriparatide; it is noted that costs for patients who are unable to self administer teriparatide could be substantially higher.

Administration of iv therapies was assumed to occur in a hospital setting. A review of HRG codes indicated that there were no HRG codes specifically associated with the administration of iv BPs and, in the absence of a general HRG code for iv administration, SB12Z and SB15Z were considered to reflect the most likely administration tariffs for both zoledronate and ibandronate patients (see section 6.5.2).

In a sensitivity analysis, the costs of iv ibandronate administration were reduced by 20%, in line with a micro costing study by Derhernais et al. (2001). The microcosting study by Derhernais et al. (2001) estimated the proportion of nursing time taken for the administration of zoledronate. It was estimated that 24 minutes (out of a total 44 minutes for the complete visit) was for the zoledronate iv infusion itself. In view of the faster administration of iv ibandronate compared to iv zoledronate, administration costs were re-estimated using data from this study, assuming iv infusion time for ibandronate is 15 seconds (approximately 24 minutes less than for zoledronate). In this scenario, total variable costs (including clinician and nursing time, and supplies) were then estimated to be 20% lower than the previously reported total cost in the study (Dehernais et al., 2001).

It has been assumed that monitoring of all osteoporosis therapies requires a once yearly GP visit. Costs were based on an 11.7 minute visit (£37 per visit), estimated from Personal Social Services (PSS) unit costs of health and social care GP services (Curtis, 2008). Costs for a bone mineral density measurement (£66 per measurement) were assumed to be incurred every second year and estimated from NHS reference costs for HRG RA15Z (DXA scan). NHS reference costs and PSS costs were indexed to 2009 costs (second quarter) using the health component of the UK consumer price index (CPI) (UK National Statistics, 2009).

The total annual drug cost for each therapy suggests that denosumab would be the least expensive non-oral drug therapy available for osteoporosis. The total annual cost of denosumab would be expected to be below that for the iv-administered BPs, ibandronate and zoledronate, and substantially lower than subcutaneously injected teriparatide.

Table B63 Unit costs associated with the primary and secondary comparator technologies in the economic model

Resource use per annum	No treatment	Deno-sumab	Stron-tium	Zoled-ronate	Iband-ronate iv	Ralox-ifene	Teripar-atide
Brand	-	Prolia	Protelos	Aclasta	Bonviva (iv)	Evista	Forsteo
	-	60mg	2 g 28-sachets	5mg	3 mg syringe	60 mg 28-tabs	3-mL pen 28 doses
Technology cost	-		£25.60	£283.74	£68.64	£17.06	£271.88
Dosing description	-	60mg/ biannually	2g/day	5 mg/ year	3mg/3 mths	60mg/ day	£0.00
Mean cost per year	£0.00	£366.00	£333.71	£283.74	£274.56	£222.39	£3,544.15
Administration: No doses per year	-	2	365	1	4	365	365
Route of administration	-	sc injection	Oral	iv	iv	Oral	sc injection
Administration cost		£37.23		£163.80	£657.66		£37.23
Monitoring cost (1 GP visit per year)	£0.00	£37.23	£37.23	£37.23	£37.23	£37.23	£37.23
BMD (once every 2 years)	£0.00	£33.18	£33.18	£33.18	£33.18	£33.18	£33.18
Total cost per year	£0.00	£473.65	£404.13	£517.95	£1,002.63	£292.80	£3,651.80

*Additional GP monitoring/ administration management assumed for subcutaneous injections
sc, subcutaneous

The cost values reported in this table have been rounded to two decimal places

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

The following states have been included in the model:

- Well
- Hip fracture
- Vertebral fracture

- Wrist fracture
- Other fracture
- Post-vertebral fracture
- Post-hip fracture
- Dead

The costs of hip, vertebral and wrist fractures are based on the total average fracture costs per patient estimated based on the proportion of patients treated as day case patients, admitted patients and with a surgical procedure. Costs for accident and emergency assessment and outpatient costs were also included. The cost of 'other fractures' was calculated as an average weighted cost, based on the age-specific fracture incidence of different fracture types from a UK general practice research database study (GPRD) undertaken in the UK by Van Staa et al. (2001). The 'other fractures' that were included were pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other distal femur fractures.

The costs for the second and following years after hip fracture were based on the probability of going to a nursing home after a hip fracture. A review of evidence applied in previous UK cost literature (see section 6.3.5) did not identify potential UK data sources for age-dependent estimates of nursing home admission post fracture published since the HTA review by Kanis et al. (2002a). Unpublished UK data from the Second Anglian Audit of Hip Fracture, Todd et al. (1999) (reported by Kanis et al., 2002a), describes the short-term probability of going to a nursing home (up to 90 days post fracture). It is acknowledged that the study may underestimate nursing home admission due to the limited 90-day follow-up period. However, expert opinion indicated the 90-day follow-up was likely to capture most admissions. Furthermore, given that this study offered UK data and was previously applied in the economic model for NICE TA160 and TA161 (Stevenson et al., 2006d; Stevenson et al., 2006e), the data reported by Todd et al. (1999) was considered to offer the most appropriate values for this appraisal. Patients residing in a nursing home were assumed to remain there for the rest of their lives (Strom et al., 2008a).

Nursing home costs were sourced from Unit Costs of Personal and Social Services Resource Use 2008 (Curtis, 2008); cost estimates were published for local authority

residential care (£915 per week), private nursing home care (£678 per week) and private residential care (£467 per week). The lower cost of £467 per week was conservatively applied and indexed to year 2009 costs to derive a cost per day of £69 per patient (£25,202 per annum). This cost was the lowest cost identified from PSSRU data but was consistent with previous cost estimates used in the economic analysis for NICE TA160 and TA161 (£22,620 to £23,897, age dependent) although this assumption was tested in one-way sensitivity analyses.

Table B64 List of health states and associated costs in the economic model

Health states	Items	% patients	Indexed costs 2009 women 60-74 years	Indexed costs 2009 women 75+ years	Reference in submission
All health states	Drug therapy costs	All	Therapy dependent	Therapy dependent	Table B63
	BMD monitoring costs every 2 years	All	£33	£33	Section 6.5.5
	GP visit		£37	£37	Section 6.5.5
	H2 antagonists	Therapy dependent	£2.20	£2.20	Table B66
Well	N/A				
Hip fracture	Hip fracture cost	All	£9,165	£10,560	Table B59 and Table B60
	Nursing home costs	All	£25,201	£25,201	Table B59 and Table B60
Vertebral fracture	Vertebral fracture cost	All	£1,318	£1,581	Table B59 and Table B60
Wrist fracture	Wrist fracture cost	All	£2,311	£2,771	Table B59 and Table B60
Other fracture	Other fracture cost	All	£2,510	£3,747	Table B59 and Table B60
Hip fracture post vertebral fracture	Hip fracture cost	All	£9,165	£10,560	
	Nursing home costs per year	All	£25,201	£25,201	Table B59 and Table B60
Vertebral fracture post hip fracture	Vertebral fracture cost	All	£1,318	£1,581	Table B59 and Table B60

Table B65 Proportion going to nursing home after a hip fracture (Strom et al., 2008a; Zethraeus et al., 2006)

Age at fracture (years)	Proportion going to nursing home
50	0.067
60	0.065
70	0.102
80	0.147
90	0.226

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Adverse events relating to oral therapies primarily include GIAEs. The assumptions relating to GIAEs were chosen to be the same as those used in the NICE economic analysis base-case for TA160/161. It was therefore assumed that oral treatments are associated with an increased risk of upper gastrointestinal side-effects that will require a GP consultation. The rate of this (over and above an average background rate for women) is assumed to be 23.5 per 1,000 patient-months in the initial treatment month, and 3.5 per 1,000 patient-months in subsequent months. Each treated patient was, therefore, modelled to require 0.041 extra GP consultations during the first cycle (6 months) and 0.021 GP consultations during each of the following cycles whilst on treatment. GIAEs requiring GP consultation are assumed to require a course of H2 receptor antagonists or equivalent. In the sensitivity analysis on persistence, the costs associated with GIAEs were applied only to persistent patients.

Other therapy-related adverse events were not included. Therapy-related adverse events not considered in the model were osteonecrosis of the jaw for BPs and strontium, venous thromboembolism (VTE) (deep vein thrombosis and pulmonary embolism), for strontium and raloxifene as well as infusion reactions for zoledronate and ibandronate. Other adverse events not included are described in section 6.4.12.

These events were excluded from the economic analysis in line with previous economic models, including the NICE analysis for TA160/161 as a conservative assumption that would favour comparators other than denosumab.

The FREEDOM RCT indicated that patients could be at an excess risk of skin infection with denosumab. However, RCT evidence suggested that serious skin infections affected only 0.3% of patients (Cummings et al., 2009). Inclusion of the costs and QALYs resulting from serious skin infection would not, therefore, generate important cost or QALY differences between therapies and, applying the same rationale as for osteonecrosis of the jaw and VTE, skin infection events could be potentially excluded from the model. Serious skin infections have nevertheless been included in the analysis as a conservative approach (i.e., that would favour all alternative comparators versus denosumab). It has been assumed that 0.3% of denosumab patients will suffer serious skin infection (cellulitis), and require hospital admission as observed in the FREEDOM RCT data. The NHS cost applied relates to the HRG (JD04B) that includes the ICD diagnosis code.

Table B66 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Patients	Data source	Indexed 2009 cost per event
Skin reaction (cellulitis)	Hospital admission	Dmab treated only	NHS reference costs	£1,434
Total				**£1,434**
Gastrointestinal side effects	GP visit	Therapy dependent	PSS	£37.23
	H2 antagonists	Therapy dependent	BNF	£2.20
Total				**£39.43**

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

All costs have been described above.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8 and 5.9.4 to 5.9.12.
Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented, and each alternative analysis should present separate results.
The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.
All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost-effectiveness of the options being compared.
For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Structural assumptions were tested using the following sensitivity analyses. Analyses were performed for the base-case population (women aged 70 years, femoral neck T-score –2.5 SD), with and without prior fracture:

- time horizon (5 years to lifetime in 5-year increments)
- treatment duration (5 and 10 years)
- baseline fracture risk — estimates based on the FRAX® algorithm
- persistence data
  - using GPRD data (Weibull regression), for relevant comparators, with denosumab modelled to have persistence equivalent to monthly ibandronate

(incorporates a dynamic offset assumption capped at 1 year for patients who discontinue their treatment) (see section 6.2.8)

  - using GPRD data (Weibull regression), for relevant comparators, with denosumab persistence modelled according to its relative risk versus weekly alendronate in DAPS (incorporates a dynamic offset assumption capped at 1 year for patients who discontinue their treatment) (see section 6.2.8)

- compliance — reduced FoB for oral BPs, strontium and raloxifene (see section 6.2.8)
- treatment offset (oral and iv BPs: 5 years offset rather than 1 year)
- the percentage of patients hospitalised and undergoing surgery (Bouee/Stevenson)
- multi-way analysis employing NICE TA160 clinical efficacy and utility data where feasible.

In structural sensitivity analyses the model time horizon was varied between 5 years and lifetime in 5-year increments to provide ICER estimates for different decision time horizons. The treatment duration was extended to 10 years, selected to be consistent with previous NICE sensitivity analyses TA160/161(NICE, 2008b; NICE, 2008a).

Two alternative scenarios employing fracture risk estimates based on the FRAX® algorithm were undertaken. NICE TA160/161 included parental history of hip fracture, daily alcohol intake and rheumatoid arthritis from the FRAX® independent clinical risk factors. Our implementation of FRAX® algorithm is limited to parental history of hip fracture and rheumatoid arthritis because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from 3 or more to 4 or more units per day and we do not have the details of this adjustment (NICE, 2008b; NICE, 2008a).

In the initial FRAX® analysis, fracture risk estimates were obtained assuming that women had a BMI of 26 with independent clinical risk factor coefficient indicators set to 0 (i.e., no parental history of fracture or rheumatoid arthritis). The fracture risk estimates produced in this analysis would therefore be expected to be lower than those of an average population used in our base-case analyses. In the second FRAX® analysis, independent clinical risk factor coefficients were set to 1 for

rheumatoid arthritis and parental history of fracture. In this cohort all patients were therefore assumed to suffer both rheumatoid arthritis and have a parental history of fracture, so the overall fracture risk would therefore be expected to be higher than an average population used in our base-case analyses.

In two further sensitivity analyses, persistence and compliance were included. The assumptions behind these analyses may be found in section 6.2.8. Treatment offset for oral and iv BPs was varied to 5 years in line with previous NICE models TA160/161 (NICE, 2008b; NICE, 2008a). Data sources were varied for the percentage of patients admitted to inpatient care following fracture and the percentage of patients undertaking surgery, due to weak evidence in current literature for this parameter (see section 6.5.1), and evidence from Stevenson et al. (2006; Bouee et al., 2006; Stevenson et al., 2006c) was employed rather than data from Bouee et al. (2006). In the final structural sensitivity analysis, treatment efficacy and utility data used in the NICE model TA160/161 (NICE, 2008b; NICE, 2008a) were employed in a multi-way sensitivity analysis. The data employed in the model are detailed in Table B67 and Table B68.

Table B67 NICE TA160/161 modelled clinical efficacy data (NICE, 2008b; NICE, 2008a)

	Vertebrae	95% CI		Hip	95% CI		Wrist	95% CI		Non-vertebral	95% CI	
Alendronate	0.58	0.51	0.67	0.71	0.58	0.87	1	N/A	N/A	0.78	0.69	0.88
Risedronate	0.58	0.51	0.67	0.71	0.58	0.87	1	N/A	N/A	0.78	0.69	0.88
Etidronate	0.4	0.2	0.83	1	N/A	N/A	1	N/A	N/A	1	N/A	N/A
Raloxifene	0.65	0.53	0.79	1	N/A	N/A	1	N/A	N/A	1	N/A	N/A
Strontium	0.6	0.53	0.69	1	N/A	N/A	0.84	0.73	0.97	0.84	0.73	0.97
Teriparatide	0.35	0.22	0.55	1	N/A	N/A	1	N/A	N/A	1	N/A	N/A

Table B68 NICE TA160/161 modelled utility data

Fracture site	Utility multipliers
Hip (yr1)	0.792
Hip (> yr1)	0.813
Vertebrae (yr1)	0.792
Vertebrae (> yr1)	0.909

Wrist (yr1)	0.977
Gastrointestinal side effects	0.91

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way sensitivity analyses were conducted on key base-case model parameters. In order to maintain acceptable level of reporting, the parameters selected were limited to those parameters deemed be particularly uncertain and likely to have an important impact on ICER estimates. The following parameters were therefore selected:

- administration costs of iv ibandronate (20% lower than base-case)
- administration costs of denosumab (0-£127)
- clinical vertebral fracture utility (proportion of decrement 0.5, 0.75, 1.25 and 1.5)
- mortality due to fracture (100%)
- discount rate (0% for both costs and outcomes and 1.5% for outcomes with 6% for costs)
- nursing home costs (increased from £415 to £678 per week).

Key cost parameters explored in one-way sensitivity analyses included administration costs for iv ibandronate. It was acknowledged that iv ibandronate administration costs could be lower than iv zoledronate due to faster administration time. These costs were therefore modelled to be 20% lower than base-case values in a one-way sensitivity analysis (see section 6.5.5 for detailed explanation of rationale and methods). A further one-way sensitivity analysis was included to assess the impact on ICER estimates if denosumab was self-administered or administered in a secondary care setting (outpatient specialist consultation). The cost of the first annual injection was therefore varied between £0 and £127. Clinical vertebral fracture utility was considered to be a controversial variable in the NICE TA160/161 (NICE, 2008a; NICE, 2008b) analyses and the value employed in the current model was therefore varied in sensitivity analyses to assess the potential

impact of alternative higher and lower estimates. The proportion of the clinical vertebral fracture multiplier applied in the analysis was varied from 0.5 to 1.5. Causal mortality attributable to fracture was increased to 100% in order to test the potential impact of assuming that all excess mortality post fracture was due to the fracture outcome. Discount rates were varied to 0% for both costs and outcomes and NICE previously recommended rates (6% for costs and 1.5% of outcomes). Finally the cost of nursing home care was increased from £467 per week (equivalent to private residential care) to £678 per week (equivalent to private nursing home care) to test the effect of higher nursing home care costs following hip fracture.

Key parameters excluded from the deterministic and structural analyses include population utility estimates, adverse events, HRG cost estimates, PSSRU cost estimates and the number of DXA scans. Population utility estimates were sourced from established UK data (Kind et al., 1998; Bouee et al., 2006). The proportion of adverse events had previously been increased tenfold for BPs in analyses for NICE TA160/161 (NICE, 2008a; NICE, 2008b). This analysis was conservatively not undertaken although it is noted that applying these assumptions would favour denosumab versus oral therapies. HRG cost estimates were included in probabilistic sensitivity analyses, and additional one-way analyses were considered unnecessary. PSSRU costs were not varied in sensitivity analyses and were considered to be deterministic. The number of DXA scans per year was excluded from sensitivity analyses since this variable was modelled to be common across all comparators and considered unlikely to have an important impact on ICER estimates.

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA has been undertaken (see section 6.3.6 for details of distributions applied to model parameters). Parameters included in the PSA were those parameters for which the variance could be modelled from available data. Key model parameters not entered as probability distributions, but considered likely to affect model

outcomes, were varied in one-way and structural sensitivity analyses. Parameters excluded from the PSA are detailed below:

- the proportion of patients who persist with treatment (alternative assumptions addressed in one-way sensitivity analyses)
- the proportion of patients who comply with treatment (alternative assumptions addressed in one-way sensitivity analyses)
- the number of DXA scans per year (assumption-based estimates, variance unknown excluded from PSA)
- offset time (varied in one-way sensitivity analyses)
- population utility (considered deterministic)
- PSSRU costs (considered deterministic)
- fracture risk (data limitations prohibitive of PSA analysis, FRAX® coefficients not accessible)—alternative fracture risk estimates applied in structural sensitivity analysis
- causal mortality for fracture (varied from 30% to 100% in one-way sensitivity analyses)
- proportion of patients entering nursing home care (uncertainty not reported, estimates modelled to be deterministic).

Further details of sensitivity analyses can be found in section 6.6.1 and 6.6.2.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.

- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost-effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Denosumab is expected to be an appropriate option where oral BPs are unsuitable. The primary comparators for the economic evaluation are therefore strontium, raloxifene and no treatment. Comparisons with iv BPs (ibandronate and zoledronate) and teriparatide are considered secondary comparators, as these management strategies are not standard care, and the mode of administration for iv BPs limits their use to a secondary care setting. Comparisons with oral BPs are presented in section 9.15 (appendix 15) for completeness.

The results of the economic modelling are therefore presented in the following three groups:

1. Primary comparisons: denosumab compared to strontium, raloxifene and no treatment
2. Secondary comparisons: denosumab compared to ibandronate iv, zoledronate iv and teriparatide
3. Supplementary comparisons: denosumab compared to oral BP therapy (alendronate (daily), etidronate, risedronate (daily), oral ibandronate). Daily administration is assumed, as efficacy for daily and weekly modes is modelled to be equivalent, this represents a conservative portrayal of these treatments costs. These comparisons are presented in section 9.15.

Where products have not been recognised by NICE in TA160/161 for specific patient groups, these have been flagged under the cost-effectiveness results tables (raloxifene and teriparatide are not recommended by NICE for patients with no prior fracture).

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical

trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B69 Summary of base-case model results compared with FREEDOM trial data

Outcome	FREEDOM trial result N = 3,886 36 month data denosumab	Base-case Model result (5 years)
Hip fracture	26 (0.7%)	2.61%
Clinical vertebral fracture	29 (0.8%)	1.47%
Wrist fracture	n/r	3.73%

The model has been designed to estimate costs and effects for different time horizons (5, 10, 20 years and a lifetime). Five-year estimates are reported in Table B69, and assume a base-case population of women aged 70 years with a femoral neck T-score of –2.5 SD across all sites and no prior fracture. These characteristics differ to the baseline characteristics of patients in the FREEDOM trial. Specifically, mean age 72.3 years; mean T-scores of –2.82, –1.89 and –2.15 SD at the lumbar spine, total hip and femoral neck respectively; and 73.4% with no prior fracture (see table B9 section 5.3.4). Further, the percentage of patients in the model with fracture at 5 years would be expected to be higher than those reported in the denosumab FREEDOM trial (36-months time horizon). A description of analyses performed to demonstrate internal validity is presented in section 6.8. These demonstrate that the model predicts FREEDOM trial fracture outcomes very closely when model parameters are set to reflect the FREEDOM trial population characteristics.

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Please see Excel model sheets *'Comp 1-5'* for full Markov traces.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Please see Excel model sheets *'Comp 1-5'* for full Markov traces.

6.7.4 Please indicate the life years and QALYs gained for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Hip, vertebral, wrist and other fractures predicted by the model over a 10-year period for the primary comparators are summarised below, along with life years and QALYs.

Table B70 Primary comparisons: predicted fractures, life years and QALYs for denosumab, strontium, raloxifene and no treatment

	Denosumab	Strontium	Raloxifene	No Treatment
No prior fracture				
Fractures over 10 years				
Hip fractures	0.084	0.098	0.103	0.103
Vertebral fractures	0.052	0.068	0.058	0.086
Wrist fractures	0.074	0.079	0.080	0.078
Other fractures[a]	0.161	0.158	0.158	0.155
QALYs and life years (lifetime)				
Life years (undiscounted)	15.828	15.798	15.806	15.772
Life years (discounted)	11.642	11.622	11.628	11.606
QALYs	8.048	8.007	8.009	7.991
Prior fracture				
Fractures over 10 years				
Hip fractures	0.128	0.151	0.160	0.160
Vertebral fractures	0.133	0.178	0.149	0.227
Wrist fractures	0.084	0.088	0.090	0.085
Other fractures	0.234	0.222	0.225	0.212
QALYs and life years (lifetime)				
Life years (undiscounted)	15.720	15.651	15.678	15.590
Life years (discounted)	11.576	11.531	11.548	11.492
QALYs	7.917	7.841	7.852	7.797

[a] The model estimates fewer 'other' fractures with no treatment than with active treatments; this is an artefact of the model structural assumptions. Post-vertebral patients are not modelled to incur any further wrist or other fractures. Post-hip fracture patients can not incur any further vertebral, wrist or other fractures. Comparators with greater hip or vertebral fracture efficacy will have fewer patients moving into the post-hip or post-vertebral fracture state and will have a larger population at risk of other fracture types. Since patients in the no treatment group are at higher risk of hip and vertebral fractures, the model essentially prevents them from incurring further other fractures. This is a conservative assumption and favours the no-treatment comparison versus denosumab. See section 6.2.5 for further clarification.

6.7.5 For incremental analysis, please present the results in the following format or, if this is not possible, in disaggregated form. A suggested format is presented below.

Disaggregated results for the primary comparisons are provided in Table B70 (section 6.7.4).

Table B71 presents a summary of costs by health state for the primary comparators.

Table B71 Primary comparisons: morbidity costs for denosumab, strontium, raloxifene and no treatment (£)

	Denosumab	Strontium	Raloxifene	No Treatment
No prior fracture				
Hip	6,654	6,958	7,087	7,067
Vertebral	265	301	277	342
Wrist	462	477	483	472
Other	1,656	1,609	1,616	1,574
Total morbidity cost	**9,038**	**9,345**	**9,463**	**9,455**
Prior fracture				
Hip	8,380	8,866	9,092	9,029
Vertebral	552	651	580	763
Wrist	486	489	502	470
Other	2,029	1,901	1,935	1,798
Total morbidity cost	**11,447**	**11,907**	**12,110**	**12,060**

Table B72 presents a summary of resource use for the primary comparators.

Table B72 Primary comparisons: resource use costs for denosumab, strontium, raloxifene and no treatment (£)

	Denosumab	Strontium	Raloxifene	No Treatment
No prior fracture				
Total morbidity cost	**9,038**	**9,345**	**9,463**	**9,455**
Drug cost	1,617	1,474	982	0
Treatment management	476	311	311	0
Side effects	4	8	8	0
Total Intervention cost	2,097	1,793	1,301	0
Total cost	**11,135**	**11,138**	**10,764**	**9,455**
Prior fracture				
Total morbidity cost	**11,447**	**11,907**	**12,110**	**12,060**
Drug cost	1,616	1,473	982	0
Treatment management	475	311	311	0
Side effects	4	8	8	0
Total Intervention cost	2,096	1,792	1,301	0
Total cost	**13,543**	**13,698**	**13,410**	**12,060**

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Base-case cost-effectiveness results are presented in Table B73a and Table B73b below. As above, analyses are for patients aged 70 with a femoral neck T score of –2.5 SD. Separate tables are presented below for the primary and secondary comparison groups as defined above. Results are presented first on the basis of deterministic model analyses that are consistent with the tables presented above. Cost-effectiveness is also tabulated based on probabilistic analyses (see section 6.7.8).

Primary comparisons

Denosumab is a cost-effective treatment option for diagnosed patients for whom oral BPs are unsuitable. Compared with the primary comparators, regardless of prior fracture status, denosumab dominates strontium and is cost-effective against both raloxifene and no treatment. In patients with no prior fracture the incremental cost-effectiveness ratios per QALY gained are £9,289 and £29,223 compared with raloxifene and no treatment, respectively. In patients with a prior fracture the incremental cost-effectiveness ratios per QALY gained are £2,046 and £12,381 compared with raloxifene and no treatment respectively.

The results of the base-case analysis show that denosumab is more effective and less costly than strontium (dominant) and more effective and more costly than both raloxifene and no treatment with incremental cost-effectiveness ratios per QALY gained within the cost-effective threshold range.

Secondary comparisons

Against secondary comparators in patients with or without prior fracture denosumab is dominant versus ibandronate iv, while zoledronate and teriparatide are both estimated to be marginally more effective and more expensive than denosumab.

The results of the secondary comparisons versus iv BP treatments show that denosumab is likely to be more effective and less costly than ibandronate iv (dominant) and less costly and marginally less effective than zoledronate iv. Both ibandronate iv and zoledronate iv are administered in a hospital setting and patients may or may not persist with therapy in the same fashion as other osteoporosis therapies. Adherence data were not available for either product, therefore potential persistence and the associated impact on the ICER values is unknown. The results of the secondary comparison versus teriparatide show that denosumab is likely to be less effective and less costly than teriparatide. It is noted that none of the treatments in the secondary comparison are standard care in the UK.

Table B73a Primary comparisons: base-case cost-effectiveness for denosumab, strontium, raloxifene and no treatment

				vs. lowest cost comparator			ICER vs. low-cost comparator		ICER for comparison with Denosumab[a]	
	LYs	QALY	Cost	Δ LY	Δ QALY	Δ Cost	LYs	QALYs	LYs	QALYs
No prior fracture										
No Treatment	11.606	7.991	9,455	0.000	0.000	0	—	—	47,220	29,223
Raloxifene[b]	11.628	8.009	10,764	0.022	0.018	1,310	60,786	74,239	26,383	9,289
Denosumab	11.642	8.048	11,135	0.036	0.057	1,680	47,220	29,223	—	—
Strontium	11.622	8.007	11,138	0.016	0.016	1,684	104,069	102,592	Denosu-mab dominant	Denosu-mab dominant
Prior fracture										
No Treatment	11.492	7.797	12,060	0.000	0.000	0	—	—	17,719	12,381
Raloxifene	11.548	7.852	13,410	0.056	0.055	1,351	24,021	24,524	4,820	2,046
Denosumab	11.576	7.917	13,543	0.084	0.120	1,483	17,719	12,381	—	—
Strontium	11.531	7.841	13,698	0.039	0.044	1,638	41,767	37,123	Denosu-mab dominant	Denosu-mab dominant

[a] Pairwise ICERs for denosumab versus each strategy are presented to demonstrate the cost-effectiveness of denosumab relative to the existing guidance recommendations in TA160 and TA161.

[b] Raloxifene is not recommended by NICE in patients with no prior fracture.

Table 73b Secondary comparisons: base-case cost-effectiveness for denosumab, ibandronate iv, zoledronate iv and teriparatide

				vs. lowest cost comparator			ICER vs. low-cost comparator	
	LYs	**QALYs**	**Costs**	**Δ LY**	**Δ QALY**	**Δ Cost**	**LYs**	**QALYs**
No prior fracture								
Denosumab	11.642	8.048	11,135	0.000	0.000	0	—	—
Zoledronate (iv)	11.646	8.053	11,490	0.004	0.005	355	88,386	70,900
Ibandronate (iv)	11.624	8.011	13,890	–0.017	–0.037	2,756	Denosumab dominant	Denosumab dominant
Teriparatide**	11.648	8.066	24,710	0.007	0.018	13,576	2,073,082	772,424
Prior fracture								
Denosumab	11.576	7.917	13,543	0.000	0.000	0	—	—
Zoledronate (iv)	11.586	7.930	13,903	0.010	0.012	360	34,292	29,029
Ibandronate (iv)	11.540	7.849	16,526	–0.036	–0.068	2,984	Denosumab dominant	Denosumab dominant
Teriparatide	11.584	7.947	26,867	0.008	0.030	13,324	1,580,601	451,269

ICERs compared with denosumab are not presented separately, as denosumab is the lowest cost treatment in this scenario

**Teriparatide is not recommended by NICE in patients with no prior fracture. NICE have not appraised ibandronate iv or zoledronate iv.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Sensitivity analyses are presented in the following three tables on the base-case analysis for the primary comparisons above.

Sensitivity analyses are broadly consistent by prior fracture status. Denosumab dominates strontium in the majority of sensitivity analyses. Base-case results remained largely unchanged when varying treatment duration, utilities, fracture costs, institutional costs, and compliance and when using NICE assumptions for comparator efficacy and utilities. As one would expect, the results were sensitive to the modelled time horizon. With shorter time horizon the superior efficacy of denosumab, and associated health outcomes gains and cost savings, is not yet fully realised, while treatment costs are fully incurred by 5 years. Results for strontium and raloxifene are sensitive when incorporating non-persistence as patients are

modelled to discontinue proportionally more than with denosumab and so revert to no treatment efficacy with associated reductions in treatment costs. However, denosumab remains cost-effective. Discounting has only a marginal impact on the cost-effectiveness of denosumab. When assuming that 100% of mortality post fracture is attributable to the fracture, the cost-effectiveness of denosumab improved up to almost two-fold. When assuming no administration cost for denosumab, the cost-effectiveness of denosumab improves. When assuming significantly higher administration costs for denosumab (one administration per year in secondary care) than would reasonably be expected in clinical practice, the cost-effectiveness of denosumab deteriorates. Denosumab remains below the cost-effective threshold range for all comparators in patients with a prior fracture and below the cost-effective threshold range compared with strontium and raloxifene in patients with a prior fracture.

Base-case run using FRAX®

In the base-case baseline risk of fracture has been estimated from epidemiological evidence. Sensitivity analyses using the FRAX® algorithm to generate baseline fracture risk yield results that are broadly consistent with the base-case approach. The FRAX® algorithm enables the user to include or exclude independent clinical risk factors,[8] while the epidemiological approach automatically includes average independent clinical risk factors across the population. Therefore, as one would expect, the absolute baseline risk of fracture in the FRAX® sensitivity analysis with no independent clinical risk factors is lower than the base case, while the absolute baseline risk of fracture in the FRAX® sensitivity analysis with two independent clinical risk factors is higher than the base case. When the absolute baseline risk of fracture is lower (higher) the opportunity to demonstrate cost-effectiveness for treatments with improved efficacy is lower (higher). Therefore, in the primary comparisons denosumab is more cost-effective when using the FRAX® algorithm with two independent clinical risk factors than with no independent clinical risk factors.

[8] Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table B74 Sensitivity analyses: primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment (no prior fracture)

Description		QALYs				Costs				ICERs for comparison with Denosumab		
Treatment		Denosumab	Strontium	Raloxifene*	No Treat-ment	Denosumab	Strontium	Raloxifene*	No Treat-ment	Strontium	Raloxifene*	No Treat-ment
Time horizon	Life	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	20 yrs	7.67	7.63	7.63	7.62	9,273	9,282	8,905	7,605	Domt	9,595	30,668
	15 yrs	6.91	6.87	6.87	6.86	6,988	7,007	6,621	5,340	Domt	10,725	35,429
	10 yrs	5.47	5.45	5.45	5.44	4,773	4,789	4,392	3,130	Domt	14,687	51,988
	5 yrs	3.17	3.15	3.15	3.16	3,070	3,024	2,596	1,345	3,528	35,701	161,647
Tx duration	5 yrs	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	10 yrs	8.08	8.01	8.01	7.99	12,135	12,308	11,716	9,455	Domt	6,196	29,550
Persist-ence[#]	off	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	On: GPRD+ DAPS	8.02	7.99	8.00	7.99	10,420	9,794	9,858	9,455	21,323	20,897	30,166
	On: GPRD only	8.03	7.99	8.00	7.99	10,498	9,794	9,858	9,455	22,029	21,699	30,145
Utilities *Proportion of decrement applied for vertebral fractures*	1	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	0.5	8.06	8.02	8.02	8.01	11,135	11,138	10,764	9,455	Domt	9,528	32,625
	0.75	8.05	8.02	8.02	8.00	11,135	11,138	10,764	9,455	Domt	9,407	30,830
	1.25	8.04	8.00	8.00	7.98	11,135	11,138	10,764	9,455	Domt	9,175	27,775
	1.5	8.04	7.99	7.99	7.97	11,135	11,138	10,764	9,455	Domt	9,063	26,464

Domt, denosumab dominant.

*Raloxifene is not recommended by NICE in patients with no prior fracture.

[#]Non-persistent patients are modelled to revert to no treatment

N.B. figures are rounded to 2 decimal points, therefore small differences between strontium and raloxifene may not be apparent in the table

Description		QALYs				Costs				ICERs for comparison with Denosumab		
Treatment		Denosumab	Strontium	Raloxifene*	No Treat-ment	Denosumab	Strontium	Raloxifene*	No Treat-ment	Strontium	Raloxifene*	No Treat-ment
Discount rate	3.5%	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	0%	10.82	10.77	10.77	10.74	17,588	17,598	17,216	15,756	Domt	6,851	22,125
	1.5% & 6%	9.47	9.42	9.42	9.40	8,454	8,451	8,087	6,864	52	7,757	22,593
Mortality attribu-table to fracture	30%	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	100%	7.95	7.88	7.89	7.84	10,696	10,649	10,280	8,934	721	7,358	17,454
Fracture costs	Bouee	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	Stevens on	8.05	8.01	8.01	7.99	10,927	10,924	10,547	9,243	65	9,520	29,299
Insti-tutional costs	private residential	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	private nursing	8.05	8.01	8.01	7.99	12,132	12,176	11,819	10,506	Domt	7,867	28,291
Dmab admin costs	£37	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	£0	8.05	8.01	8.01	7.99	10,970	11,138	10,764	9,455	Domt	5,160	26,361
Altern-ative	£127	8.05	8.01	8.01	7.99	11,535	11,138	10,764	9,455	9,648	19,334	36,185
FOB (compli-ance)	off	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	on	8.05	8.01	8.01	7.99	11,135	11,146	10,764	9,455	Domt	8,932	29,223
NICE assump-tions	off	8.05	8.01	8.01	7.99	11,135	11,138	10,764	9,455	Domt	9,289	29,223
	on	8.06	8.01	8.01	8.00	11,135	11,156	10,761	9,455	Domt	7,526	27,098

Domt, denosumab dominant.

*Raloxifene is not recommended by NICE in patients with no prior fracture.

N.B. figures are rounded to 2 decimal points, therefore small differences between strontium and raloxifene may not be apparent in the table

Table B75 Sensitivity analyses: primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment (prior fracture)

Description		QALYs				Costs				ICERs for comparison with Denosumab		
Treatment		Denosumab	Strontium	Raloxifene	No Treat-ment	Denosumab	Strontium	Raloxifene	No Treat-ment	Strontium	Raloxifene	No Treat-ment
Time horizon	Life	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	20 yrs	7.55	7.48	7.49	7.44	11,553	11,725	11,427	10,102	Domt	2,027	12,791
	15 yrs	6.82	6.75	6.76	6.72	8,953	9,152	8,836	7,560	Domt	2,106	14,228
	10 yrs	5.43	5.38	5.38	5.36	6,148	6,371	6,024	4,811	Domt	2,992	19,784
	5 yrs	3.15	3.13	3.13	3.13	3,664	3,815	3,413	2,249	Domt	13,074	59,208
Tx duration	5 yrs	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	10 yrs	7.97	7.86	7.87	7.80	14,358	14,808	14,361	12,060	Domt	Domt	13,192
Persist-ence[#]	off	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	on (GPRD+ DAPS)	7.87	7.80	7.81	7.80	12,919	12,393	12,475	12,060	8,594	8,479	12,517
	on (GPRD only)	7.87	7.80	7.81	7.80	12,990	12,393	12,475	12,060	8,917	8,863	12,505
Utilities *Proportion of decrement applied for vertebral fractures*	1	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	0.5	7.94	7.88	7.88	7.84	13,543	13,698	13,410	12,060	Domt	2,123	14,122
	0.75	7.93	7.86	7.87	7.82	13,543	13,698	13,410	12,060	Domt	2,084	13,194
	1.25	7.90	7.82	7.84	7.78	13,543	13,698	13,410	12,060	Domt	2,010	11,662
	1.5	7.89	7.81	7.82	7.76	13,543	13,698	13,410	12,060	Domt	1,975	11,022

Domt, denosumab dominant.

*Raloxifene is not recommended by NICE in patients with no prior fracture.

[#]Non-persistent patients are modelled to revert to no treatment

Description		QALYs				Costs				ICERs for comparison with Denosumab		
Treatment		Denosumab	Strontium	Raloxifene	No Treat-ment	Denosumab	Strontium	Raloxifene	No Treat-ment	Strontium	Raloxifene	No Treat-ment
Dis-counting	3.5%	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	0%	10.62	10.51	10.53	10.45	21,062	21,202	20,944	19,369	Domt	1,322	9,868
	1.5% and 6%	9.30	9.21	9.22	9.15	10,367	10,520	10,224	8,990	Domt	1,851	9,423
Mortality attribu-table to fracture	30%	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	100%	7.73	7.60	7.64	7.51	12,826	12,860	12,601	11,134	Domt	2,321	7,665
Fracture costs	Bouee	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	Stevens on	7.92	7.84	7.85	7.80	13,317	13,471	13,178	11,841	Domt	2,152	12,322
Insti-tutional costs	private residential	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	private nursing	7.92	7.84	7.85	7.80	14,772	14,988	14,729	13,369	Domt	658	11,710
Dmab admin costs	£37	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	£0	7.92	7.84	7.85	7.80	13,378	13,698	13,410	12,060	Domt	Domt	11,008
	£127	7.92	7.84	7.85	7.80	13,943	13,698	13,410	12,060	3,232	8,227	15,720
FOB (compli-ance)	off	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	on	7.92	7.84	7.85	7.80	13,543	13,708	13,406	12,060	Domt	1,976	12,381
NICE assump-tions	off	7.92	7.84	7.85	7.80	13,543	13,698	13,410	12,060	Domt	2,046	12,381
	on	7.92	7.84	7.83	7.79	13,543	13,752	13,390	12,060	Domt	1,671	11,230

Domt, denosumab dominant.

Table B76 Sensitivity analyses (base-case run on FRAX®): primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
No prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	3.80%	14.23%	8.36	8.33	8.33	8.32	8,079	7,950	7,517	6,216	4,631	21,878	51,271
–2.75	4.86%	16.00%	8.26	8.23	8.23	8.22	9,107	9,019	8,603	7,300	2,823	16,921	43,344
–3	6.20%	18.04%	8.16	8.12	8.13	8.11	10,334	10,296	9,903	8,596	1,077	12,420	36,240
–3.25	7.90%	20.43%	8.05	8.01	8.01	8.00	11,795	11,819	11,453	10,143	Domt	8,389	29,900
–3.5	10.03%	23.20%	7.93	7.89	7.89	7.87	13,529	13,630	13,298	11,982	Domt	4,818	24,263
–3.75	12.68%	26.42%	7.81	7.76	7.75	7.73	15,579	15,775	15,484	14,163	Domt	1,670	19,260
–4	15.97%	30.14%	7.67	7.61	7.61	7.59	17,992	18,306	18,066	16,737	Domt	Domt	14,818
No prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	11.12%	29.30%	8.13	8.08	8.08	8.05	16,209	16,324	16,014	14,658	Domt	3,672	20,246
–2.75	14.05%	32.88%	8.00	7.94	7.94	7.91	18,595	18,808	18,544	17,176	Domt	823	16,280
–3	17.65%	36.93%	7.86	7.79	7.79	7.76	21,390	21,725	21,516	20,135	Domt	Domt	12,676
–3.25	22.04%	41.49%	7.71	7.63	7.62	7.59	24,652	25,136	24,996	23,600	Domt	Domt	9,380
–3.5	27.28%	46.54%	7.55	7.46	7.45	7.42	28,445	29,115	29,056	27,644	Domt	Domt	6,329
–3.75	33.43%	52.06%	7.37	7.27	7.26	7.23	32,836	33,734	33,775	32,345	Domt	Domt	3,454
–4	40.44%	57.93%	7.19	7.08	7.06	7.03	37,892	39,070	39,231	37,784	Domt	Domt	677
Prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	5.82%	22.09%	8.27	8.23	8.24	8.22	11,110	11,045	10,651	9,320	1,669	13,049	32,239
–2.75	7.42%	24.62%	8.16	8.12	8.12	8.10	12,572	12,562	12,195	10,856	236	9,229	27,248
–3	9.43%	27.49%	8.05	8.00	8.00	7.98	14,299	14,356	14,022	12,674	Domt	5,800	22,715
–3.25	11.95%	30.77%	7.92	7.87	7.87	7.84	16,332	16,473	16,178	14,819	Domt	2,739	18,601
–3.5	15.06%	34.48%	7.79	7.73	7.73	7.70	18,718	18,964	18,717	17,346	Domt	10	14,862
–3.75	18.89%	38.67%	7.65	7.58	7.57	7.54	21,510	21,885	21,698	20,311	Domt	Domt	11,450
–4	23.51%	43.35%	7.50	7.41	7.41	7.38	24,766	25,299	25,185	23,782	Domt	Domt	8,312

T score	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
Prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	16.65%	42.66%	7.97	7.89	7.89	7.86	22,363	22,595	22,393	20,928	Domt	Domt	13,139
–2.75	20.83%	47.06%	7.82	7.74	7.73	7.70	25,572	25,934	25,797	24,308	Domt	Domt	10,350
–3	25.86%	51.85%	7.66	7.57	7.56	7.52	29,300	29,824	29,766	28,253	Domt	Domt	7,701
–3.25	31.79%	56.96%	7.49	7.39	7.38	7.34	33,619	34,344	34,380	32,844	Domt	Domt	5,143
–3.5	38.60%	62.31%	7.31	7.19	7.18	7.14	38,597	39,573	39,723	38,163	Domt	Domt	2,612
–3.75	46.20%	67.75%	7.11	6.99	6.97	6.93	44,297	45,586	45,873	44,292	Domt	Domt	31
–4	54.33%	73.08%	6.91	6.77	6.75	6.71	50,762	52,440	52,890	51,292	Domt	Domt	Domt

Domt, denosumab dominant.

* Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of the PSA support the results of the deterministic base-case analyses and demonstrate that the base-case results are robust to variability in probabilistic model input parameters.

Regardless of prior fracture status among the primary comparators the most cost-effective treatment options are no treatment and denosumab. In patients with no prior fracture the cost-effectiveness acceptability curves for no treatment and denosumab intersect at £30,000 per QALY gained (Figure B12). This is mirrored in the cost-effectiveness acceptability frontier, which demonstrates the acceptability of denosumab at approximately £30,000 per QALY gained (Figure B13). The case for denosumab is even stronger in patients with a prior fracture, with the cost-effectiveness acceptability curves for no treatment and denosumab intersecting at approximately £13,000 per QALY with over 80% probability of cost-effectiveness at £20,000 per QALY gained and approximately 90% probability at £30,000 per QALY gained (Figure B15). Again, this is mirrored in the cost-effectiveness acceptability frontier, which demonstrates the acceptability of denosumab at approximately £13,000 per QALY gained (Figure B16). The cost-utility planes for both no prior fracture and prior fracture (Figure B14 and Figure B17) demonstrate a consistently tight spread of incremental costs and QALYs for denosumab gained compared with the strontium reference, illustrating the robustness of the denosumab data.

Table B77 PSA: primary comparisons: denosumab, strontium, raloxifene and no treatment (no prior fracture)

				Pairwise (vs. lowest cost)			ICERs vs. lowest cost	
	LYs	**QALYs**	**Costs**	**Δ LY**	**Δ QALY**	**Δ Cost**	**LY**	**QALY**
No Treatment	11.606	7.993	9,638	0.000	0.000	0		
Raloxifene	11.615	7.997	10,953	0.009	0.004	1,315	141,513	329,243
Strontium	11.622	8.009	11,327	0.016	0.016	1,690	106,451	105,768
Denosumab	11.641	8.049	11,333	0.035	0.056	1,695	48,465	30,347

** Raloxifene is not recommended by NICE in patients with no prior fracture.

Figure B12 Cost-effectiveness acceptability curves

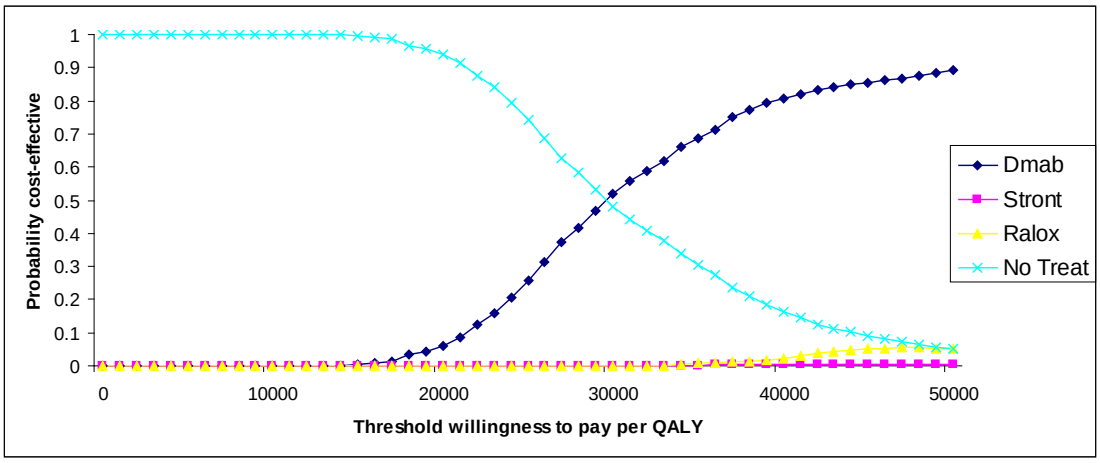


Figure B13 Cost-effectiveness acceptability frontier

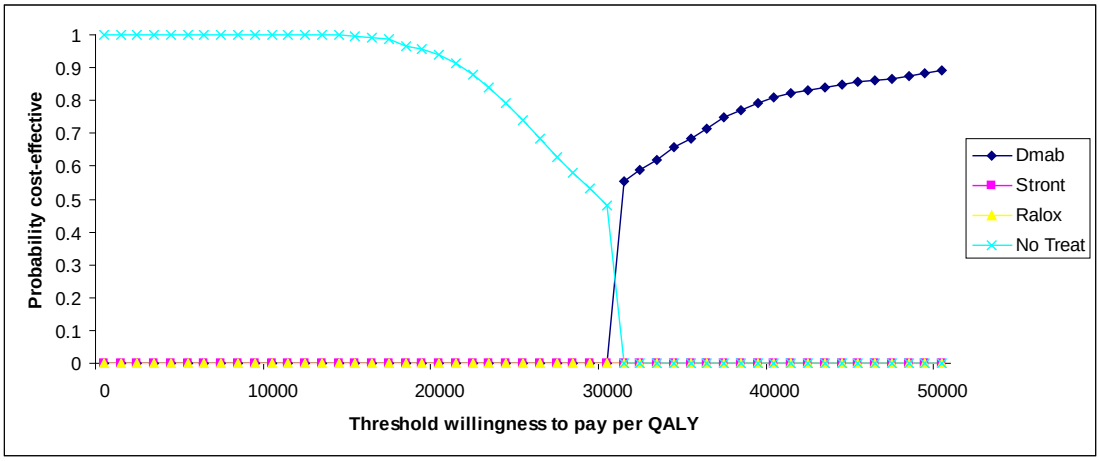


Figure B14 Cost-utility plane: denosumab, raloxifene and no treatment versus strontium

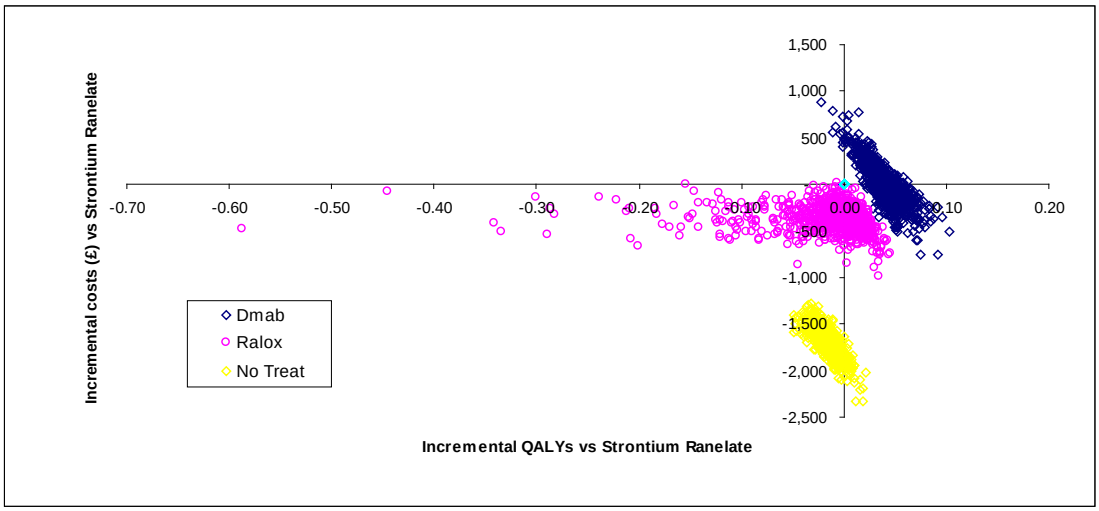


Table B78 PSA: primary comparisons: denosumab, strontium, raloxifene and no treatment (prior fracture)

				Pairwise (vs. lowest cost)			ICERs vs. lowest cost	
	LYs	QALYs	Costs	Δ LY	Δ QALY	Δ Cost	LY	QALY
No Treatment	11.492	7.795	12,295	0.000	0.000	0		
Raloxifene	11.516	7.814	13,646	0.023	0.019	1,351	57,505	69,981
Denosumab	11.575	7.912	13,816	0.082	0.117	1,521	18,466	13,016
Strontium	11.531	7.838	13,954	0.038	0.043	1,659	43,282	38,804

Figure B15 Cost-effectiveness acceptability curves

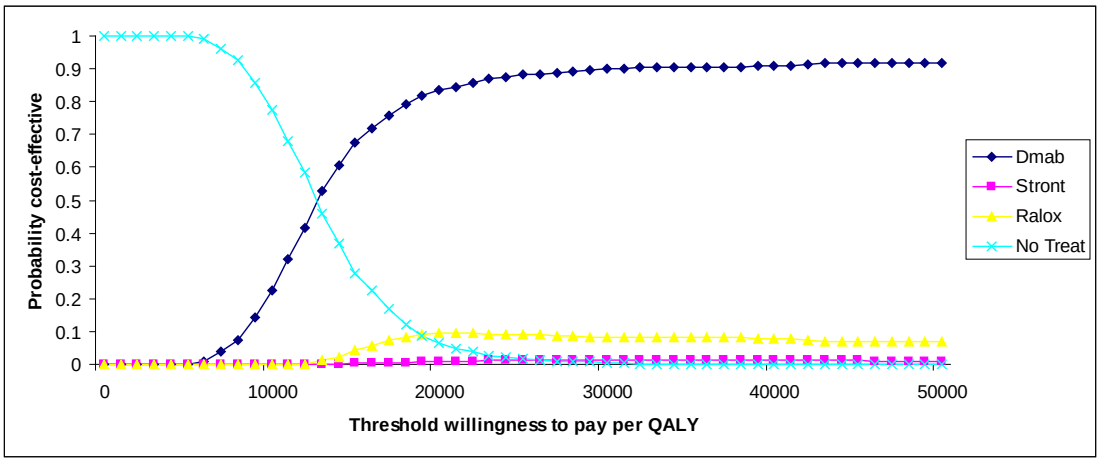


Figure B16 Cost-effectiveness acceptability frontier

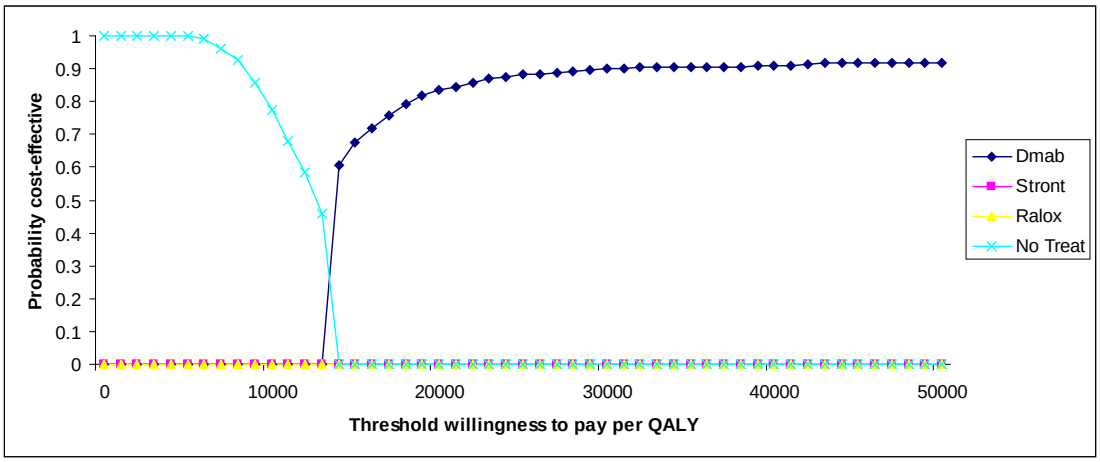
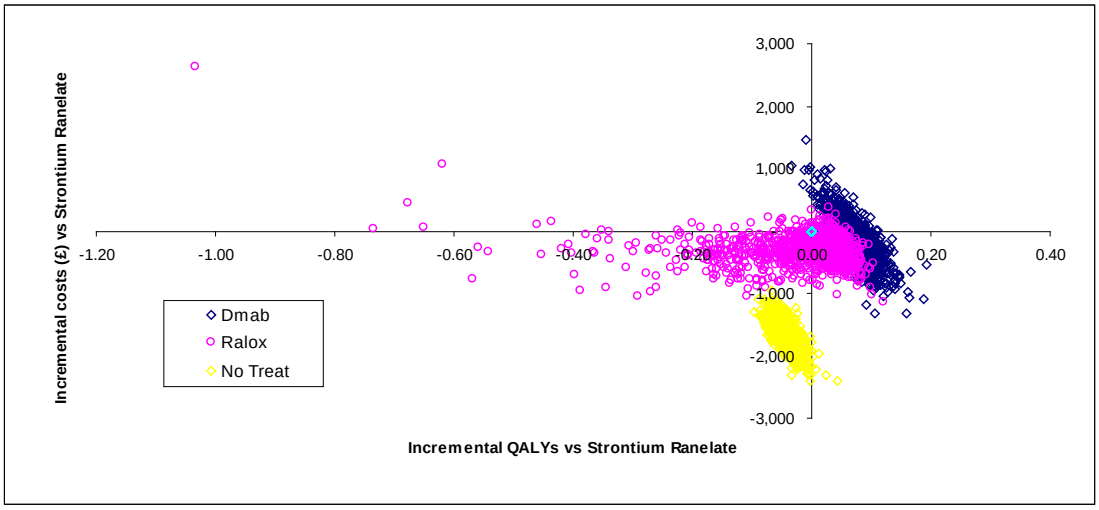


Figure B17 Cost-utility plane: denosumab, raloxifene and no treatment versus strontium



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Please see section 6.7.7 for results of both sensitivity analyses.

6.7.10 What were the main findings of each of the sensitivity analyses?

Please see section 6.7.7 for findings of both sensitivity analyses.

6.7.11 What are the key drivers of the cost-effectiveness results?

Primary comparisons

The results against strontium were driven by the improved efficacy of denosumab versus strontium for hip, vertebral and wrist fracture. This leads to quality of life and survival gains. Whilst the annual treatment cost of denosumab is expected to be approximately £70 more than strontium, this is more than offset by cost savings from a reduction in the expected number of fractures with denosumab compared with strontium. The total lifetime costs with denosumab are estimated to be approximately £3 and £155 less than the total lifetime cost with strontium for no prior fracture and prior fracture groups, respectively.

The results against raloxifene are driven by the improved efficacy of denosumab versus raloxifene for hip, vertebral and wrist fracture, which lead to quality of life and survival gains. Higher total lifetime costs of denosumab are estimated to be

approximately £371 and £133 more than the total lifetime cost of raloxifene for no prior fracture and prior fracture groups respectively.

The results against no treatment are driven by improved efficacy of denosumab versus no treatment for hip, vertebral and wrist fracture, and higher total costs of denosumab associated with the intervention costs.

Secondary comparisons

The results against ibandronate iv are driven by the improved efficacy of denosumab versus ibandronate iv for hip, vertebral and wrist fractures. The annual treatment cost of denosumab is estimated to be approximately £3,178 lower than the annual treatment cost of ibandronate iv. In addition there are cost savings associated with the reduction in fractures with denosumab compared with ibandronate iv. The total lifetime costs with denosumab are estimated to be approximately £2,756 and £2,984 less than the total lifetime cost with zoledronate iv for no prior fracture and prior fracture groups, respectively. It is noted that clinical efficacy estimates modelled for ibandronate iv were based on oral ibandronate data owing to the lack of efficacy data for the iv formulation.

The results against zoledronate iv are driven by the marginally lower relative risk reduction for denosumab for hip and vertebral fractures, combined with greater relative risk reduction for denosumab for wrist and other fractures. Denosumab is expected to incur lower annual treatment costs of approximately £44 than zoledronate iv in addition to reduced fracture related costs. The total lifetime costs with denosumab are estimated to be approximately £355 and £360 less than the total lifetime cost with zoledronate iv for no prior fracture and prior fracture groups, respectively.

The results of the secondary comparison versus teriparatide are driven by the lower risk reduction for denosumab for hip and wrist fractures resulting in lower expected QALYs for denosumab versus teriparatide, coupled with substantially lower therapy related costs. The total lifetime costs with denosumab are estimated to be approximately £13,576 and £13,324 less than the total lifetime cost with teriparatide for no prior fracture and prior fracture groups, respectively. It is noted that clinical

efficacy estimates for vertebral fracture modelled for teriparatide were based on morphometric fracture data.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was adapted from a global model developed for a more general application than in the UK. The global Markov cohort model (based on the Swedish setting) was therefore designed as a flexible analytic framework intended to meet the needs of multiple jurisdictions. Data sources used in the UK model were substituted for those in the global model to reflect the most appropriate UK values for NICE appraisal purposes. Validation steps were undertaken separately for the global model and subsequently for the adapted UK version; both sets of validation activities are described below.

Phase I Validation global Markov cohort model

The global model was validated using the following steps:

1. comparison of fracture incidence predicted by the global model to a previously published osteoporosis model
2. comparison of model predicted fracture incidence to Swedish normal population fracture rates
3. inclusion of a dynamic fracture adjustment term to test sensitivity of results to cohort model transition restrictions
4. full model rebuild using a microsimulation model framework in an alternative software package (TreeAge Pro 2008) and comparison of model results
5. independent review of the model by an external analyst not involved in the global model development
6. reproduction of the results of the FREEDOM trial.

1. Comparing to a published osteoporosis model

The global model was validated against a previously published state-transition model by Ström et al. (2008a) (the Adherence model). Both models were run with identical settings, incorporating the same features and assumptions, and populated with the same Swedish data. Simulated fracture rates were compared between the models and are presented in Table B79. The two models produced very similar results (average numbers of fractures), and the small differences between the two were the result of structural differences, transition restrictions in the global model, and the stochastic nature of the Monte Carlo simulations (in the Adherence model). The simulated number of sustained and saved vertebral fractures was in even closer agreement when the *dynamic fracture risk adjustment function* was turned on (see point 3 below, *Inclusion of a dynamic fracture adjustment term to test sensitivity of results to cohort model transition restrictions***,** for further details).

The fact that the simulated number of avoided fractures was very similar between the two models validates the persistence calculations that were used to emulate drop outs.

Table B79 Comparison of simulated average number of fractures between the global Markov cohort model and the published model (both populated with the same Swedish data)

	Global model, with adjustment	**Global model, no adjustment**	**Adherence model Ström et al., (2008a)**
10-year risk, placebo arm			
Hip	0.111	0.111	0.110
Vertebral	0.111	0.105	0.108
Fractures avoided during 10 years, Perfect vs. partial adherence			
Hip	0.0272	0.0272	0.0274
Vertebral	0.0285	0.0272	0.0286

2. Validation against Swedish normal population fracture rates

The cumulative rate of fractures simulated in the model was also validated against the Swedish incidence of fractures and mortality in the normal population (Statistics Sweden, 2007). The global model predicted slightly fewer fractures when the *dynamic fracture risk adjustment function* was turned off but returned otherwise identical amounts to the Swedish normal population. Fractures per 1,000 women over a period of 10 years when increased relative risks of fracture and mortality were removed are shown in Table B80 below.

Table B80 Predicted fractures/1,000 women over 10 years in the global model and Swedish normal population (women, age = 72)

	Global model, With adjustment	Global model, No adjustment	population prediction
Hip	67	67	67
Vertebral	57	55	57
Wrist	62	59	62
Other	130	123	130

3. Inclusion of a dynamic fracture adjustment term to test sensitivity of results to cohort model transition restrictions

An adjustment term was included as an optional feature of the global model to account for any missed fractures due to cohort model structural restrictions. In the global model, patients are not modelled to incur further wrist or other fractures after vertebral fractures. Patients in the post-hip fracture state can only remain in the post-hip fracture state, sustain another hip fracture or die. Thus, a hip fracture patient is only at risk of sustaining a new hip fracture and is not at risk of the other fracture types. This was considered to be a conservative simplifying assumption, though one that would result in some underestimation of fracture incidence in the base-case model. The results of the global model were analysed with and without the dynamic fracture risk adjustment to test the potential sensitivity of the model to transition restrictions.

The adjustment was performed by using age-specific data regarding the number of vertebral, wrist and other fractures occurring in the normal population (Statistics Sweden, 2007). The adjustment was estimated using the difference in fracture incidence between the expected number of fractures over a 10-year period for the untreated population with the model's predictions for the same timeframe after taking

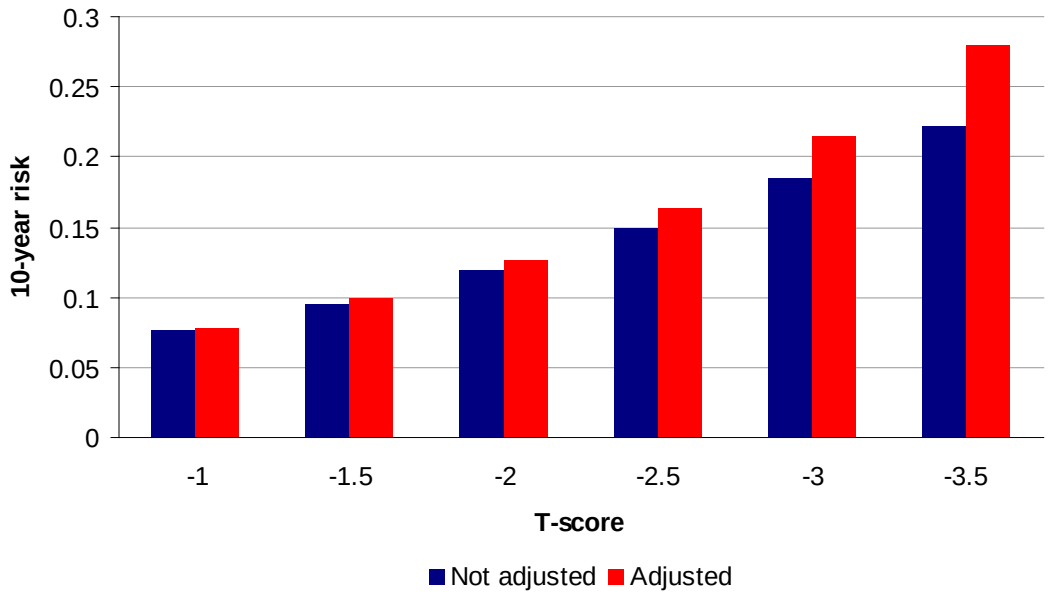
deaths into account. The adjustment factor was assumed to be 1.0 for hip fractures—which are not restricted in the model—and greater than 1.0 for vertebral, wrist and other osteoporotic fractures, since these fracture types are subject to structural restrictions.

Fracture incidence for clinical vertebral fractures with and without the adjustment term is shown in Figure B18 (70-year-old patients treated with denosumab, without previous fracture, and with T-scores at or below the indicated values). Overall, inclusion of the dynamic fracture risk adjustment was considered to make little difference to the results, and its use in the cost-effectiveness analysis for this NICE submission was—for transparency reasons—deemed unnecessary. Moreover, the adjusted indirect treatment comparison presented in section 5.7.6 reports the following:

- no statistical difference in denosumab efficacy to prevent hip fractures against all comparators
- denosumab has a statistically lower risk of morphometric vertebral fracture than strontium, raloxifene, alendronate and risedronate and no statistically significant difference in risk of morphometric vertebral fracture than all other comparators
- denosumab has a statistically significant lower risk of clinical vertebral fracture than strontium and no statistically significant difference in risk of clinical vertebral fracture than all other comparators.

Therefore, our exclusion of the dynamic fracture risk adjustment in the analyses presented in this appraisal should be considered conservative in favour of comparators strontium, raloxifene, alendronate, risedronate and no treatment versus denosumab and neutral for all other comparisons.

Figure B18 T-score and 10-year clinical vertebral fracture risk for a denosumab patient with and without adjustment



4. Full model rebuild using microsimulation framework (TreeAge Pro 2008)

The fracture risk output from the Excel-based global Markov cohort model was compared to that of a microsimulation model constructed in TreeAge Pro 2008. The microsimulation model had no structural restrictions, and a living patient could thus sustain any type of fracture in any cycle. In the event of multiple fractures the mortality, disutility and cost were taken from the 'worst' fracture. The comparisons of fracture incidence for different time periods are presented in the Figure B19 to Figure B22 below. The risks are from the 'no treatment' arm for a population with a T-score *at* –2.5 SD without previous vertebral fracture. Values generated by the global Markov cohort model with the dynamic fracture risk adjustment turned on are labelled 'Markov cohort adj.'

Figure B19 Average number of hip fractures

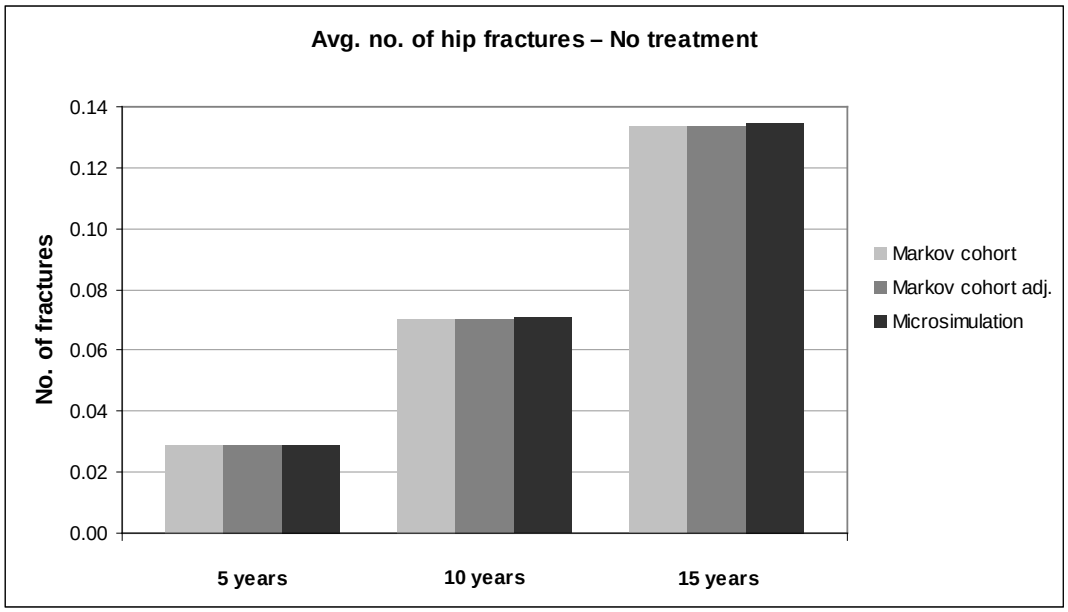


Figure B20 Average number of vertebral fractures

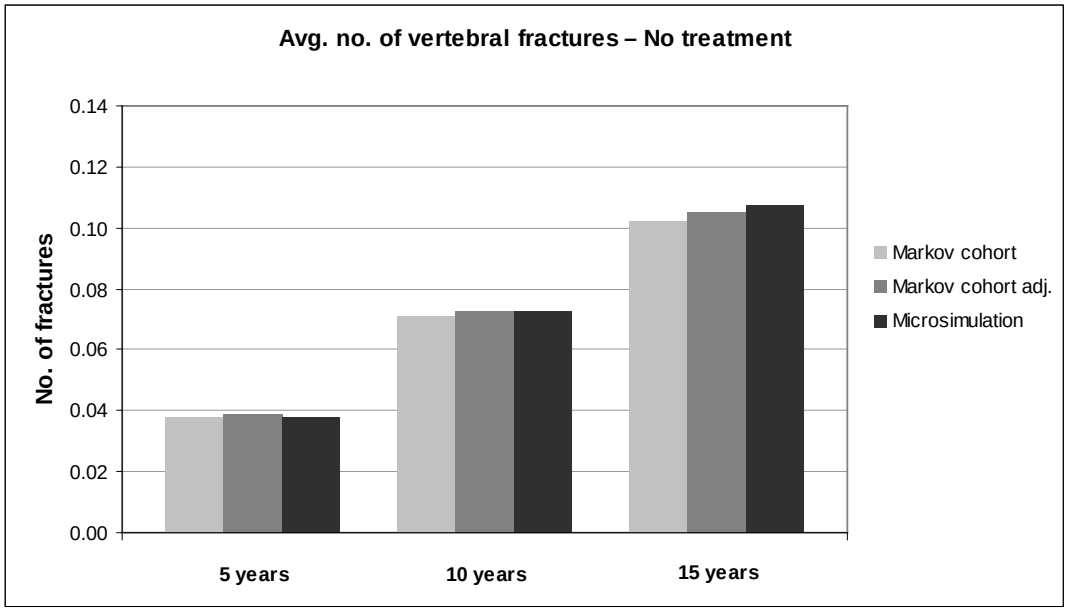


Figure B21 Average number of wrist fractures

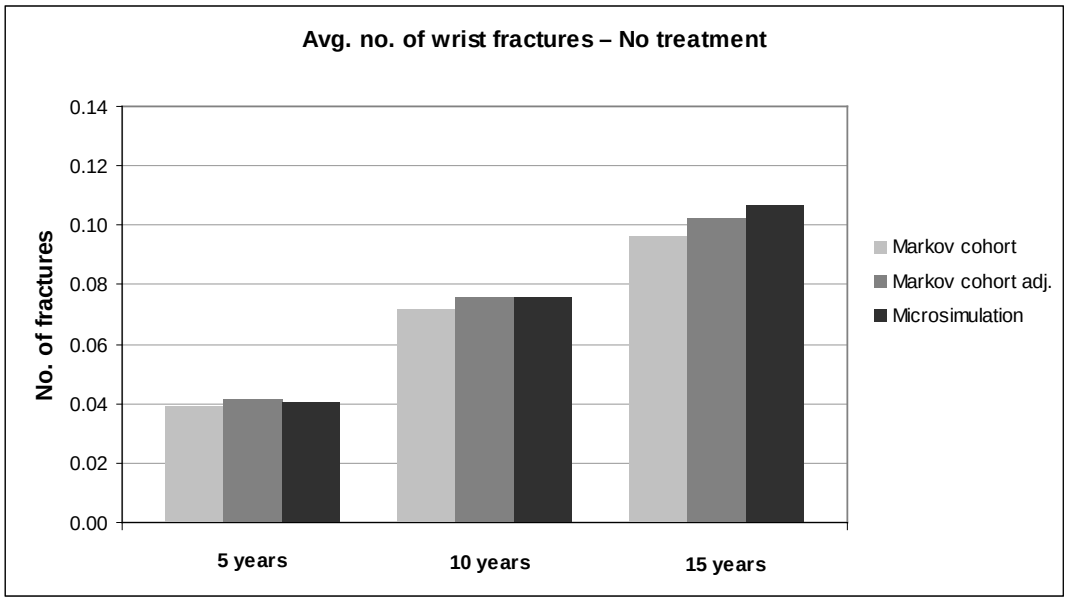
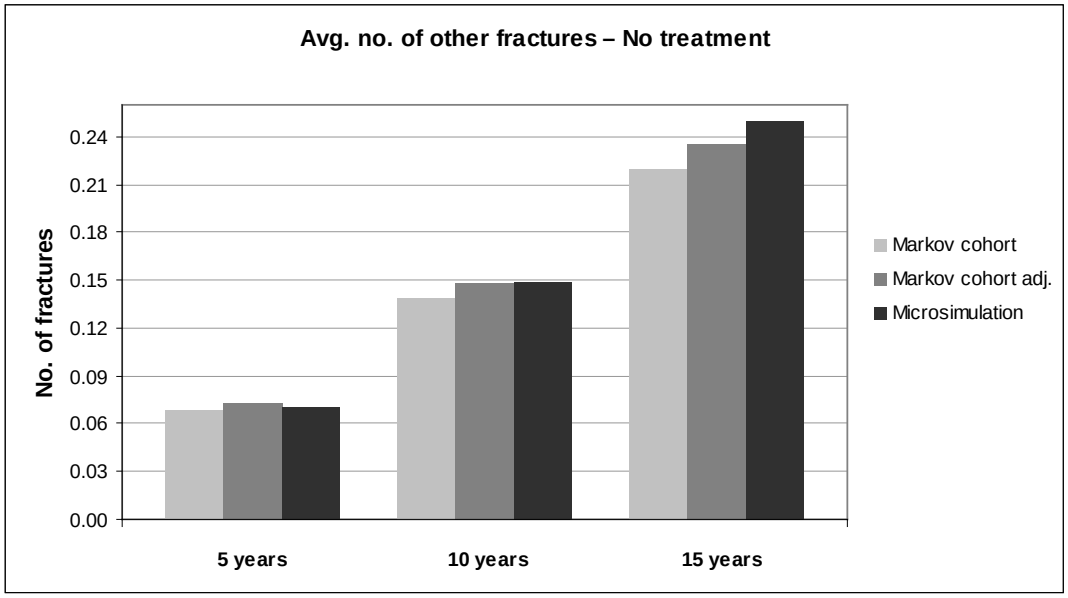


Figure B22 Average number of other osteoporotic fractures



The average number of fractures is almost identical when comparing outputs from the global Markov cohort model and the microsimulation model. As expected, there were practically no differences in hip fracture risks because no such restriction is present in the global Markov cohort model. As can be seen for vertebral, wrist and other fractures, the differences between the models become larger with longer analytic time horizons

5. Independent review of the model by an external analyst not involved in the development of the global model

The global Markov cohort model was reviewed by an external analyst not involved in the initial model development. The purpose of this review was to critically assess the model to enable the development team to make appropriate subsequent improvements. The model review included the technical validity of the model (i.e., correct implementation of model design and calculations), model assumptions, data inputs and face validity of the model.

6. Reproduction of the results of the FREEDOM trial

The global Markov cohort model was used to reproduce the results of the FREEDOM trial by using the following four steps:

1. Setting the relative risk of mortality due to fracture to 0 as well as the normal population mortality to 0, since deaths are already implicitly included in the FREEDOM trial
2. Setting the normal population risks to the overall FREEDOM trial placebo risks (Table B81)
3. Setting the relative risk of fracture to 100% for all fracture types, since we already have the fracture risk of the FREEDOM population incorporated through step 2
4. Setting the persistence to 100%

Table B81 Annual FREEDOM trial placebo risks used in the model for validation

Hip	Vertebral	Wrist	Other
0.003670	0.00080	0.00913	0.01246

Table B82 Efficacy of denosumab from FREEDOM trial used in the model for validation

Hip	Vertebral	Wrist	Other
0.60	0.32	0.80	0.80

Table B83 presents model-derived cumulative incidences of fractures after 3 years. The differences observed in risk ratios derived from the model (Table B83) compared with input parameters (Table B82) are due to the model's absorbing states. Specifically, post-vertebral patients are not modelled to incur further wrist or

other fractures. Patients in the post-hip fracture state are only at risk of sustaining a new hip fracture and are not at risk of the other fracture types.

Table B83 Model Derived Cumulative incidences of fractures after 3 years (6 cycles)

	Hip	Vertebral	Wrist	Other
Placebo	1.1%	7.1%	2.6%	3.6%
Denosumab	0.7%	2.3%	2.2%	3.0%
Risk Ratio	**0.60**	**0.32**	**0.82**	**0.82**

When only one fracture state (i.e., hip, vertebral, wrist or other) was activated at a time, observed risk ratios derived from the model (Table B84) were identical to model input parameters (Table B82). Furthermore, the rates of fractures from the model (Table B84) were almost identical to the trial results (Table B85).

Table B84 Model derived cumulative incidences of fractures over 3 years (*Activating one fracture state at a time*)

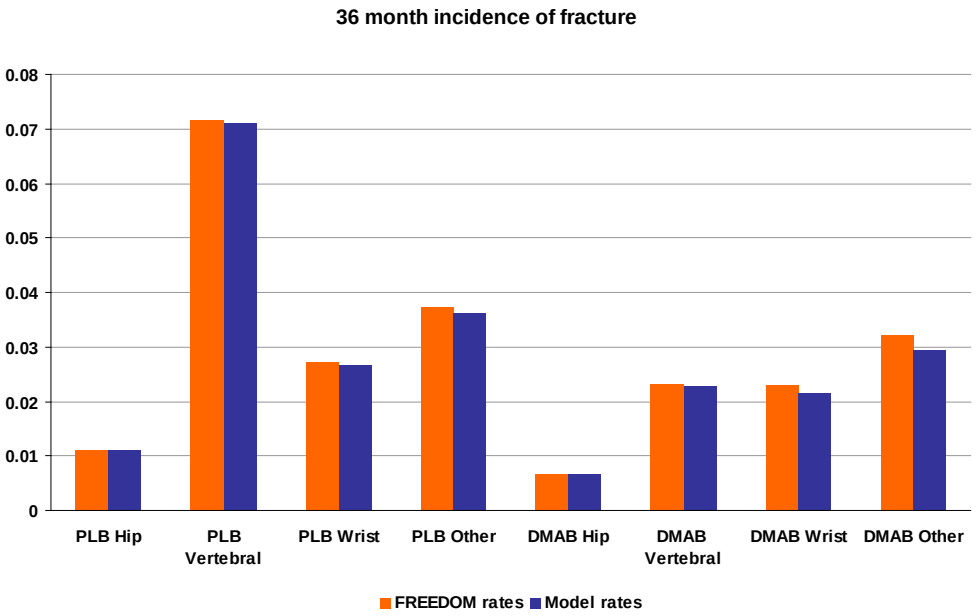
	Hip	Vertebral	Wrist	Other
Placebo	1.1%	7.2%	2.7%	3.7%
Denosumab	0.7%	2.3%	2.2%	3.0%
Risk Ratio	**0.60**	**0.32**	**0.80**	**0.80**

Table B85 The fracture rates over 3 years from the FREEDOM trial (Cummings et al., 2009).

	Hip	Vertebral	Wrist	Other
Placebo	1.1%	7.2%	2.7%	3.7%
Denosumab	0.7%	2.3%	2.3%	3.2%

Figure B23 compares FREEDOM trial fracture incidence rates with model derived rates. Small differences in the fracture rates derived from the global Markov cohort model compared with the FREEDOM trial rates are due to the absorbing states detailed above.

Figure B23 Comparison of FREEDOM fracture incidence rates vs. model-derived rates for both denosumab and placebo groups



Note: The rates in the graph were produced when all fracture states were simultaneously turned on.

Phase II validation of UK adapted model

The further validation of the UK adaptation is set against a bench-mark of the global Markov cohort model. The UK model adaptation was validated using the following steps:

1. Comparison of the UK adapted model to previously published UK osteoporosis models NICE TA160/161 (NICE, 2008a; NICE, 2008b) and Kanis et al. (2008b)
2. Comparison of model predicted fracture incidence and costs of the UK model and the global Markov cohort model
3. A review of the model by an independent analyst not involved in the model development. The review included reprogramming of key areas of the adaptation UK model and comparing the reprogrammed sheets with a full model version.

Comparison of overall costs and QALYs—global Markov cohort model versus UK adapted model

See section 6.10.1.

Comparison model predicted fracture incidence and costs of the UK model and the global Markov cohort model

Model comparisons between the global model and the UK adapted model demonstrated exact agreement in terms of undiscounted life years, QALYs and treatment costs when identical parameter values were employed. Costs relating to fracture events were not compared due to the range of input modifications that would be required to support this comparison. This provides strong empiric evidence of agreement between the models and is a reasonable basis for concluding that the risk of errors arising through model adaptation is minimal.

Review of model by an independent analyst

A work in progress UK model was supplied to an independent analyst (one not involved with the model adaptation itself). This independent analyst reviewed the model and provided verbal and written comments to the modelling team. These included queries relating to potential errors in the work in progress model. These comments were addressed by the modelling team as the work in progress model moved toward completion. The independent analyst additionally reprogrammed key areas of the model and compared the reprogrammed sheets with a full work-in-progress version.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost-effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost-effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Subgroup analyses have been presented for women with and without prior fracture (prevalence to prior vertebral fracture set to 0 and 1) aged 55-75 (5-year age bands) and femoral neck T-scores between –2.5 to –4.0 SD. These subgroup analyses were performed consistent with analyses undertaken for the previous NICE economic analyses for TA160 and TA161 and in line with expert clinical opinion on the most relevant populations for decision makers. These analyses were therefore considered to be in the most relevant populations of interest, although the model is capable of other subgroup analyses based on different combinations of age and T-score and FRAX® independent clinical risk factors (rheumatoid arthritis and parental history of hip fracture).

Subgroup analyses by prior fracture status, age (55-75 years) and T-score (–2.5 to –4 SD) demonstrate that denosumab becomes more cost-effective the greater the underlying risk of fracture (i.e., prior fracture, increasing age, and decreasing T-score). Denosumab is always a cost-effective option (within the cost-effective threshold range) compared with strontium and raloxifene. For the majority of subgroups, denosumab dominates strontium and is cost-effective in all other subgroups. Denosumab dominates raloxifene in many subgroups and is cost-effective in all other subgroups. Compared with no treatment in patients without a prior fracture, denosumab is always cost-effective in patients over 70 years of age regardless of T-score and is cost-effective in the majority of subgroups with T-score at or below –3.5 SD. In patients with a prior fracture denosumab is always a cost-effective option compared with no treatment regardless of T-score or age.

Table B86 Subgroup analysis: primary comparison: denosumab, strontium, raloxifene and no treatment (no prior fracture)

		QALYs				Costs				ICERs for comparison with Denosumab				
T	age	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment	Highest NMHB	Position for Denosumab
–2.5	55	12.997	12.972	12.974	12.967	11,392	11,182	10,714	9,368	8,421	29,572	**68,330**	No Treat	2
–2.5	60	11.368	11.344	11.345	11.340	11,316	11,126	10,667	9,328	7,966	28,175	**71,319**	No Treat	2
–2.5	65	9.772	9.742	9.743	9.734	11,318	11,187	10,755	9,425	4,348	19,390	**49,140**	No Treat	2
–2.5	70	8.048	8.007	8.009	7.991	11,135	11,138	10,764	9,455	Domt	9,289	**29,223**	Dmab	1
–2.5	75	6.538	6.504	6.502	6.493	10,578	10,759	10,455	9,201	Domt	3,346	**30,359**	No Treat	2
–3	55	12.857	12.825	12.826	12.816	14,628	14,474	14,030	12,678	4,787	19,306	**47,436**	No Treat	2
–3	60	11.239	11.209	11.209	11.201	14,493	14,362	13,929	12,583	4,269	18,317	**49,597**	No Treat	2
–3	65	9.656	9.617	9.617	9.604	14,462	14,413	14,018	12,678	1,250	11,396	**34,194**	No Treat	2
–3	70	7.953	7.899	7.898	7.875	14,182	14,326	14,015	12,690	Domt	3,069	**19,313**	Dmab	1
–3	75	6.468	6.422	6.419	6.407	13,402	13,785	13,563	12,301	**Domt**	Domt	18,007	Dmab	1
–3.5	55	12.670	12.627	12.627	12.613	19,144	19,081	18,679	17,316	1,453	10,711	**31,786**	No Treat	2
–3.5	60	11.069	11.028	11.026	11.015	18,895	18,858	18,466	17,110	932	10,140	**33,504**	No Treat	2
–3.5	65	9.502	9.451	9.449	9.432	18,789	18,867	18,530	17,174	Domt	4,893	**22,977**	Dmab	1
–3.5	70	7.825	7.754	7.751	7.722	18,344	18,700	18,486	17,136	**Domt**	Domt	11,728	Dmab	1
–3.5	75	6.375	6.315	6.309	6.293	17,223	17,897	17,794	16,519	**Domt**	Domt	8,600	Dmab	1
–4	55	12.426	12.367	12.364	12.345	25,434	25,523	25,187	23,809	Domt	3,962	**20,198**	Dmab	1
–4	60	10.848	10.794	10.789	10.775	24,971	25,081	24,755	23,384	Domt	3,670	**21,665**	Dmab	1
–4	65	9.303	9.237	9.232	9.210	24,713	24,986	24,737	23,359	**Domt**	Domt	14,512	Dmab	1
–4	70	7.660	7.567	7.559	7.524	23,985	24,660	24,591	23,206	**Domt**	Domt	5,772	Dmab	1
–4	75	6.255	6.177	6.167	6.147	22,334	23,426	23,496	22,200	**Domt**	Domt	1,238	Dmab	1

NMHB, Net Monetary Health Benefit

ICERs for treatments that are recommended by NICE according to age, T-score and prior fracture are provided in bold text to enable readers to compare with recommendations in TA160/161

Table B87 Subgroup analysis: primary comparison: denosumab, strontium, raloxifene and no treatment (prior fracture)

		QALYs				Costs				ICERs for comparison with Denosumab				
T	age	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment	Highest NMHB	Position for Denosumab
–2.5	55	15,201	15,192	14,813	13,448	144	7,007	18,750	144	144	7,007	**18,750**	Dmab	1
–2.5	60	14,469	14,440	14,054	12,697	541	8,638	22,957	541	541	8,638	**22,957**	Dmab	1
–2.5	65	14,077	14,081	13,719	12,361	Domt	6,995	19,113	Domt	Domt	6,995	**19,113**	Dmab	1
–2.5	70	13,543	13,698	13,410	12,060	Domt	2,046	12,381	Domt	**Domt**	**2,046**	12,381	Dmab	1
–2.5	75	12,533	12,877	12,644	11,380	Domt	Domt	14,436	Domt	**Domt**	**Domt**	14,436	Dmab	1
–3	55	19,904	20,072	19,773	18,389	Domt	1,703	12,289	Domt	Domt	1,703	**12,289**	Dmab	1
–3	60	18,756	18,875	18,557	17,180	Domt	3,044	15,590	Domt	Domt	3,044	**15,590**	Dmab	1
–3	65	18,104	18,258	17,970	16,585	Domt	1,979	13,309	Domt	**Domt**	**1,979**	13,309	Dmab	1
–3	70	17,299	17,660	17,481	16,087	Domt	Domt	7,986	Domt	**Domt**	**Domt**	7,986	Dmab	1
–3	75	15,886	16,493	16,376	15,087	Domt	Domt	7,741	Domt	**Domt**	**Domt**	7,741	Dmab	1
–3.5	55	26,599	27,058	26,885	25,475	Domt	Domt	6,969	Domt	**Domt**	**Domt**	6,969	Dmab	1
–3.5	60	24,755	25,109	24,897	23,495	Domt	Domt	9,632	Domt	**Domt**	**Domt**	9,632	Dmab	1
–3.5	65	23,663	24,050	23,873	22,454	Domt	Domt	8,479	Domt	**Domt**	**Domt**	8,479	Dmab	1
–3.5	70	22,412	23,089	23,069	21,621	Domt	Domt	4,197	Domt	**Domt**	**Domt**	4,197	Dmab	1
–3.5	75	20,387	21,371	21,422	20,098	Domt	Domt	2,195	Domt	**Domt**	**Domt**	2,195	Dmab	1
–4	55	36,169	37,102	37,131	35,690	Domt	Domt	2,329	Domt	**Domt**	**Domt**	2,329	Dmab	1
–4	60	33,168	33,894	33,844	32,410	Domt	Domt	4,561	Domt	**Domt**	**Domt**	4,561	Dmab	1
–4	65	31,328	32,077	32,066	30,608	Domt	Domt	4,149	Domt	**Domt**	**Domt**	4,149	Dmab	1
–4	70	29,337	30,501	30,713	29,205	Domt	Domt	579	Domt	**Domt**	**Domt**	579	Dmab	1
–4	75	26,369	27,896	28,186	26,819	Domt	Domt	Domt	Domt	**Domt**	**Domt**	Domt	Dmab	1

NMHB, Net Monetary Health Benefit

ICERs for treatments that are recommended by NICE according to age, T-score and prior fracture are provided in bold text to enable readers to compare with recommendations in TA160/161.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Women with and without prior fracture (prevalence to prior vertebral fracture set to 0 and 1), age range between 55 and 75 years in 5-year age bands and femoral neck T-scores between –2.5 to –4.0 SD.

6.9.3 Please describe how statistic analysis was undertaken.

The following key model parameters were assumed to be age-dependent:

- Baseline fracture risk
- Fracture costs
- Probability of nursing home admission.

The relative risk of fracture given any osteoporosis therapy and HRQL associated with fracture were both assumed to be age-independent.

6.9.4 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Subgroup analyses were not presented for patients by different clinical risk factors. Other clinical risk factors that may influence the potential risk of fracture include the following:

- BMI
- Glucocorticoid use
- Parental history of fracture
- Alcohol use
- Smoking status
- Rheumatoid arthritis.

Subgroup analyses were performed in line with analyses previously undertaken for NICE. These analyses were considered to be the most relevant populations of interest, although the model is capable of other subgroup analyses based on different combinations of age and T-score and FRAX® independent clinical risk factors.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Two NICE TA guidance documents have been produced for osteoporosis in postmenopausal women. The first guidance (TA160), considered five drugs for the primary prevention of osteoporosis in postmenopausal women (those at risk of a fragility fracture but without a prior fragility fracture). The second document (TA161), evaluated six drugs in the secondary prevention of osteoporosis in postmenopausal women (those who had previously sustained a fragility fracture). Cost-effectiveness estimates were reported in TA160 and 161 using the net monetary benefit approach. A threshold of £20,000 per QALY was applied for women without a prior fracture and £30,000 per QALY for women with a prior fracture.

These earlier NICE analyses showed that alendronate dominated other treatment options and had the lowest cost but equal efficacy compared to other therapies. The cost per QALY gained in primary populations for patients treated with alendronate (women with no prior fracture) was shown to be less than £20,000 for women aged 70 years with confirmed osteoporosis. The cost per QALY gained in secondary prevention populations (women with prior fracture), was shown to be less than £30,000 for women aged 55 years or older with confirmed osteoporosis. The current analysis also shows that alendronate dominates other treatment options for women with a prior fracture, a starting age of 70 years, and a T-score of –2.5 SD, with alendronate shown to be both less costly and more effective than no treatment (dominant). The costs of treatment with alendronate were, therefore, more than offset by the cost savings resulting from the reduction in fracture incidence; this cost

offset may be expected to be greater in patient subgroups with higher fracture risk (see appendix (section 9.15) . The current model therefore offers a more favourable analysis for alendronate versus no treatment than previously published NICE models.

It is noted that stakeholders criticised key assumptions underpinning the NICE economic analyses, particular the following. Firstly, it was thought inappropriate to pool efficacy data for alendronate and risedronate for the economic model. Secondly, HRG costs applied in the model were considered potentially to underestimate actual incurred medical expenses. Thirdly, adverse events were suggested to have been overstated by the Appraisal Committee given that intolerable adverse events were likely to result in a patient simply switching therapy (a 10-fold increase in the rate of adverse events was applied in the NICE reported analyses). Finally GPs were considered unlikely to assess women opportunistically for osteoporosis, since this is not included in the Quality and Outcomes Framework (QOF) section of the General Medical Service contract. The current model has been designed to reflect the primary issues previously identified with the NICE analysis. The current model does not pool efficacy data for BPs (an assumption likely to favour alendronate and other BPs versus denosumab). NHS reference costs have been applied based on a scoping search of HRGs, with parameters chosen to reflect the average length of stay of elderly osteoporotic fracture patients. GIAEs have been modelled to affect 2.35% of oral therapy patients in the first year—the 10-fold increase applied in the earlier NICE analyses was not applied (also likely to favour the oral BP comparators versus denosumab).

Kanis et al. (2008b) also recently produced an economic model comparing the costs of alendronate versus no treatment from an NHS perspective, and other interventions were considered in a sensitivity analysis. The model was published following the NICE appraisal reports and was presented as an alternative analysis to that undertaken by NICE. Alendronate was found to be cost-effective in primary prevention populations for all ages in women with defined osteoporosis (T-score –2.5 SD or below), and in all secondary populations in women with any BMD. Alendronate was found to have a cost per QALY gained versus no treatment of £3,701 for women with no prior fracture and £871 for women with a prior fracture.

The results of the current model are consistent with those presented in Kanis et al. (2008b) in that these analyses also show a lower cost per QALY for alendronate versus no treatment than was predicted by the NICE analyses. However, it is noted that the assumptions in the two models differ in two principal respects; fragility fracture costs in the current model are higher than those applied by Kanis et al. (2008b), while the utility multipliers are more conservative than the current model. Overall the current model presents a more favourable analysis for alendronate than in Kanis et al. (2008b) due to the higher modelled costs for fracture management.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The economic evaluation has been designed to explore the potential cost-effectiveness of denosumab versus existing standard care therapies for different population subgroups by age, T-score and prior fracture status. These population subgroups were considered to the most clinically relevant patients groups in feedback in expert opinion (see section 6.3.5) and were consistent with subgroup analyses previously undertaken by NICE for TA160 and TA161.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The evidence used to populate the model has been based a number of systematic reviews of the literature, including the following searches:

- Clinical RCT data
- Fracture risk epidemiological data
- Mortality data
- Economic evaluations in osteoporosis
- Cost data
- Adherence and compliance
- QoL
- Treatment offset.

Two further studies have also been commissioned to specifically address evidence gaps for osteoporosis therapy treatment adherence and compliance (Amgen data on file, 2009; Boston Collaborative group, 2009). This model is therefore considered to employ the best available current evidence in osteoporosis.

The model is also noted to be particularly flexible, and the model can apply FRAX® algorithm derived baseline fracture risk estimates or more traditionally based baseline fracture risk estimates. The model is also designed to consider persistence, compliance and treatment offset assumptions and allows denosumab to be compared to a broad range of comparators.

It is acknowledged that this model has some limitations. The cohort methodology in this model is associated with structural limitations that will lead to a slight underestimation of the number of vertebral, wrist and other fractures. An adjustment function was constructed to compensate for these 'lost' fractures, but it was not used in the reported analyses. The impact of the missed fractures was marginal, and inclusion of the adjustment was, for reasons of transparency, deemed unnecessary (see section 6.8 for further details). The model additionally cannot track multiple fractures in individual patients but as a cohort model distributes these fractures as an average across the whole cohort. A different model technique (microsimulation) would be to let each patient start with a low risk that would increase in steps when fractures are sustained. However, such an approach would be expected to give very similar results as the present one but would be more demanding in terms of data requirements. It would be necessary to acquire data on incidence of 'first fracture' and the uncertainty surrounding all the commonly referenced risk elevation estimates that would possibly lead to an over- or underestimation of the total number of simulated fractures.

It is also noted that literature searches identified several gaps in empirical data, in particular for the following:

- Utility data for more than 2 years post fracture
- The relationship between treatment duration and offset time
- The reduction in efficacy from poor compliance

- UK mortality data
- Proportion of patients entering nursing home care post fracture in the UK (by age).

It is also noted that no RCTs met inclusion criteria for fracture RR with ibandronate iv, and the modelled RR therefore reflected efficacy estimates for oral ibandronate. Furthermore, there was no consistent definition of 'other' fracture employed across RCTs that reported the fracture RR for therapies for 'other' fracture types. The RR estimates for other fractures were therefore assumed to be 1.00 across all comparators. This means that other fracture types were effectively excluded from the base-case model. Finally there were no studies identified that reported persistence data for ibandronate iv, zoledronate iv or teriparatide and the effects of treatment persistence could consequently not be taken into account in sensitivity analysis.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The model would permit further subgroup analyses to be undertaken for patients with different combinations of age, T-score, prior fracture status and independent clinical risk factors (using the FRAX® algorithm). It is noted that the net benefit of treatment would be expected to be greater in populations with higher baseline fracture risk, since the morbidity cost savings and QALY gains would increase.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

An estimated 645,000 patients will receive treatment for osteoporosis in England and Wales in 2010 (NICE 2008c, costing template updated for population projections for 2010, Office for National Statistics, 2009).

The number of women with PMO is expected to increase in the coming 5 years due to population ageing. In addition, the proportion of women with PMO that receive treatment may be expected to increase as a result of recent initiatives such as the Department of Health Fracture and Falls Prevention Toolkit (Department of Health, 2009) and the establishment of fracture liaison services. The estimated number of patients receiving treatment is projected to the period 2010 to 2015 (Table C1), taking into account the increasing population of women aged 50 years or more. Estimates are presented assuming no increase in the overall proportion of PMO patients receiving treatment (labeled ‘Low’ in Table C1), or assuming an increase of 2% each year in the treated population (labeled ‘High’ in Table C1).

Table C1 Projected number of patients receiving treatment for PMO in England and Wales; 2010-2015

	2010	2011	2012	2013	2014	2015
Low	645,118	652,729	662,286	672,633	683,234	694,225
High	645,118	665,784	688,777	712,991	737,893	763,647

Low estimates assume no increase in the overall proportion of patients with postmenopausal osteoporosis receiving treatment. High estimates assume an increase of 2% each year in the treated population.

Source: The number of treated patients in 2010 was projected to 2015 using population projections (2008-based, Office for National Statistics, 2009).

The proposed use of denosumab within the current clinical pathway is as an option for the treatment of patients for whom oral BPs are unsuitable. An estimated 93.24% of treated patients received oral BPs in 2009 (data for 2009, CSD, 2009; IMS, 2009, see Table A6); the remaining 6.76% received other interventions (Table C3); 5.00% received either strontium or raloxifene.

Denosumab may also be appropriate in some diagnosed patients that are currently untreated because they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for other interventions as recommended by NICE in TA160 and TA161 (NICE 2008a, 2008b). The number of patients in this group is difficult to estimate; however it is reasonable to anticipate that approximately 20% to 30% of diagnosed patients that are unsuitable for oral BPs fall within this category. The number of untreated patients in this group was calculated from the total number of diagnosed patients for whom oral BPs are unsuitable, which was estimated by assuming that the number currently receiving drugs other than oral BPs represents 70% to 80% of the total.

For the purposes of this analysis, denosumab is assumed to be an option for diagnosed patients that would currently receive strontium, raloxifene or no treatment because they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for other interventions. The estimated numbers of patients eligible for denosumab treatment on this basis are presented in Table C2. The low estimates assume the low estimates in Table C1 and the trends in patient share presented in Table C3 (which predict a decline in the proportion of patients receiving strontium or raloxifene) and also include patients that are currently untreated as they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for

other interventions (using the low estimate of 20% for this group). The high estimates assume the high estimates in Table C1, that a fixed 5.00% of the treated population are eligible for denosumab (the proportion of patients receiving strontium or raloxifene in 2009), and assume the high estimate (30%) for patients that are currently untreated as they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for other interventions.

Table C2 Estimated number of patients eligible for denosumab in England and Wales; 2010-2015

	2010	2011	2012	2013	2014	2015
Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breakdown for Low Estimate. Patients would otherwise receive:						
Strontium / raloxifene	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breakdown for High Estimate. Patients would otherwise receive:						
Strontium / raloxifene	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Low estimates assume the low estimates in Table C1 and the trends in patient share presented in Table C3 and also include patients that are currently untreated as they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for other interventions (assumed to represent 20% of all patients for whom oral BPs are unsuitable).

High estimates assume the high estimates in Table C1, that a fixed 5.00% of the treated population are eligible for denosumab, and also include patients that are currently untreated as they are unsuitable for oral BPs and are at insufficiently high risk of fracture to be eligible for other interventions (assumed to represent 30% of all patients for whom oral BPs are unsuitable).

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Current treatment options and the percentage of treated patients receiving each option are presented in Table C3.

Table C3 estimated market share for osteoporosis treatments in England and Wales

Treatment	Market Share (% treated patients)		
	2008	2009	Trend
Alendronate	59.40%	71.62%	12.22%
Risedronate	24.76%	15.79%	–8.97%
Etidronate	2.91%	1.49%	–1.42%
Ibandronate (oral)	5.25%	4.33%	–0.92%
Strontium	3.16%	2.78%	–0.38%
Raloxifene	3.18%	2.22%	–0.97%
Teriparatide	0.12%	0.11%	–0.01%
Ibandronate (iv)	0.58%	0.61%	0.03%
Zoledronate	0.32%	0.68%	0.36%
Calcitonin	0.21%	0.15%	–0.05%
Calcitriol	0.09%	0.21%	0.12%
Total for drugs other than oral BPs	7.68%	6.76%	–0.91%

BP, bisphosphonate; IMS, IMS Health Incorporated; iv, intravenous.

Patient shares were estimated from IMS sales data with the exception of etidronate and calcitriol, which were estimated from the CSD primary care medical records database. Patient shares were estimated from IMS regional sales analyses and hospital pharmacy audit data by dividing total sales by a compliance factor (assumed to be 60% for iv ibandronate and 100% for iv zoledronate), price and days of therapy.

Source: IMS 2009; CSD 2009.

Alternative scenarios were explored to estimate patient share for each intervention in 2010 to 2015. In the first scenario, the patient share was assumed to be static at 2009 values. In a second scenario, trends in patient share were applied (see section 9.18, appendix 18) which assumed that the increase in the use of generic alendronate will slow over time (the increase from 2008 to 2009 was assumed to approximately halve in each year), that use of strontium and raloxifene will remain static, and that the trend observed for other interventions will also slow over time (the trend from 2008 to 2009 was assumed to approximately halve in each year).

7.3 What assumption(s) were made about market share (when relevant)?

[redacted]

[redacted]

Table C4 Market forecast estimates for denosumab in England and Wales: 2010-2015

	2010	2011	2012	2013	2014	2015
Patient group. Patients who would otherwise receive:						
Strontium / raloxifene[a]	[redacted]					
No treatment[b]	[redacted]					
Number receiving denosumab						
Low	[redacted]					
High	[redacted]					
[redacted]						

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The annual costs for denosumab, strontium and raloxifene, including drug, administration and monitoring, are presented in Table C5. Equivalent data for other interventions are presented in section 9.18 (Appendix 18). No other significant costs that may be of interest to commissioners were identified.

Table C5 Annual costs for osteoporosis treatments (£, 2009)

Treatment	Brand	Drug	Adminis-tration	Monitor-ing	Total
Denosumab	Prolia	£366.00	£37.23	£70.47	£473.70
Strontium	Protelos	£333.71	£0.00	£70.47	£404.19
Raloxifene	Evista	£222.39	£0.00	£70.47	£292.86
Source: All sources were as reported in section 6 for the cost-utility model.					

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs and cost calculations were as reported in section 6 for the cost-utility model.

7.6 Were there any estimates of resource savings? If so, what were they?

Cost-offsets associated with a reduction in the incidence of fractures compared with no treatment, as estimated by the cost-utility model, are presented in Table C6 for the first 5 years after treatment initiation, and over patients' lifetimes.

Table C6 Cost-offsets associated with a reduction in the incidence of fractures compared with no treatment (£, 2009)

Treatment	First 5 years	Patient's lifetime
Denosumab	–£66.25	–£397.49
Strontium	-£18.29	–£109.75
Raloxifene	+£1.28	+£7.70

Costs represent the mean total morbidity cost for patients receiving the intervention minus that for patients receiving no treatment. Future costs are discounted at 3.5% per annum. Negative values indicate a lower mean cost associated with fractures for patients receiving the intervention than for patients receiving no treatment.

Source: Cost-utility model (see section 6).

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Estimated costs to NHS budgets in England and Wales are presented in Table C7 and Table C8 for scenarios in which denosumab is recommended and is not recommended. The estimated budget impact of recommending denosumab is presented in Table C9. Low and high estimates are presented representing the low and high estimates of patient numbers in Table C4.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No other opportunities for resource savings have been identified.

Table C7 Estimated costs in England and Wales (low estimates for number of patients receiving denosumab)

	Cost (£)					
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Cost of denosumab treatment						
Drug	£1,295,286	£2,721,833	£4,140,175	£5,514,944	£6,915,684	£8,356,908
Other direct	£381,170	£800,966	£1,218,348	£1,622,907	£2,035,109	£2,459,225
Total	£1,676,456	£3,522,799	£5,358,523	£7,137,851	£8,950,793	£10,816,133
Cost offsets[a]						
First 5 years	–£234,453	–£258,212	–£256,726	–£248,839	–£253,540	–£260,868
Lifetime	–£1,406,716	–£1,549,269	–£1,540,358	–£1,493,037	–£1,521,242	–£1,565,209
Cost of other interventions if denosumab is not recommended						
Drug	£53,334,608	£48,100,303	£46,138,022	£46,664,581	£47,359,975	£48,101,650
Other direct	£49,085,752	£50,061,967	£51,185,304	£52,134,527	£53,028,386	£53,917,735
Total	£102,420,360	£98,162,270	£97,323,326	£98,799,108	£100,388,362	£102,019,385
Cost offsets[a]						
First 5 years	–£50,663,896	–£3,461,097	–£2,206,900	–£1,021,322	–£925,860	–£927,242
Lifetime	–£303,983,377	–£20,766,584	–£13,241,400	–£6,127,930	–£5,555,160	–£5,563,451
Cost of other interventions if denosumab is recommended						
Drug	£53,125,344	£47,399,012	£44,719,911	£44,529,502	£44,486,592	£44,463,628
Other direct	£49,035,866	£49,894,786	£50,847,241	£51,625,546	£52,343,401	£53,050,468
Total	£102,161,210	£97,293,798	£95,567,152	£96,155,047	£96,829,993	£97,514,096
Cost offsets[a]						
First 5 years	–£50,655,689	–£3,459,628	–£2,203,855	–£1,020,287	–£923,251	–£923,611
Lifetime	–£303,934,135	–£20,757,770	–£13,223,132	–£6,121,723	–£5,539,506	–£5,541,664
Total costs if denosumab is recommended						
Drug	£54,420,630	£50,120,844	£48,860,086	£50,044,446	£51,402,276	£52,820,536

	Cost (£)					
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Other direct	£49,417,035	£50,695,752	£52,065,589	£53,248,453	£54,378,510	£55,509,693
Total	£103,837,665	£100,816,596	£100,925,675	£103,292,898	£105,780,787	£108,330,229
Cost offsets[a]						
First 5 years	–£50,890,142	–£3,717,840	–£2,460,582	–£1,269,127	–£1,176,791	–£1,184,479
Lifetime	–£305,340,851	–£22,307,039	–£14,763,490	–£7,614,759	–£7,060,748	–£7,106,874

Estimates assume the high estimates in Table C4 and the trends in patient share presented in Table C3.

[a] Cost offsets were calculated by multiplying the number of new patients receiving treatment (i.e. number treated in the current year minus the number in the previous year) by the cost offset in Table C7. These estimates therefore represent an approximation of the offset expected over the first 5 years of treatment, or over patients' lifetimes, for patients that started treatment in the year in question.

Table C8 Estimated costs in England and Wales (high estimates for number of patients receiving denosumab)

	Cost (£)					
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Cost of denosumab treatment						
Drug	£2,407,633	£4,750,806	£6,906,800	£9,211,559	£11,667,240	£14,282,898
Other direct	£708,505	£1,398,041	£2,032,495	£2,710,727	£3,433,371	£4,203,092
Total	£3,116,138	£6,148,847	£8,939,294	£11,922,286	£15,100,611	£18,485,990
Cost-offsets[a]						
First 5-years	–£435,793	–£424,125	–£390,245	–£417,172	–£444,490	–£473,446
Lifetime	–£2,614,755	–£2,544,750	–£2,341,468	–£2,503,032	–£2,666,937	–£2,840,675
Cost of other interventions if denosumab is not recommended						
Drug	£67,329,890	£69,486,748	£71,886,507	£74,413,702	£77,012,636	£79,700,555
Other direct	£48,628,024	£50,185,783	£51,918,974	£53,744,203	£55,621,245	£57,562,555
Total	£115,957,915	£119,672,531	£123,805,481	£128,157,905	£132,633,881	£137,263,111

	Cost (£)					
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Cost offsets[a]						
First 5 years	–£42,820,671	–£1,371,725	–£1,526,206	–£1,607,253	–£1,652,878	–£1,709,471
Lifetime	–£256,924,027	–£8,230,348	–£9,157,237	–£9,643,520	–£9,917,268	–£10,256,827
Cost of other interventions if denosumab is recommended						
Drug	£67,054,563	£68,539,589	£69,926,769	£71,370,752	£72,813,668	£74,268,653
Other direct	£48,559,790	£49,951,048	£51,433,291	£52,990,068	£54,580,614	£56,216,366
Total	£115,614,353	£118,490,638	£121,360,060	£124,360,821	£127,394,282	£130,485,019
Cost offsets[a]						
First 5 years	–£42,811,363	–£1,361,785	–£1,515,147	–£1,595,607	–£1,640,901	–£1,697,084
Lifetime	–£256,868,177	–£8,170,711	–£9,090,884	–£9,573,643	–£9,845,408	–£10,182,506
Total Costs if denosumab is recommended						
Drug	£69,462,196	£73,290,396	£76,833,568	£80,582,311	£84,480,908	£88,551,550
Other direct	£49,268,295	£51,349,089	£53,465,786	£55,700,795	£58,013,985	£60,419,458
Total	£118,730,490	£124,639,485	£130,299,355	£136,283,106	£142,494,893	£148,971,008
Cost offsets[a]						
First 5 years	–£43,247,155	–£1,785,910	–£1,905,392	–£2,012,779	–£2,085,391	–£2,170,530
Lifetime	–£259,482,932	–£10,715,462	–£11,432,351	–£12,076,675	–£12,512,345	–£13,023,181

Estimates assume the high estimates in Table C4 and the trends in patient share presented in Table C3.

[a] Cost offsets were calculated by multiplying the number of new patients receiving treatment (i.e. number treated in the current year minus the number in the previous year) by the cost offset in Table C7. These estimates therefore represent an approximation of the offset expected over the first 5 years of treatment, or over patients' lifetimes, for patients that started treatment in the year in question.

Table C9 Estimated impact of recommending denosumab on NHS budgets in England and Wales

	Cost (£)					
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Low estimate						
Denosumab patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug	£1,086,022	£2,020,541	£2,722,065	£3,379,865	£4,042,301	£4,718,887
Other direct	£331,283	£633,785	£880,285	£1,113,926	£1,350,124	£1,591,958
Total	£1,417,305	£2,654,326	£3,602,349	£4,493,791	£5,392,425	£6,310,844
Cost offsets[a]						
First 5 years	–£226,246	–£256,743	–£253,682	–£247,805	–£250,931	–£257,237
Lifetime	–£1,357,474	–£1,540,455	–£1,522,090	–£1,486,829	–£1,505,588	–£1,543,423
High estimate						
Denosumab patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug	£2,132,305	£3,803,648	£4,947,062	£6,168,609	£7,468,272	£8,850,995
Other direct	£640,270	£1,163,306	£1,546,812	£1,956,592	£2,392,740	£2,856,902
Total	£2,772,575	£4,966,954	£6,493,874	£8,125,201	£9,861,012	£11,707,897
Cost offsets[a]						
First 5 years	–£426,484	–£414,186	–£379,186	–£405,526	–£432,513	–£461,059
Lifetime	–£2,558,905	–£2,485,113	–£2,275,114	–£2,433,155	–£2,595,077	–£2,766,354

NHS, National Health Service.

[a] Cost-offsets were calculated by multiplying the number of new patients receiving treatment (i.e. number treated in the current year minus the number in the previous year) by the cost offset in Table C7. These estimates therefore represent the offset expected over the first 5 years of treatment, or over patients' lifetimes, for patients that started treatment in the year in question.

References

Abrahamsen B, Van Staa T, Ariely R. Excess mortality following hip fracture a systematic epidemiological review. Osteoporosis International 2009;20:1633-50.

Adachi J, Lynch N, Middelhoven H, Hunjan M, Cowell W. The association between compliance and persistence with bisphosphonate therapy and fracture risk: a review. BMC Musculoskeletal Disorders 2007;8:97.

Ades AD, Sculpher M, Sutton A, Abrams K, Cooper N, Welton N, Lu G. Bayesian Methods for Evidence Synthesis in Cost-Effectiveness Analysis. Pharmacoeconomics. (2006)24 (1); 1-19.

Amgen data on file. Summary of Clinical Safety - Module 2.7.4 of Prolia Marketing Authorisation Application, 2009

Amgen data on file. 20010223 clinical study report. 7 December 2007.

Amgen data on file. 20030216 (FREEDOM) clinical study report. 2 November 2008)

Amgen data on file. 20040132 (DEFEND) clinical study report. 24 August 2007.

Amgen data on file. 20040135 (HALT) clinical study report. 17 November 2008)

Amgen data on file. 20050141 (DECIDE) clinical study report. 29 July 2008)

Amgen data on file. 20050172 clinical study report. 30 May 2008.

Amgen data on file. 20050179 clinical study report. 5 September 2008.

Amgen data on file. 20050233 protocol. 25 March 2008.

Amgen data on file. 20050234 (STAND) clinical study report. 11 August 2008.

Amgen data on file. 20060232 (DAPS) 12-month interim analysis (flash memo and slide presentation). 31 August 2009.

Amgen data on file. 20060232 (DAPS) protocol. 8 August 2008.

Amgen data on file. 20060237 clinical study report. 2 February 2009.

Amgen data on file. 20060289 protocol. 9 March 2009.

Amgen data on file. 20080287 protocol. 24 February 2009.

Amgen data on file. 20080747. protocol 10 March 2009.

Amgen data on file. A multicentre, randomized, cross-over open label study to evaluate the adherence, preference and satisfaction of denosumab and alendronate in post menopausal women with low bone mineral density. 2009.

Amgen data on file. QCT study 179. 2009.

Anastasilakis AD, Toulis KA, Goulis DG, Polyzos SA, Delaroudis S, Giomisi A, Terpos E. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. Horm Metab Res. 2009 Jun 17. [Epub ahead of print]

Banks E, Beral V, Reeves G, Balkwill A, Barnes I. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. JAMA 2004;291: 2212–20.

Barrett JA, Baron JA, Beach ML. Mortality and pulmonary embolism after fracture in the elderly. Osteoporos Int 2003;14(11):889-94.

Barrett-Connor E, Wehren LE, Siris ES, et al. Recency and duration of postmenopausal hormone therapy: effects on bone mineral density and fracture risk in the National Osteoporosis Risk Assessment (NORA) study. Menopause 2003;10:412–9.

Beck TJ, Lewiecki EM, Miller PD, Felsenberg D, Liu Y, et al. (2008) Effects of denosumab on the geometry of the proximal femur in postmenopausal women in comparison with alendronate. J Clin Densitom. 11(3): 351-359.

Bekker PJ, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Min Res 2004;19(7):1059-66.

Berecki-Gisolf J, Hockey R, Dobson A. Adherence to bisphosphonate treatment by elderly women. Menopause 2008 Sep-Oct;15(5):984-90.

Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348(9041):1535-41.

Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296:2927–38.

Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809-22.

Blomfeldt R, Törnkvist H, Ponzer S, Söderqvist A, Tidermark J. Comparison of internal fixation with total hip replacement for displace femoral neck fractures. randomized controlled trial performed at 4 years. J Bone Joint Surg Br 2005;87(8):1680.

Blouin J, Dragomir A, Ste-Marie LG, Fernandes JC. Perreault S. Discontinuation of antiresorptive therapies: a comparison between 1998-2001 and 2002-2004 among osteoporotic women. J Clin Endocrinol Metab 2007 Mar; 92(3):887-94.

BMJ Group. British National Formulary. 2009 Available at: http://www.bnf.org/bnf/extra/current/450053.htm.

Bone H, Hosking G, Devogelaer J. Ten years experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99

Bone HG, Downs RW, Jr., Tucci JR, Harris ST, Weinstein RS, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab 1997;82(1): 265-274.

Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, San Martin J. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008 Jun;93(6):2149-57.

Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller P, Yang Y-C,. Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women With Low Bone Mass. Conference abstract, 31st Annual Meeting of the American Society of Bone and Mineral Research; Denver, Colorado, USA. 2009.

Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, et al. (2006) Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab. 91(7): 2631-2637.

Borgström F, Johnell O, Kanis JA, Oden A, Sykes D, Jönsson B. Cost-effectiveness of Raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation of the MORE study. Pharmacoeconomics 2004;22(17):1153-65.

Borgstrom F, Zethraeus N, Johnell L, Lidgren L, Ponzer S, Svensson O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int 2006a;17(5):637-50.

Boston Collaborative Group. Final report for the study of compliance and persistence to anti-osteoporosis medications in the United Kingdown using the General Practice Research Database (GPRD). 2009. The Boston Collaborative Drug Surveillance Program.

Bouee S, Lafuma A, Fagnani F, Meunier PJ, Reginster JY. Estimation of direct unit costs associated with non-vertebral osteoporotic fractures in five European countries. [Review] [41 refs]. Rheumatology International 2006 Oct;26(12):1063-72.

Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003 May 15;423(6937):337-42.

Brankin E, Walker M, Lynch N. The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases. Current medical research and opinion 2006;22(7):1249-56.

Breart G, Cooper C, Meyer O, Speirs C, Deltour N, Reginster JY. Osteoporosis and venous thromboembolism: a retrospective cohort study in the UK General Practice Research Database. Osteoporos Int. 2009 Oct 6. [Epub ahead of print]

British Orthopaedic Association. The care of patients with fragility fractures. 2007.

Brown MA, Bradlow J, Gray AM. Cost effectiveness of bone density measurements. Journal of the British Menopause Society 2001;7(3):130-35.

Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res 2009 Jan;24(1):153-61.

Bucher HC, Guyatt GH, Griffith LE and Walter SD. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. J Clin Epidemiol 1997;50(6):683-91.

Burge RT, Worley D, Johansen A, Bhattacharyya S, Bose U. The cost of osteoporotic fractures in the UK: Projections for 2000-2020.
Journal of Medical Economics 2001;4:51-62.

Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, et al. Geriatric rehabilitation following fractures in older people: A systematic review. Health Technology Assessment 2000;4(2):i-iii, 1-102.

Capparelli C, Morony S, Warmington K, Adamu S, Lacey D, et al. Sustained antiresorptive effects after a single treatment with human recombinant osteoprotegerin (OPG): a pharmacodynamic and pharmacokinetic analysis in rats. J Bone Miner Res 2003;18(5):852-8.

Carfora E, Sergio F, Bellini P et al. (1998) Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures. Gazzetta Medica Italiana – Archivio Per Le Scienze Mediche 157: 105–9.

Caro J, Huybrechts K, Raggio G. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporosis Int 2004;15(12):1003-8.

Casemix service NHS. HRG4 Chapter listings. 2008.

Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1995;122:9–16.

Chesnut-III C, Skag A, Christiansen C. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. Journal of Bone and Mineral Research 2004; 9:1241-9.

Cockerill W, Lunt M, Silman A. Health-related quality of life and radiographic vertebral fracture. Osteoporosis Int 2004;15:113-9.

Cooper C, O'Neil T, Silman A. The epidemiology of vertebral fractures. Bone 1993;14(S89-S97).

Cooper A, Drake J, Brankin E; PERSIST Investigators. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. Int J Clin Pract 2006 Aug;60(8):896-905.

Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. J Bone Miner Res 2001;16(5): 925-931.

Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, et al. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 2005;353(6):566-75.

Cotte F, Mercier F, De PG. Relationship between compliance and persistence with osteoporosis medications and fracture risk in primary health care in France: a retrospective case-control study. Clin Ther 2008;30(12):2410-22.

Cramer J, Rosenheck R, Kirk G, et al. Medication Compliance Feedback and Monitoring in a Clinical Trial: Predictors and Outcomes. Value Health 2003;6: 566-73.

Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. Value Health 2008 Jan-Feb;11(1):44-7.

CSD. Patent Data. March 2009. Cegedim Strategic Data UK Ltd.

Cummings S, Martin J, McClung et al. Denosumab for the prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:1-10.

Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280(24):2077-82.

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009 Aug 20;361(8):756-65.

Curtis L. Unit costs of health and social care. 2008. Personal Social Services Research Unit, the University of Kent. Available at: http://www.pssru.ac.uk/pdf/uc/uc2008/uc2008.pdfhttp://www.pssru.ac.uk/pdf/uc/uc2008/uc2008.pdf. Accessed March 2009.

de Lusignan S, van Vlymen J, Hague N. Using computers to identify non-compliant people at increased risk of osteoporotic fractures in general practice: a cross-sectional study. Osteoporosis Int 2006;17(12):1808-14.

Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002;87(8):3609-17.

Department of Health, National Service Framework for Older People. 2001 (Standard 6). Department of Health, London. Available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4003066. Accessed 5 October 2009.

Department of Health. Falls and fractures, Effective interventions in health and social care. 2009. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_103146. Accessed 16 December 2009.

Department of Health. NHS reference costs. 2006. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571

Derhernais C, Bajwa K, Markle J et al. A microcosting analysis of zoledronic acid and pamidronate therapy in patients with metastatic bone disease. Support Care in Cancer 2001;9:545-51.

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7(4):177-88.

Dolan P, Torgerson D. The Cost of Treating Osteoporotic Fractures in the United Kingdom female population. Osteoporosis International 1998;8:611-7.

Dolan P, Torgerson D, Kakarlapudi T. Health-related quality of life of Colles' fracture patients. Osteoporos Int 1999;1999(9):196-9.

Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract 2001;55(8):505-509.

Eisman JA, Civitelli R, Adami S et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. Journal of Rheumatology 2008;35:488-97.

Eli Lilly and Company Limited. Summary of Product Characteristics, teriparatide (Forsteo 20 micrograms/80 microlitres, solution for injection, in pre-filled pen). Eli Lilly and Company Limited, Basingstoke, Hampshire, UK Last updated on the eMC: 17/09/2009. Available at: http://emc.medicines.org.uk/medicine Accessed 23 September 2009.

Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 2008;26:4875-4882.

Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Fan M, Kim D. Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. Breast Cancer Res Treat. 2009 Nov;118(1):81-7.

Ensrud KE, Barrett-Connor EL, Schwartz A, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res 2004;19:1259–69.

Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al.; for the Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene results from a 3-year randomized clinical trial. JAMA 1999;282(7):637-45.

European Medicines Agency. Committee For Medicinal Products For Human Use (CHMP) draft guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis. London; 14 December 2005.

Evio S, Tiitinen A, Laitinen K, Ylikorkala O, Valimaki MJ. Effects of alendronate and hormone replacement therapy, alone and in combination, on bone mass and markers of bone turnover in elderly women with osteoporosis. J Clin Endocrinol Metab 2004;89(2):626-31.

Fayers P, Hand D. Generalisation from phase III clinical trials: survival, quality of life and health economics. Lancet 1997;350:9083.

Ferretti JL, Cointry GR, Capozza RF, Frost HM. Bone mass, bone strength, muscle–bone interactions, osteopenias and osteoporoses. Mech Ageing Dev 2003;124:269–79.

Finnern HW, Sykes DP. The hospital cost of vertebral fractures in the EU: estimates using national datasets. Osteoporosis International 2003 Jun;14(5):429-36.

Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, et al. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab 2000;85(5):1895-900.

Franzo A, Francescutti C, Simon G. Risk factors correlated with post-operative mortality for hip fracture surgery in the elderly: a population-based approach. Eur J Epidemiol 2005;20(12):985.

Frost HM. The mechanostat: a proposed pathogenic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. Bone Miner 1987a;2:72–85.

Frost HM. Bone “mass” and the “mechanostat”: a proposal. Anat Rec 1987b;219:1–9.

Frost HM. A 2003 update of bone physiology and Wolff's Law for clinicians. Angle Orthod 2004;74:3–15.

Fuller K, Wong B, Fox S, Choi Y, Chambers TJ. TRANCE is necessary and sufficient for osteoblast-mediated activation of bone resorption in osteoclasts. J Exp Med 1998;188:997-1001.

Gallagher JC, Rapuri PB, Haynatzki G, Detter JR. Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. J Clin Endocrinol Metab 2002;87:4914–23.

Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res. 2008 Oct;23(10):1569-75.

Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. J Bone Miner Res 2000;15:1526–36.

Gillespie W, Walenkamp. Antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures. Cochrane review. 2001. Available at: http://www.cochrane.org/reviews/en/ab000244.html

Greenspan S, Emkey R, Bone H. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis: a randomized double blind placebo controlled trial. Ann Intern Med 2002;137:875-83.

Groeneveld PW. Quality of life measurement clarifies the cost-effectiveness of helicobacter pylor eradication in peptic ulcer disease and uninvestigated dyspepsia. Am J Gastroenterology 2001;96(2):338-47.

Halpern R, Becker L, Usman Iqbal S, Badamgarav E, Macarios D. Impact of Adherence to Osteoporosis Medication on Risk of Fracture (Abstract). 31st Annual Meeting of the American Society of Bone and Mineral Research, September 11-15, 2009. Denver, Colorado, USA.

Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med. (1998); 17(8):841-56.

Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282(14):1344-52.

Herd RJ, Balena R, Blake GM, Ryan PJ, Fogelman I. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. Am J Med 1997;103(2):92-9.

Heron evidence development. Risk of fracture with osteoporosis associated with medication non-adherence. 2009.

Higgins JPT, Thompson SG, Deeks JJ and Altman DG. Measuring Inconsistency in Meta-Analyses. British Medical Journal 2003;327:557-560.

Hiligsmann M, Reginster JY. Cost-utility of denosumab for the treatment of postmenopausal osteoporotic women. ECCEO Conference Abstract, 2009.

Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 2004;292(4):490-5.

Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, et al. (2005) Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric 8(3): 251-262.

Human Mortality Database. 2009. Available at: www.humanmortality.de Accessed August 2009.

Huybrechts K, Ishak K, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;38(6):922-8.

Ichinose Y, Tanaka H, Inoue M, Mochizuki S, Tsuda E, Seino Y. Osteoclastogenesis inhibitory factor/osteoprotegerin reduced bone loss induced by mechanical unloading. Calcif Tissue Int 2004;75(4):338-43.

IMS (Intercontinental Marketing Services). Regional sales analysis and hospital pharmacy audit data. March 2009. IMS Health UK Ltd.

Jalava T, Sarna S, Pylkkanen L, Mawer B, Kanis JA, Davies M, et al. Association between vertebral fracture and increased mortality in osteoporotic patients. Journal of Bone and Mineral Research 2003;18:1254-60.

Johnell O, Kanis J, Oden A, Sernbo I. Mortality after osteoporotic fracture. Osteoporosis International 2004a;15(1):38-42.

Johnell O, Kanis JA, Black DM, Balogh A, Poor G, et al. (2004b) Associations between baseline risk factors and vertebral fracture risk in the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. J Bone Miner Res. 19(5): 764-772.

Johnell O, Kanis J, Oden A, Johansson H, De Laet C, Delmas P. Predictive value of bone mineral density for hip and other fractures. J Bone Miner Res, 2005;20(7):1185-94.

Jonsson et al. Cost-effectiveness of alendronate treatment of osteoporosis in Denmark. An economic evaluation based on the fracture intervention trial (FIT). Ugeskr Laeger 2003;165(43):4112-6.

Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmö. Osteoporos Int 2000;11(8):669-74.

Kanis JA. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 2001;12(5):417-27.

Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 2001;12(5):417-27.

Kanis JA, Brazier J, Stevenson M, et al. Treatment of established osteoporosis: a systematic review and cost-utility analysis. Health Technology Assessment 2002a;6(29).

Kanis JA, Brazier JE, Stevenson M, Calvert NW, Jones ML. Treatment of established osteoporosis: A systematic review and cost-utility analysis 1118. Health Technology Assessment 2002b;6(29).

Kanis JA, Johnell O, Oden A, De Laet C, Oglesby A, Jonsson B. Intervention thresholds for osteoporosis. Bone 2002c;31(1): 26-31.

Kanis J, Johnell O, De Laet H, Johansson A, Oden P, Delmas J, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004a;35(2):375-82.

Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, et al. The risk and burden of vertebral fractures in Sweden. Osteoporos Int 2004b;15(1):20-6.

Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisations for vertebral fracture. Osteoporosis International 2004c;15:108-12.

Kanis JA, Borgström F, Johnell O, Oden A, Sykes D, Jönsson B. Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. Osteoporos Int 2005;16(1):15-25.

Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. [Review] [114 refs]. Health Technology Assessment (Winchester, England) 2007;Jan 23;11(7):iii-iiv.

Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008a Apr;19(4):385-97.

Kanis J, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. Bone 2008b;42:4-15.

Kanis J. WHO fracture risk assessment tool. University of Sheffield, School of Health and Related Research. 2009. at: http://www.shef.ac.uk/FRAX/

Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res. 2009 Jul 13. [Epub ahead of print] Digital Object Identifier: 10.1359/JBMR.090716.

Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Br Med J 1998;(316):736-41.

Klotzbeucher CM, Ross P, Lo S, et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. Journal of Bone and Mineral Research 2000;15:721-39.

Kostenuik PJ, Ominsky MS, Cranmer P, Atkinson J. The RANKL antagonist OPG-Fc causes significant increases in cortical bone thickness, density, and bone strength index in adult female cynomolgus monkeys. Abstract/poster presented at: 5th European Congress on Clinical & Economic Aspects of Osteoporosis & Osteoarthritis, 16-19 March 2005; Rome, Italy.

Kothawala P. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 2007;82(12):1493-501.

Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165-76.

Lacey DL, Tan HL, Lu J, Kaufman S, Van G, Qiu W, et al. Osteoprotegerin Ligand Modulates Murine Osteoclast Survival in Vitro and in Vivo. Am J Pathol 2000;157:435-48.

Lawrence TM, White CT, Wenn R, Moran CG. The current hospital costs of treating hip fractures. Injury 2005;36(1):88-91.

Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, et al.; AMG 162 Bone Loss Study Group. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res 2007 Dec;22(12):1832-41.

[redacted]

Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333(22):1437-43.

Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. J Clin Endocrinol Metab 1999; 84(9): 3076-3081.

Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med 2004; 164(18):2024-30.

Liu JL, Zhu HM, Huang QR, Zhang ZL, Li HL, et al. Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in Chinese postmenopausal women with osteoporosis: a multi-center, randomized, placebo-controlled clinical trial. Chin Med J (Engl). 2004;117(7): 1029-1035.

Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause 2004;11(4):405-415.

Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J Bone Miner Res 1998;13(11):1747-54.

Lyles KW, Colon-Emeric CS, Magaziner JS et al. Zoledronic acid and clinical fractures and mortality after hip fracture. New Eng J Med 2007;357:1799–809.

Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996; 18;312(7041):1254-9.

McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344(5):333-340.

McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al., Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006 Feb 23;354(8):821-31.

Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis--a 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002;87(5):2060-6.

Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350(5):459-68.

Michalska D, Stepan J, Basson B. The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2009;91:870-7.

Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M; Amg Bone Loss Study Group. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 2008a Aug;43(2):222-9.

Miller PD, Epstein S, Sedarati F, Reginster JY. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. Curr Med Res Opin 2008b;24(1):207-13.

Miller P, Bolognese M, Lewiecki EM, McClung M, Weinstein R, Ding B. Effects of denosumab on bone mineral density and biochemical markers of bone turnover: 6 year results of a phase 2 clinical trial (abstract). 31st Annual Meeting of the American Society of Bone and Mineral Research, September 11-15, 2009. Denver, Colorado, US.

Mochizuki S, Fujise N, Higashio K, Tsuda E. Osteoclastogenesis inhibitory factor/osteoprotegerin ameliorates the decrease in both bone mineral density and bone strength in immobilized rats. J Bone Miner Metab 2002;20(1):14-20.

Morii H, Ohashi Y, Taketani Y, Fukunaga M, Nakamura T, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. Osteoporos Int 2003;14(10): 793-800.

Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC, Jr. (1998) Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab. 83(2): 396-402.

Murray C, Walters S, Brazier J. Utility following a fracture in a group of elderly women. Qual life Res 2002;11:642.

National Collaborating Centre for Nursing & Supportive Care Osteoporosis: evidence review, Systematic reviews of clinical effectiveness prepared for the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. 2008. Available at: http://www.nice.org.uk/guidance/index.jsp?action=folder&o=42361 Accessed 24 November 2009.

National Institute for Health and Clinical Excellence (NICE). CG21 Clinical practice guideline for the assessment and prevention of falls in older people. 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/CG021fullguideline.pdf Accessed 5 October 2009.

National Institute for Health and Clinical Excellence (NICE). TA161 Osteoporosis—secondary prevention including strontium ranelate: guidance. 29 October 2008a. Available at: http://guidance.nice.org.uk/TA161/Guidance/pdf/English Accessed 5 October 2009.

National Institute for Health and Clinical Excellence (NICE). TA160 Osteoporosis—primary prevention. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for

the primary prevention of osteoporotic fragility fractures in postmenopausal women: guidance 29 October 2008b. http://guidance.nice.org.uk/TA160/Guidance/pdf/English Accessed 5 October 2009.

National Institute for Health and Clinical Excellence (NICE). Osteoporosis—primary prevention: costing template 10 December 2008c. Available at: http://guidance.nice.org.uk/TA160/CostTemplate/xls/English Accessed 13 November 2009.

National Institute for Health and Clinical Excellence (NICE). Clinical Guideline (under development) Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. 2009a. Available at: http://guidance.nice.org.uk/CG/Wave7/32 Accessed 5 October 2009.

National Institute for Health and Clinical Excellence (NICE). CG76 Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. 2009b. Available at: http://guidance.nice.org.uk/CG76/Guidance/pdf/English Accessed 5 October 2009.

National osteoporosis Society patient information leaflet. 2009. Available at: http://www.nos.org.uk/NetCommunity/Document.doc?id=483. Accessed July 3rd 2009.

National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporosis International 1998;Suppl.4:S7-S80.

Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, et al. (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 344(19): 1434-1441.

Netten et al. Unit Costs of Health and Social Care. Personal Social Services Research Unit; 1998.

NHS. HES online. 2009 Available at: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=192

NHS. OPCS Classification of Interventions and Procedures: chemotherapy regimens and guidance for clinical coders. Version 2.0. April 2008.

Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H. Clinical guidelines and evidence review for medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. 2009. Available at: http://www.nice.org.uk/nicemedia/pdf/CG76FullGuideline.pdf Accessed 17 December 2009.

Oden A, Dawson A, Dere W, Johnell O, Jonsson B. Lifetime risk of hip fractures is underestimated. Osteoporos Int 1998;8(6):599-603.

Office for National Statistics Population Projections, England and Wales; 2008-based. Available at: http://www.statistics.gov.uk/downloads/theme_population/NPP2008/wEW085y.xls Accessed 30 October, 2009.

Oleksik A, Lips P, Dawsome A. Health-related quality of life in postmenopausal women with low BMD with or without prevalence vertebral fractures. J Bone Miner Res, 2000;(15):1384.

Palomba S, Orio F, Jr., Russo T, Falbo A, Tolino A, et al. BsmI vitamin D receptor genotypes influence the efficacy of antiresorptive treatments in postmenopausal osteoporotic

women: a 1-year multicenter, randomized and controlled trial. Osteoporos Int 2005;16(8):943-52.

Parker, M, Anand J. What is the true mortality of hip fractures? Public Health 1991; 105:443-446

Parker MJ, Anand JK. What is the true mortality of hip fractures? Public Health 1999;105:443-6.

Peasgood T, Herrman K, Kanis J, Brazier J. An updated systematic review of Health State Utility Values for osteoporosis related conditions. Osteoporos Int 2009;20(6):853-68.

Penning-van Beest FJ, Erkens JA, Olson M, Herings RM. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int 2008 Apr;19(4):511-7.

Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9(5):461-8.

Pouilles JM, Tremollieres F, Roux C, Sebert JL, Alexandre C, et al. Effects of cyclical etidronate therapy on bone loss in early postmenopausal women who are not undergoing hormonal replacement therapy. Osteoporos Int 1997;7(3) 213-8.

Puffer S, Torgerson DJ, Sykes D, Brown P, Cooper C. Health care costs of women with symptomatic vertebral fractures. Bone 2004 Aug;35(2):383-6.

Recker RR, Kendler D, Recknor CP, Rooney TW, Lewiecki EM, et al. (2007) Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. Bone. 40(4): 843-851.

Redekop et al. Diabetic foot ulcers and amputations estimate of health utility for use in cost-effectiveness analyses of new treatments. Diabetes metabolism 2004;30:549-56.

Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11(1):83-91.

Reginster JY, Felsenberg D, Pavo I, Stepan J, Payer J, et al. Effect of raloxifene combined with monofluorophosphate as compared with monofluorophosphate alone in postmenopausal women with low bone mass: a randomized, controlled trial. Osteoporos Int 2003;14(9):741-9.

Reginster JY, Seeman E, de Vernejoul MC, Adami S, Compston J, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90(5): 2816-2822.

Reginster JY, Adami S, Lakatos P et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Annals of Rheumatic Diseases 2006; 65: 654-61.

Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, et al. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum 2008;58(6):1687-95.

Reginster JY, Rabenda V. Patient preference in the management of postmenopausal osteoporosis with bisphosphonates [review]. Clinical Interventions in Aging 2006;1(4):415-23.

Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: results of FACTS -international. Clin Drug Investig 2006;26(2):63-74.

Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-International. Int J Clin Pract 2008;62(4):575-84.

Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009;373(9671):1253-63.

Reid IR, Benhamou L, Bolognese M, Brown JP, Hoeck HC, Eastell R. Effects of Denosumab on Bone Histology and Histomorphometry: the FREEDOM and STAND Studies. 31st Annual Meeting of the American Society of Bone and Mineral Research; Denver, Colorado, USA. 2009.

Rietbrock S, Olson M, Van Staa T. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. Q J Med 2008;102:35-42.

Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005;20(1):141-151.

Ross AB, Bateman TA, Kostenuik PJ, Ferguson VL, Lacey DL, Dunstan CR, et al. The effects of osteoprotegerin on the mechanical properties of rat bone. J Mater Sci Mater Med 2001;12(7):583-8.

Roughead EE, Ramsay E, Priess K, Barratt J, Ryan P, Gilbert AL. Medication adherence, first episode duration, overall duration and time without therapy: the example of bisphosphonates. Pharmacoepidemiology and Drug Safety 2009;18(1):69-75.

Royal College of Physicians. Clinical Effectiveness and Evaluation Unit. National clinical audit of falls and bone health in older people. 2007. London. Available at: http://www.rcplondon.ac.uk/clinical-standards/ceeu/Documents/fbhop-nationalreport.pdf Accessed 14 September 2009.

Royal College of Physicians. Clinical Effectiveness and Evaluation Unit, Clinical Standards Department. National audit of the organisation of services for falls and bone health of older people. 2009. London. Available at: http://www.rcplondon.ac.uk/clinical-standards/ceeu/Current-work/Falls/Documents/National-Falls-and-Bone-Health-Public-Audit-Report-March-2009.pdf Accessed 14 September 2009.

Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008;19:733–59.

Sambrook PN, Geusens P, Ribot C, Solimano JA, Ferrer-Barriendos J, et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. J Intern Med 2004 255(4):503-11.

Sambrook P. Compliance with treatment in osteoporosis patients--an ongoing problem. Australian Family Physician 2006;35(3):135-7.

Scottish Intercollegiate Guidelines Network Search Filters, 2009. Available at: http://www.sign.ac.uk/methodology/filters.html#random Accessed 12 October 2009

Scottish Intercollegiate Guidelines Network. Economic search filters. Available at: http://www.sign ac uk/methodology/filters html#econ 2009

Seeman E, Thomas T, Boyd SK, Boutroy S, Shane E, Hanley DA, et al. Effects of denosumab and alendronate at the ultradistal radius in postmenopausal women with low bone mass ects. Poster. European Calcified Tissue Society, 23-27 May, 2009a; Vienna, Austria.

Seeman E, Cheung AM, Shane E, Thomas T, Boyd SK, Boutroy S. Baseline remodeling intensity and greater suppression by denosumab than alendronate: effects on HR-pQCT parameters at the radius. Abstract presented at: 31st Annual Meeting of the American Society of Bone & Mineral Research, September 11-15 2009b; Denver, Colorado, US.

Sewerynek E, Dabrowska K, Skowronska-Jozwiak E, Zygmunt A, Lewinska A. Compliance with alendronate 10 treatment in elderly women with postmenopausal osteoporosis. Endokrynologia Polska 2009 Mar-Apr;60(2):76-81.

Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 2008;23(12):1923-34.

Silverman S, Viswanathan H, Yang Y, Eis SR, Fardellone P, Gilchrist N, et al. Relationships between presence, severity, and location of prevalent vertebral fractures and health related quality of life (HRQoL). Conference abstract (draft), ACR 2009.

Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. J Bone Joint Surg Br 1998;80(2):243-8.

Siris E, Brenneman S, Barrett-Cooper E. The effect of age and bone mineral density on the absolute, excess and relative risk of fracture in post-menopausal women aged 50-99: results form the National Osteoporosis Risk Assessment. Osteoporosis International 2006;17:565-74.

Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med 2009a;122(2 suppl):S3-S13.

Siris E, Silverman S, Viswanathan H, Qian Y, Ragi-Eis S, Fardellone P. Evaluation of Health-Related Quality of Life in Postmenopausal Women Who Participated in the FREEDOM Trial. Conference abstract 1282, 31st Annual Meeting of the American Society of Bone and Mineral Research; Denver, Colorado, USA; 2009b.

Smith BB, Cosenza ME, Mancini A, Dunstan C, Gregson R, Martin SW, et al. A toxicity profile of osteoprotegerin in the cynomolgus monkey. Int J Toxicol 2003;22(5):403-12.

Söderqvist A, Miedel R, Ponzer S, Tidermark J. The influence of cognitive function on outcome after hip fracture. J Bone Joint Surg Br 2006;88:2115-23.

Sornay-Rendu E, Garnero P, Munoz F, Duboeuf F, Delmas PD. Effect of withdrawal of hormone replacement therapy on bone mass and bone turnover: the OFELY study. Bone 2003;33:159–66.

Statistics Sweden. Available at: http://www scb se/eng/databaser/ssd asp Accessed August 11, 2007.

Stevenson M, Jones ML, De NE, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide

for the prevention and treatment of postmenopausal osteoporosis 622. Health Technology Assessment 2005a;9(22):i-310.

Stevenson M, Lloyd J, De Ne et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. NHS HTA R&D; 2005b.

Stevenson M. Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, risedronate, strontium ranelate, raloxifene and teriparatide following corrections to the methodology associated with lower efficacy in some risk factors (Nov 2006). Sheffield: School of Health and Related Research; 2006a Nov.

Stevenson M, Davis S, Kanis J. The hospitalization costs and outpatient costs of fragility fractures. Women's health medicine 2006b;3:149-51.

Stevenson M, Davis S, Kanis J. The hospitalization costs and outpatient costs of fragility fractures. Women's health medicine 2006c;3:149-51.

Stevenson M, Davis S. Analyses of the cost-effectiveness of pooled alendronate and risedronate compared with strontium ranelate, raloxifene, etidronate and teriparatide (July 2006). Sheffield: School of Health and Related Research; 2006d Jul.

Stevenson M, Davis S. Analyses of the cost-effectiveness of pooled alendronate and risedronate compared with strontium ranelate, raloxifene, etidronate and teriparatide. Updated following change in price of generic alendronate (Sept 2006). Sheffield: School of Health and Related Research; 2006e Sep.

Stevenson M, Davis S, Lloyd-Jones M, Beverley C. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. [Review] [102 refs]. Health Technology Assessment (Winchester, England) 2007a Feb;11(4):1-134.

Stevenson M. Strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis - Technology Assessment Report for NICE, PjtRef 04/28/01 (project). The National Coordinating Centre for Health Technology Assessment (NCCHTA) 2007b.

Strom O. Cost-effectiveness of alendronate in the treatment of post-menopausal women in 9 European countries an economic evaluation based on the fracture intervention trial. Osteoporos Int 2007;18(8):1047-61.

Strom O, Borgström F, Kanis J, Jönsson B. Incorporating adherence in health economic modeling of osteoporosis. Osteoporos International 2008a.

Ström O, Borgstrom F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, et al. Long-term cost and effect on quality of life of osteoporosis-related fractures in Sweden. Acta Orthop 2008b;79(2):269-80.

Ström O, Macarios D, Badamgarav E, Borgström F, Jönsson B, Tosteson A, et al. Cost-effectiveness model for denosumab incorporating FRAX® and adherence in a UK setting ECCEO Conference Poster Presentation, 2009.

Summary of Product Characteristics, Ibandronate (Bonviva 3mg/3ml solution for injection in pre-filled syringe). Roche Products Limited, Welwyn Garden City, Hertfordshire UK Last updated on the eMC: 15/07/2009. Available at: http://emc.medicines.org.uk/medicine Accessed 23 September 2009.

Summary of Product Characteristics, Raloxifene (Evista 60mg film coated tablets). Daiichi Sankyo UK Limited, Gerrards Cross, Buckinghamshire, UK Last updated on the eMC: 17/09/2008. Available at: http://emc.medicines.org.uk/medicine Accessed 23 September 2009.

Sunyecz J. Optimizing dosing frequencies for bisphosphonates in the management of postmenopausal osteoporosis: Patient considerations. Clinical Interventions in Aging 2008;3(4):611-27.

Suzuki N, Ogikubo O, Hansson T. The course of acute vertebral body fragility fracture: its effects on pain, disability and quality of life during 12 months. Eur Spine 2008;17:1380-90.

Tidermark J, Zethraeus N, Svensson O, Törnkvist H, Ponzer S. Femoral neck fractures in the elderly: function outcome and quality of life according to EuroQol. Qual life Res 2002;11:473-81.

Todd C, Freeman C. Anglian audit of hip fracture 2. Cambridge Health Services Research Group; 1999.

Torgeson D, Iglesias C, Reid D. The economics of fracture prevention in primary care: key advances in the effective management of osteoporosis. UK Key Advances Series 2000.

UK National Statistics. UK consumer price index. http://www.statistics.gov.uk 2009.

Usman Iqbal S, Badamgarav E, Halpern R, Becker L, Macarios D. Association between Adherence to Osteoporosis Medication and Inpatient Stays and Medical Services Costs, (Abstract). 31st Annual Meeting of the American Society of Bone and Mineral Research, September 11-15, 2009. Denver, Colorado, USA.

Van Schoor N, Ewing S, O-Neill T. Impact of prevalent and incident vertebral fractures on utility: results from a patient based and a population -based sample. Qual life Res 2008;17:159-67.

Van Staa T, Dennison ELG, et al. Epidemiology of fractures in England and Wales. Bone 2001;29(6):517-22.

Van Staa, Leufkens H, Cooper C. Does a fracture at one site predict later fractures at other sites. A British cohort study. Osteoporosis International 2002;13:624-9.

Verma R, Rigby AS, Shaw CJ, Mohsen A. Acute care of hip fractures in centenarians-Do we need more resources?
Injury 2009;40(4):368-70.

Warriner AH, Curtis JR. Adherence to osteoporosis treatments: room for improvement. Current Opinion in Rheumatology 2009;21(4):356-62.

Wasnich RD, Bagger YZ, Hosking DJ, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. Menopause 2004;11:622–30.

Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323(2):73-79.

Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int 2006;17(11):1645-52.

Whitehead A. Meta-Analysis of Controlled Clinical Trials. Chichester: Wiley; 2002.

Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S, et al. Osteoclast differentiation factor is a ligand for osteoprotegerin osteoclastogenesis-inhibitory factor and is identical to trance/RANKL. Proc Natl Acad Sci USA 1998;95:3597-602.

Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES. Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. Obstet Gynecol 2004;103:440–6.

Zethraeus N, Strom O, Borgstrom F. What is the risk of institutionalization after hip fracture? Osteoporos Int 2006;SUP 2:S60.